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Defined Palladium–Phthalimidato Catalysts for Improved Oxidative Amination

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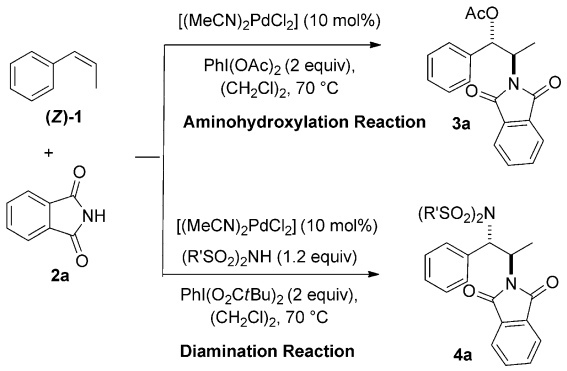
Dedicated to Professor Naoto Chatani on the occasion of his 60th birthday

Abstract: New palladium(II)–phthalimidato complexes have been synthesized, isolated, and structurally characterized. As demonstrated from over 30 examples, they constitute superior catalysts for oxidative amination reactions of alkenes with phthalimide as the 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 nitrogen-containing 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 an additional seminal transformation of hydrocarbons within this particular area.[3,4]

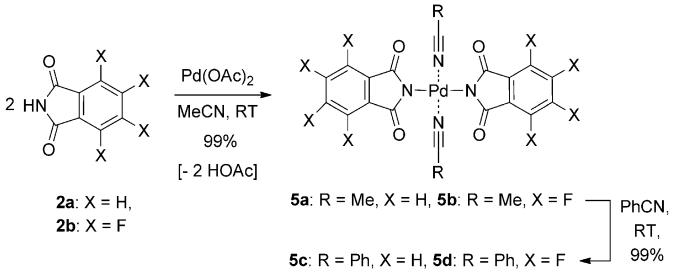
Earlier, the combination of palladium and phthalimide **2a** was found to permit unique intermolecular aminoacetoxylation[5] and diamination reactions,[6] all of which proceed under the conditions of Pd^{II}/Pd^{IV} redox catalysis.[7] This work has generated a synthetic methodology, which converts internal alkenes, such as **1**, into the corresponding difunctionalized products **3a** and **4a** with complete regio-, chemo-, and diastereoselectivity (Scheme 1),[6,8] though the structural basis for the involved palladium catalysts has so far remained undetermined. In general, although homogeneous palladium catalysis has reached paramount synthetic applicability over past decades,[9] definite knowledge on the catalyst states involved in individual



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

reactions has often remained elusive, in particular when oxidation reactions are concerned.[7,10] Herein, we report the isolation of defined palladium(II)–phthalimidato 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



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

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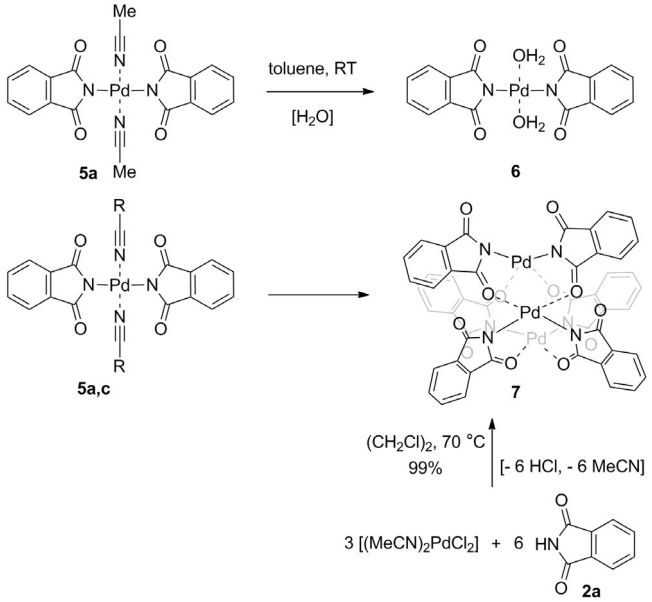
stability of the Pd–amide bond is reminiscent to those of peptide–palladium complexes.[12] Complexes **5a–d** form irreversibly and do not revert back to Pd–acetate complexes even in the presence of large excesses of the free carboxylic acid.[13] They are equally stable in the presence of hypervalent iodine reagents involved in the difunctionalization reactions.[13]

