Synthetic Methods

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Palladium-Catalyzed Intermolecular C(sp^3)–H Amidation**

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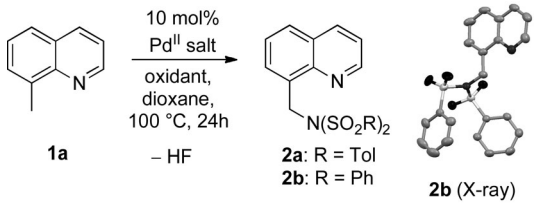
The direct amination of C–H bonds is a unique synthetic approach towards the important class of alkylated nitrogen compounds.[1] In this context, the palladium-catalyzed intermolecular C(sp^3)–H activation/amination of alkyl groups is a notably unexplored process.[2–4] On the other hand, we recently came across a reaction based on the formation of alkyl–nitrogen bonds from σ-alkyl palladium intermediates in the context of developing intermolecular diamination reactions of alkenes employing high-oxidation-state palladium catalysis.[5,6] We report herein on the successful extension of this C–N bond-forming reaction to arrive at direct palladium-catalyzed oxidative C–H amidation reactions.

8-Methylquinoline (**1a**) was chosen as model substrate,[7] and several oxidants such as iodobenzene diacetate/bistosylimide,[5a] PhI(OAc)NTs$_2$,[8] and *N*-fluorobis(phenylsulfonyl)imide (NFSI) were screened as nitrogen sources.[5b,9,10] A direct C–H activation/amidation reaction was readily accomplished with all three reagents in the presence of palladium(II) acetate as the catalyst precursor (Table 1, entries 1–3), and selective product formation was observed; however, yields were highly dependent on the reaction conditions.[11,12] 1,4-Dioxane was identified as the best solvent and a suitable rate was obtained only at high temperature. No product formed in the absence of palladium catalyst. Finally, in further catalyst screening with NFSI as the oxidant, [Pd(hfacac)$_2$] (hfacac = hexafluoroacetylacetonate) was identified as the optimum catalyst source (Table 1, entries 4–6). The general structure of the new products **2** was unambiguously secured by X-ray crystal structure analysis of compound **2b**.[13]

A number of additional C–H amidation reactions of 8-methylquinolines were accomplished with unprecedented efficiency (Scheme 1). These also include the selective monoamidation of 2-*tert*-butylpyridine (**3**) with the formation of a single C–N bond. The reaction proceeds with the commercially available catalyst [Pd(hfacac)$_2$] and commercial oxidant NFSI in an atom-economical manner, forming only HF as a by-product. Deprotection of **2b** producing 8-aminomethylquinoline was readily achieved under acidic conditions (HCl, 75%), which allows for convenient overall access to this class of interesting pharmaceutical building blocks.[14]

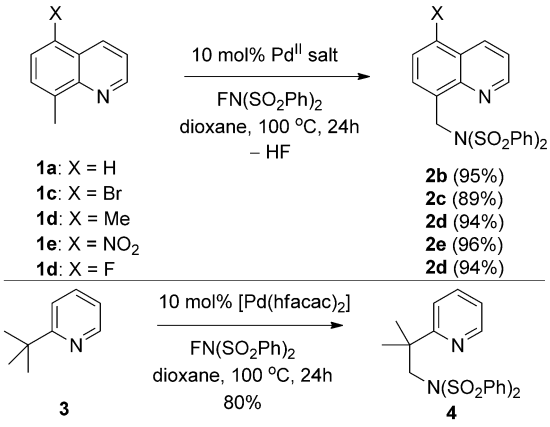
To extend the substrate scope, we were interested in a more labile coordinating group following a recent concept by Yu et al.[15] To this end, 2-methylphenyl ethers **5** were investigated (Table 2).[16] [Pd(hfacac)$_2$] and palladium dichloride were completely inefficient catalysts in this case (Table 2, entries 1 and 2), and after extensive screening, a combination of Pd(OAc)$_2$ and bathocuproine (bc) was found to be more appropriate (Table 2, entry 3). By the use of the preformed bathocuproine palladium complex [(bc)Pd(OAc)$_2$][17] the

Table 1: Palladium-catalyzed C–H amidation: optimization.



