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Intermolecular Amidation of Unactivated sp^2 and sp^3 C−H Bonds via Palladium-Catalyzed Cascade C−H Activation/Nitrene Insertion

Hung-Yat Thu, Wing-Yiu Yu,*,† and Chi-Ming Che*

Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong

Received April 25, 2006; E-mail: cmche@hku.hk; bcwyyu@polyu.edu.hk

Transition metal-catalyzed C−N bond formation is of immense interest due to the prevalence of amino groups in pharmaceuticals and bioactive natural products.[1] Notable achievements in catalytic C−H bond amidation have been achieved by using Ru and Rh catalysts with hypervalent iodine reagents and sulfonylamides.[1e,2,3] According to the reports by Che,[2] Dubois,[3] and others,[1c,e] these catalytic systems involve reactive metal−imido/nitrene species, which undergo insertion to C−H bonds. The reactivity for nitrene C−H bond insertion follows the order of 3° > 2° ≫ 1° bond, paralleling the order of increasing C−H bond dissociation energies.[2d] However, catalytic systems that can effect amidation of unactivated aromatic and aliphatic 1° C−H bonds are sparse in the literature.[2,3a,4] Recently, chelation directed/assisted transition-metal-catalyzed C−H functionalization is receiving growing attention.[5−7] We are attracted to a seminal work by Sanford and co-workers,[6] who showed that oxime and pyridine groups can direct highly regio- and chemoselective Pd(II)-catalyzed β-acetoxylation of sp^2 and sp^3 C−H bonds with $PhI(OAc)_2$ as a stoichiometric oxidant. We envisioned that cascade C−H bond activation via $Pd(OAc)_2$-mediated cyclometalation followed by nitrene insertion reactions could be a plausible approach for selective amidation of 1° or 2° C−H bonds. Prior to this study, we observed that Pd(II) complexes, such as palladium carboxylates and [Pd(TTP)] [H_2TTP = tetrakis(*p*-tolyl)porphyrin], can catalyze intramolecular nitrene C−H insertion,[2,3] which may occur via reactive Pd(II)−nitrene species. During the course of this study, Buchwald and co-workers described a related Pd-catalyzed cyclization of 2-acetaminobiphenyl to *N*-acetyl carbazole.[1b]

Our investigation began by examining the intermolecular amidation reaction of 2-phenylpyridine (Scheme 1). A series of catalysts, oxidants, and nitrene sources were screened (see Supporting Information). Thus, under the optimized conditions [$Pd(OAc)_2$ (5 mol %), trifluoroacetamide (**A2**, 1.2 equiv), $K_2S_2O_8$ (5 equiv), MgO (2 equiv), DCE, 80 °C, 7 h], the *ortho*-amidated product, *N*-(2-pyridylphenyl)-2,2,2-trifluoroacetamide, was obtained in 92% isolated yield. The molecular structure of *N*-(5-methyl-2-pyridylphenyl)-2,2,2-trifluoroacetamide has been established by X-ray crystallography (Supporting Information). It is noteworthy that this protocol was conducted *without the need for air*-/moisture-proof conditions.

Apart from 2-arylpyridines, *O*-methyl oximes were examined for the Pd-catalyzed amidation reaction, and the results are listed in Table 1. *O*-Methyl oximes derived from benzaldehyde, acetophenone, and *para*-substituted benzaldehydes were effectively converted to their corresponding anilides by regioselective *ortho*-C−H amidation (entries 1−5). Notably, the C−I bond is well tolerated in our Pd-catalyzed protocol; chemo- and regioselective *ortho*-amidation of 4-iodoacetophenone *O*-methyl oxime (**1c**) was achieved in 87% yield (entry 3). When oxime derived from 3-bromobenzaldehyde (**1g**) was employed as substrate, the 2,4-regioisomer **1g**−**A1** was obtained exclusively in 92% yield (entry 7). The analogous catalytic *ortho*-amidation reactions of sterically hindered oximes were found to be sluggish. For example, when 3,5-dimethoxybenzaldehyde *O*-methyl oxime was employed as substrate, <10% conversion was registered based on ^{1}H NMR analysis of the crude mixture.