Complexes **5a–d** engaged in rapid dissociation of neutral nitrile ligands in solution. Attempts to grow crystals were unsuccessful except for one case, in which the structure of the new bis(aqua) complex **6** (Scheme 3) formed from a toluene solu-



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

tion 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 X-ray crystallography. Instead, heating of **5a,c** or prolonged standing in solution resulted 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]

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 the previous in situ protocols, whereas 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

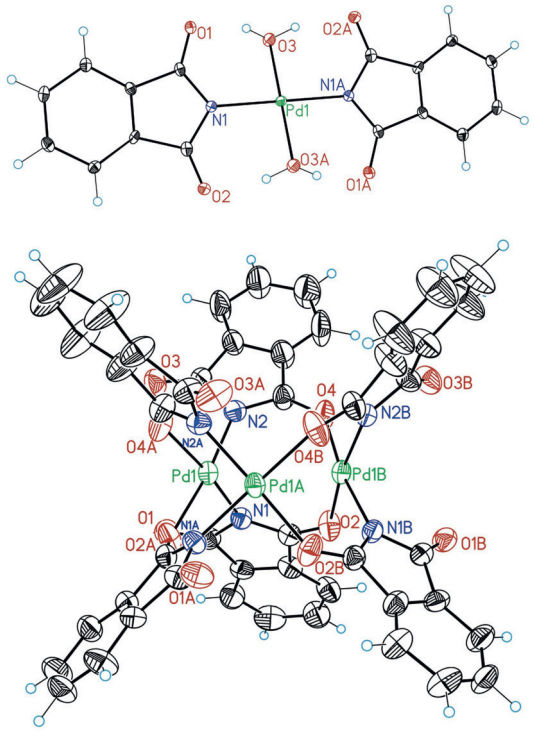
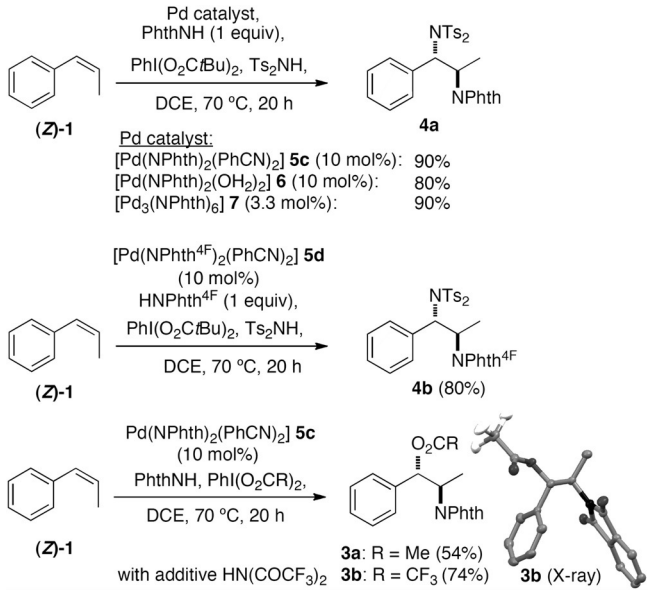


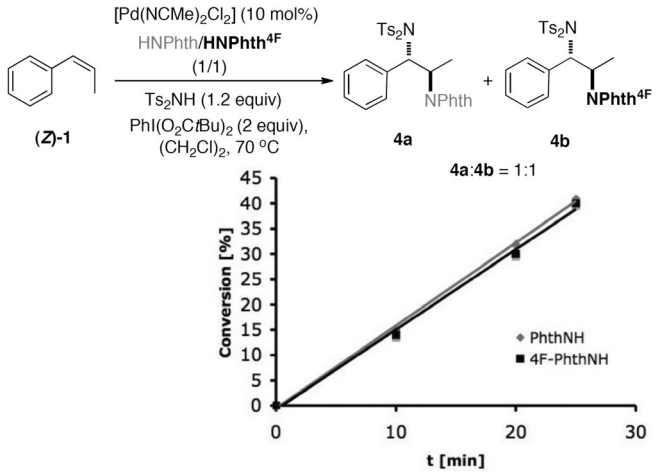
Figure 1. X-ray structures of complexes **6** (top) and **7** (bottom). Selected bond lengths (Å) and angles (°); complex **6**: Pd1—O3 2.018(3), Pd1—N1 2.046(4), O3-Pd1-O3 180.0, O3-Pd1-N1 90.25(15), O3-Pd1-N1 89.75(15) and complex **7**: Pd1—N1 1.992(4), Pd1—N2 1.975(5), Pd1—O2 2.017(4), Pd1—O4 2.026(4), 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).