Entry	Pd^{II} salt	Oxidant	Product	Yield [%][a]
1	Pd(OAc)$_2$	PhI(OAc)$_2$/HNTs$_2$	**2a**	69
2	Pd(OAc)$_2$	PhI(OAc)NTs$_2$	**2a**	54
3	Pd(OAc)$_2$	NFSI	**2b**	47
4	Pd(NCMe)$_2$Cl$_2$	NFSI	**2b**	10
5	Pd(acac)$_2$	NFSI	**2b**	57
6	Pd(hfacac)$_2$	NFSI	**2b**	95

[a] Yield of isolated product after column chromatography.



Scheme 1. Palladium-catalyzed C–H amidation of quinolines and pyridines. Yields refer to isolated material after column chromatography.

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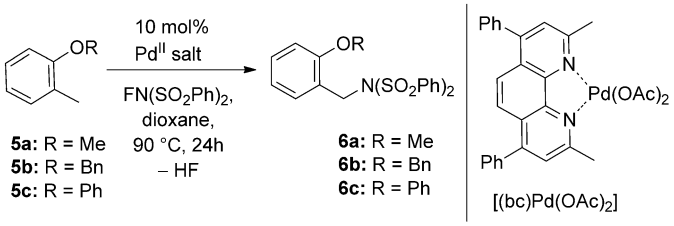
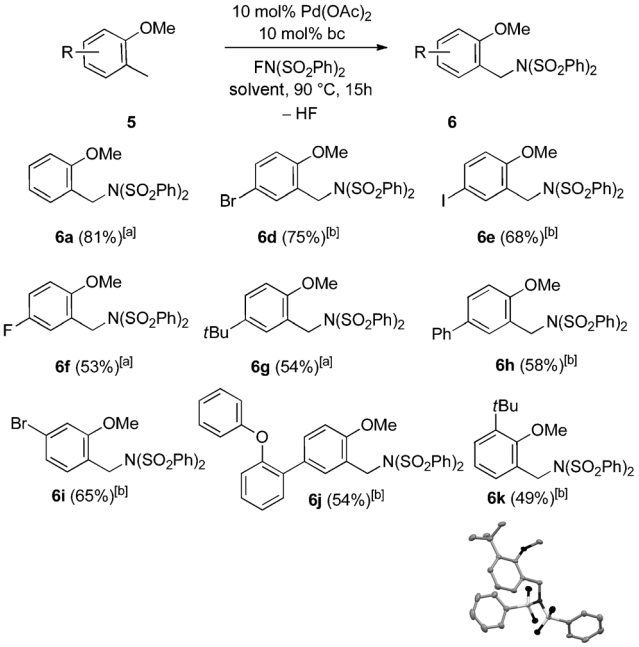
Table 2: Palladium-catalyzed C–H amidation of 2-methylphenyl ethers.



Entry	Pd^{II} catalyst Source	Product	Yield [%][a]
1	Pd(hfacac)$_2$	**6a**	0
2	Pd(NCMe)$_2$Cl$_2$	**6a**	10
3	Pd(OAc)$_2$/bathocuproine	**6a**	68
4	(bc)Pd(OAc)$_2$	**6a**	81
5	Pd(OAc)$_2$/bathocuproine	**6b**	55
6	(bc)Pd(OAc)$_2$	**6b**	45
7	Pd(OAc)$_2$/bathocuproine	**6c**	$<$10
8	(bc)Pd(OAc)$_2$	**6c**	21

[a] Yield of isolated product after column chromatography.