Scheme 1. Pd(II)-Catalyzed *ortho*-Amidation of 2-Arylpyridine

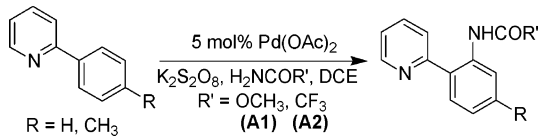
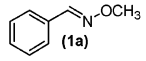
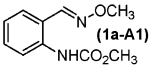
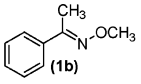
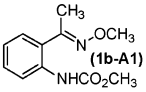
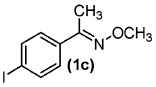
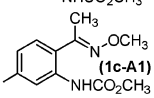
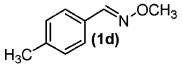
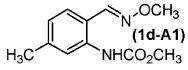
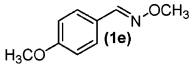
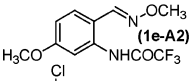
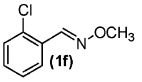
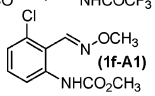
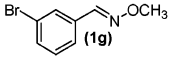
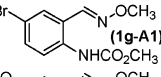
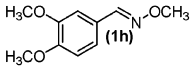
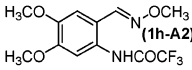
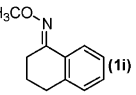
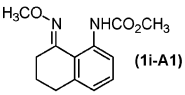
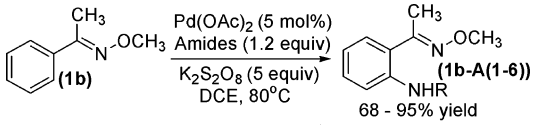


Table 1. Pd-Catalyzed *ortho*-Amidation of Aromatic Oximes[a]

entry	substrate	amide	product	conversion	yield[b]
1	 (1a)	$H_2NCO_2CH_3$ (A1)	 (1a-A1)	100%	92%
2	 (1b)	A1	 (1b-A1)	100%	93%
3	 (1c)	A1	 (1c-A1)	100%	87%
4	 (1d)	A1	 (1d-A1)	100%	95%
5	 (1e)	H_2NCOCF_3 (A2)	 (1e-A2)	100%	96%
6	 (1f)	A1	 (1f-A1)	100%	88%
7	 (1g)	A1	 (1g-A1)	87%	92%
8	 (1h)	A2	 (1h-A2)	66%	94%
9	 (1i)	A1	 (1i-A1)	88%	94%

[a] Conditions: 1 equiv of substrate, 1.2 equiv of A1/A2, 5 mol % of $Pd(OAc)_2$, 5 equiv of $K_2S_2O_8$ in DCE, 80 °C, 14−20 h. [b] Isolated yield.

Scheme 2. Effect of Amides on Amidation of **1b**



R = CO_2CH_3 **(A1)**, $COCF_3$ **(A2)**, $CO_2{}^tBu$ **(A3)**, SO_2CH_3 **(A4)**, $SO_2(p\text{-Cl-}C_6H_4)$ **(A5)**, $COCHC{=}CHC_6H_4$ **(A6)**

As shown in Scheme 2, 1° amides, including carbamates, acetamides, and sulfonamides, are effective nucleophiles for the Pd-catalyzed *ortho*-amidation of **1b**. Interestingly, amides bearing a C═C bond, such as cinnamide (**A6**), can be employed for the

† Current address: Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hunghom, Kowloon, Hong Kong.

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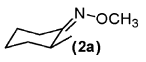
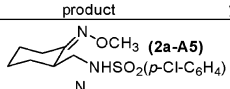
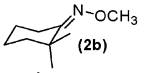
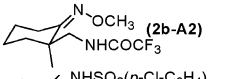
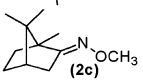
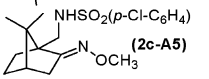
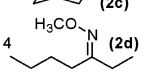
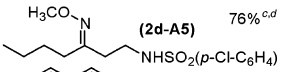
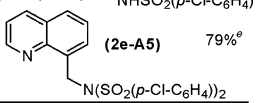
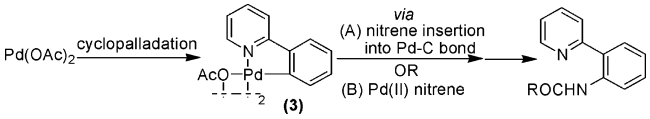
Table 2. Pd-Catalyzed *ortho*-Amidation of Aliphatic Oximes[a]

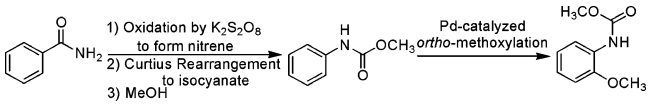
entry	substrate	amide	product	yield[b]
1	 (2a)	$H_2NSO_2(p\text{-Cl-}C_6H_4)$ (A5)	 (2a-A5)	88%
2	 (2b)	H_2NCOCF_3 (A2)	 (2b-A2)	89%
3	 (2c)	A5	 (2c-A5)	93%
4	 (2d)	A5	 (2d-A5)	76%[c,d]
5	 (2e)	A5	 (2e-A5)	79%[e]

[a] Conditions: 1 equiv of substrate, 1.2 equiv of A2/A5, 5 mol % of $Pd(OAc)_2$, 5 equiv of $K_2S_2O_8$ in DCE, 80 °C, 14−20 h. [b] Isolated yield. [c] Obtained as an *E*/*Z* mixture. [d] Yield based on 77% conversion. [e] See ref 8.