the absence of any alkene isomerization pathway over the course of the difunctionalization reactions from Scheme 1 and Scheme 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 the 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 the palladium than nitriles, in which 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 the alkene coordination within the initial aminopalladation.[8b,c]

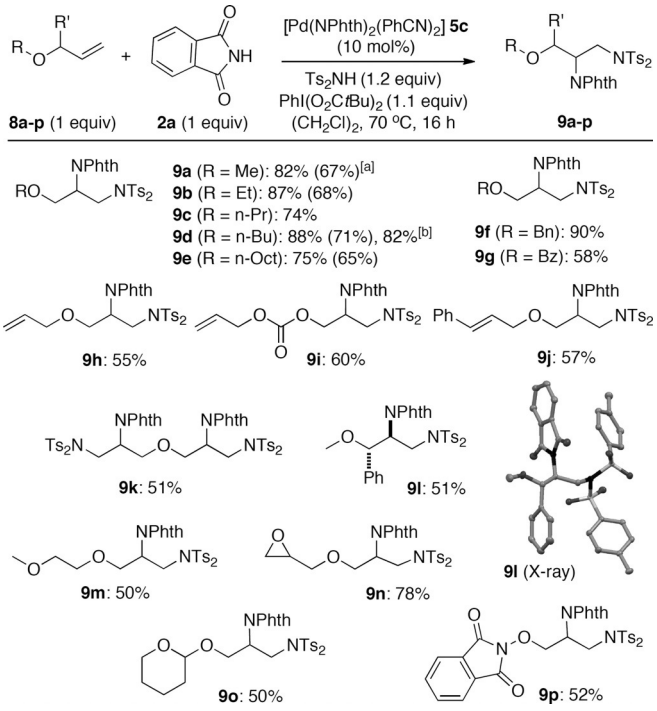


Scheme 4. Reactivity of palladium–phthalimidato complexes. HNPhth = phthalimide, HNPhth^{4F} = tetrafluorophthalphthalimide.



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

In addition to the identification of complexes **5** and **7** as 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 a 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 scaled-up conveniently. Besides common allylic substrates **8a–g**, the scope

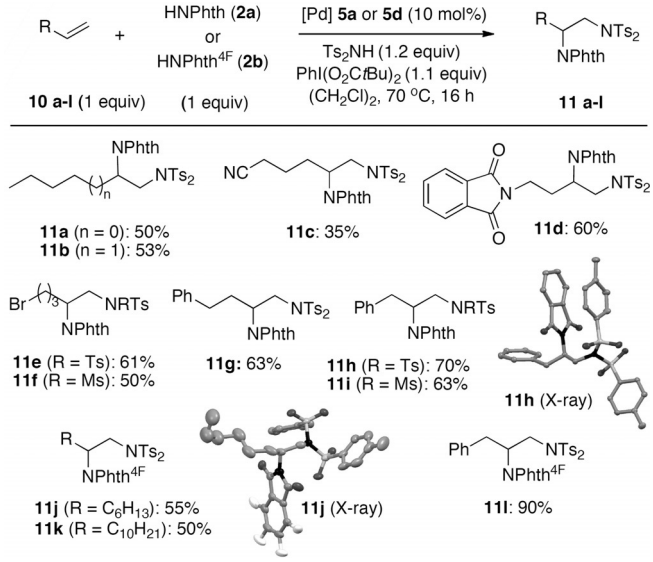


Scheme 6. Palladium-catalyzed diamination of allylic ethers employing preformed phthalimidato complexes. [a] Yields in brackets refer to the outcome from the in situ conditions. [b] Yield from a 4 mmol scale reaction.

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**).

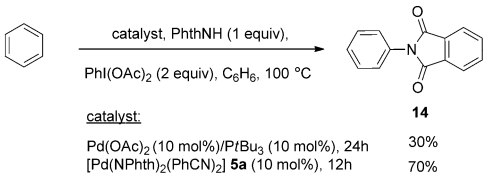
More importantly, terminal alkenes, which according to our previous protocols required the use of saccharine as a nitrogen source,[20] can now be employed in the palladium-catalyzed diamination with more readily removable[13] phthalimide (Scheme 7). Examples include representative aliphatic alkenes **10a,b**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

Functionalized alkenes are equally tolerated (**11d–g**), including the nitrile **10c**. The latter is entirely nonreactive without the 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



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

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



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.

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