Scheme 2. Palladium-catalyzed C–H amidation of 2-methylanisoles. Yields refer to isolated material after column chromatography. [a] 10 mol% [(bc)Pd(OAc)$_2$], substrate (1 equiv), NFSI (2 equiv), dioxane/DMF (4:1) or dioxane/MeCN (3:1), 90°C, 15 h. [b] 10 mol% Pd(OAc)$_2$, 10 mol% bc, substrate (1 equiv), NFSI (2 equiv), dioxane/DMF (4:1), 90°C, 15 h.

yield of isolated **6a** could be improved further to 81% (Table 2, entry 4). In contrast to the amidation of 8-methylquinoline, the substrate 2-methylanisole tolerated only NFSI as the oxidant and nitrogen source.

This combination of palladium(II) acetate, bathocuproine, and NFSI also effected the C–H amidation of other 2-methylphenyl ethers such as **5b** and **5c**, albeit in lower yields (Table 2, entries 5–8). As a result, a series of 2-methylanisole derivatives were investigated, which underwent selective C(sp^3)–H amidation under the optimized conditions (Scheme 2). The reaction worked well for all kinds of 2-methylanisoles bearing *para*, *meta*, and *ortho* substituents on the arene ring. Notably, the oxidation proceeded selectively at the methyl position, even for **6j**, which displays an additional biphenyl ether. The C–H functionalization was also selective in favor of the methyl substituent over a potential *ortho-tert*-butyl group, as demonstrated for **5k**. The corresponding product **6k** was characterized unambiguously by X-ray crystal structure analysis.[13] All these examples demonstrate the control of C–H amidation by weak metal coordination.[15]

The successful realization of the oxidative direct amidation of an alkyl group under palladium catalysis led us to engage in a preliminary mechanistic investigation with 8-methylquinoline (**1a**) as the substrate. Starting from the palladium(II) salt, chelation-assisted C–H activation forms palladacycle **7**, which was confirmed through a stoichiometric control reaction. Product **7** was unambiguously characterized by X-ray structure analysis,[13] which proved that its composition is indeed monomeric.

The formation of **7** represents the initial step of the proposed catalytic cycle for this new intermolecular amidation (Figure 1). Under catalysis conditions, a large primary kinetic isotope effect k_H/k_D of 5.9 was determined for competition between **1a** and its [D$_3$]methyl derivative,[11] indicating that formation of **7** is either rate-limiting or reversible. The next step, oxidation of **7** with NFSI to an anticipated fluorinated high oxidation state intermediate,[18] could not be monitored by NMR spectroscopy, suggesting that reductive elimination takes place rapidly even at 298 K.[19] In agreement with this assumption, a control experiment with an equimolar mixture of **7** and the corresponding complex deuterated at the methylene position proceeded without detectable secondary kinetic isotope effect.[11] Oxidation of **7** with a stoichiometric amount of NFSI led to **2b** in 88% yield. While these experiments point to monomeric complex **7** as an intermediate in the catalytic cycle,[20] the exact nature of the high-oxidation-state intermediate could not be determined experimentally.

Theory provides a more versatile tool to address the underlying individual steps involved in the oxidation of **7** (Figure 1).[11,21,22] On the basis of *N*-fluorobis(methylsulfonyl)imide [FN(SO$_2$Me)$_2$] as an electrophilic two-electron oxidant, a linear transition state must be involved in the oxidation from Pd^{II} to Pd^{IV} (**TS7-A**, Figure 1). This results in the formation of a cationic fluorinated Pd^{IV} intermediate **A** with a square-planar pyramidal geometry, in which the methylene group occupies the apical position.[23] The computed activation energy for the oxidation step in dioxane using a continuum solvation model is 35.2 kcal mol^{-1}.[24] The cationic Pd^{IV} intermediate **A** and bissulfonylimide should not combine to a neutral Pd complex[9b] but rather engage in direct nucleophilic substitution at the electrophilic carbon in the α position to install the new C–N bond (**TSA-B**, Figure 1), since the stabilization of cationic Pd^{IV} is better accomplished by formal reductive elimination to Pd^{II} than by anion recombination to neutral Pd^{IV}. The