Scheme 3. Mechanistic Proposal for the Amidation Reaction



Scheme 4. Conversion of Benzamide to Methyl *N*-(2-Methoxyphenyl)carbamate



amidation of **1b**, and the *ortho*-amidated product **1b**−**A6** was formed in 68% yield. However, benzamide, 2° amides (e.g., pyrrolidinone, succinimide, *N*-methylformamide) and 1°/2° amines are found to be ineffective nucleophiles for the *ortho*-amidation of **1b**, and the substrate was recovered quantitatively.

Importantly, catalytic amidation of unactivated sp^3 C−H bonds has also been achieved (Table 2). Employing the following protocol: [$Pd(OAc)_2$ (5 mol %), sulfonamide **A5** (1.2 equiv), $K_2S_2O_8$ (5 equiv), DCE, 80 °C], aliphatic *O*-methyl oximes (**2a**−**d**) would undergo regioselective β-amidation of a 1° sp^3 C−H bond to give the corresponding monoamidated product in 76−88% yield (entries 1−4). Amidation at the 2° sp^3 C−H bond was not observed. No diamidation product was obtained even employing excess nucleophile (5 equiv). The observed preference for activation of 1° C−H bond versus 2° C−H bonds is probably due to steric effect.

As depicted in Scheme 3, we propose that the Pd-catalyzed amidation reaction is initiated by chelation-directed cyclopalladation to form **3** (in the case of 2-phenylpyridine),[6−7] followed by nitrene insertion to the Pd−C bond.

To probe the intermediacy of nitrene species, we treated benzamide with 2-phenylpyridine employing the "$Pd(OAc)_2$ + $K_2S_2O_8$" protocol in the presence of methanol (3 equiv), and methyl *N*-(2-methoxyphenyl)carbamate was obtained in 55% yield without formation of any amidation product (Scheme 4).[9] The carbamate formation is best accounted for by a nitrene intermediate which underwent Curtius rearrangement to isocyanate. Nucleophilic attack of the isocyanate by methanol gave methyl *N*-phenylcarbamate, and subsequent C−H activation/*ortho*-methoxylation gave methyl *N*-(2-methoxyphenyl)carbamate as the product.

At this juncture, the nature of the nitrene intermediate remains uncertain: metal-free (Scheme 3, path A) versus metal-bound (Scheme 3, path B) nitrene. Reactive Pd(II)−nitrene species (alternative formulation of a Pd(IV)−imido species cannot be excluded) is evidenced by the following: (1) analogy of the reactivity of Pd(TTP) and Ru(Por) (Por = porphyrinato dianion) in the catalytic intramolecular nitrene C−H bond insertion reaction; (2) some Pd(IV) complexes have been characterized from reactions involving strong oxidants;[6b,10] and (3) examples of Pd imido[11a] and Pd nitrene[11b,c] complexes are known in the literature.

We also noted that treatment of **3** with excess of PhI=NSO_2-(p-Cl−C_6H_4) or stoichiometric PhI=NSO_2(p-Cl−C_6H_4) and 1 mol % of [Ru(TTP)(CO)] gave a yellow complex. This complex has the "**3** + [NSO_2(p-Cl−C_6H_4)]" formulation based on ESI-MS analysis.[9] Treating this yellow complex with HCl afforded the corresponding monoamidated product of 2-phenylpyridine in 85% yield (based on the amount of **3** employed).

In conclusion, a catalytic alkane amidation protocol based on cascade chelation-directed cyclopalladation/amidation reactions was developed. This protocol enables intermolecular amidation of unactivated sp^2 and sp^3 C−H bonds with remarkable regio- and chemoselectivities. Further investigation on the scope and the mechanism of the reaction is in progress.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Using the "$Pd(OAc)_2$ + $K_2S_2O_8$" protocol, treatment of 8-methylquinoline (**2e**) led to chlorination (76% yield) of the α-methyl group. Nevertheless, reacting **2e** with PhI=NSO_2(p-Cl−C_6H_4) (3 equiv), [Ru(TTP)(CO)] (1 mol %), and $Pd(OAc)_2$ (5 mol %) in CH_2Cl_2 afforded the product amide **2e**−**A5** in 79% yield without any chlorination products.

(9) See Supporting Information for experimental details and ESI-MS spectrum of "3 + [NSO_2Ar]" complex.

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