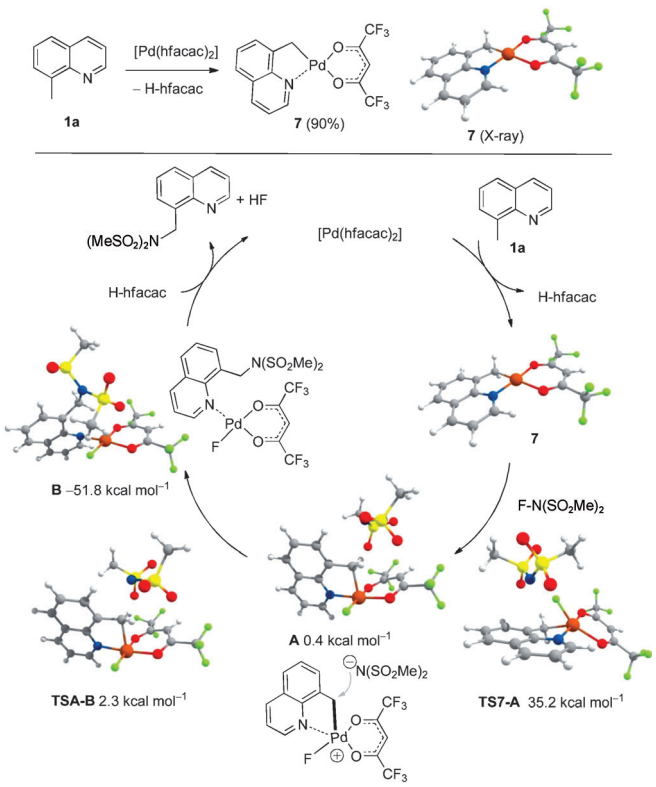


Figure 1. Proposed catalytic cycle incorporating calculated oxidation to Pd^{IV} and C–N bond-formation steps for the $Pd(hfacac)_2$-catalyzed C–H amidation of 2-methylquinoline (**1a**) using model $FN(SO_2Me)_2$ (ωB97X-D/6-31G*-LANL2DZ level in dioxane solution using PCM (polarizable continuum model)). Atom colors: S yellow, O red, N blue, Pd orange, C gray, F green.

activation energy for this step was calculated to be less than 2 kcal mol^{-1}.[25]

The nature of NFSI as an electrophilic oxidant[18] is further supported by a competition experiment, in which a 1:1 mixture of **7** and its acetylacetonate (acac) derivative were submitted to oxidation conditions. Exclusive oxidation of the more electron-rich acac complex was evident in the NMR spectrum, and again, this observation was supported by calculations.[11]

After C–N bond installment, the resulting Pd^{II} intermediate **B** must then be cleaved by free H-hfacac to release the amidated product **2** and HF, thereby regenerating the original catalyst. This step explains the observed counterion influence on the overall catalytic cycle (Table 1).[26] The importance of hexafluoroacetylacetonate for the turnover is further documented by the fact that isolated **7** is a much less active catalyst for the amidation of **1a** (50% conversion after 24 h), while **7** in combination with 1 equiv of H-hfacac led to 92% yield of **2b**, an outcome identical to the result from Table 1, entry 6. It is important to note that a priori NFSI does not represent an amidating reagent, but rather a fluorinating agent for Pd^{II}.[18a] As the bissulfonimide anion represents the only nucleophile in the presence of the reactive cationic Pd^{IV} catalyst state **A**, formation of the alkyl–nitrogen bond through nucleophilic substitution is the only feasible reaction. It follows the pathway that was originally proposed for C–N bond formation in our diamination of alkenes.[5a,b,27,28]

In summary, we have identified NFSI as the decisive reagent for the development of a new palladium-catalyzed oxidative amidation of C(sp^3)–H bonds. Theoretical studies have further clarified the role of NFSI as the oxidant in these processes and demonstrated the low energy barrier for reductive C–N bond formation from a high-oxidation-state palladium catalyst.

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