ACS Catalysis

Research Article

pubs.acs.org/acscatalysis

Aerobic Oxidation of Pd^{II} to Pd^{IV} by Active Radical Reactants: Direct C−H Nitration and Acylation of Arenes via Oxygenation Process with Molecular Oxygen

Yu-Feng Liang,[†] Xinyao Li,[†] Xiaoyang Wang,[†] Yuepeng Yan,[†] Peng Feng,[†] and Ning Jiao*[,†,‡]

[†]State Key Laboratory of Natural and Biomimetic Drugs, Peking University, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd. 38, Beijing 100191, China

[‡]State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200062, China

Supporting Information

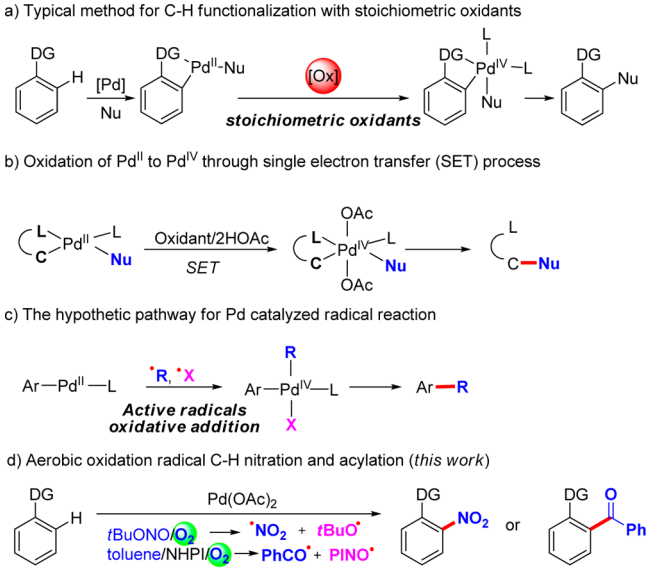
ABSTRACT: A Pd-catalyzed aerobic oxidative C−H nitration and acylation of arenes with simple and readily available *tert*-butyl nitrite (TBN) and toluene as the radical precursors has been developed. Molecular oxygen is employed as the terminal oxidant and oxygen source to initiate the active radical reactants. Many different directing groups such as pyridine, pyrimidine, pyrazole, pyridol, pyridylketone, oxime, and azo groups can be employed in these novel transformations. The Pd^{II}/Pd^{IV} catalytic cycle through a radical process is the most likely pathway for these oxidative C−H nitration and acylation reactions.

KEYWORDS: *C−H functionalization, oxygen, nitration, acylation, palladium, radicals, regioselectivity*

INTRODUCTION

Palladium-catalyzed C−H functionalizations of organic substrates have been developed over the past decades as powerful and versatile tools in synthetic organic chemistry.[1,2] Among them, the catalytic cycle between Pd^{II} and Pd^{IV} is one of the major pathways, in which a number of oxidants such as $K_2S_2O_8$, TBHP, BQ, DDQ, PIDA, among others, have been widely employed (Scheme 1a). With respect to green and sustainable chemistry, molecular oxygen is considered as an ideal oxidant and offers attractive academic and industrial prospects.[3,4] Therefore, the development of Pd-catalyzed oxidative C−H functionalization with molecular oxygen as oxidant is highly desirable. Although many protocols have been achieved on this topic under Pd/O_2 conditions, they were almost limited to oxidative Heck-type reactions with Pd^0/Pd^{II} catalytic cycle.[4,5] It is well-known that O_2 could oxidize Pd^0 to Pd^{II} based on the standard electrode potential, but can hardly oxidize Pd^{II} to high-valent Pd species under ordinary conditions.[6] Therefore, only a few examples of palladium-catalyzed aerobic oxidation formation of the C−N,[7] C−C,[8] and C−O[9] bonds were reported through a reductive elimination process from high-valent Pd intermediates. Despite the significances of these reactions, the mechanism for the direct oxidation of Pd^{II} to high-valent Pd species is still unclear yet. More recently, Stahl[7a] and Sanford[9a] developed a significant palladium-catalyzed aerobic oxidative C−H functionalization, in which the Pd^{II} intermediates were probably oxidized to Pd^{IV} through a single-electron-transfer (SET) process (Scheme 1b). Inspired by these reactions and our efforts on the aerobic oxidative C−H bond functionalization,[10] we hypothesized that the active radical partner generated *in situ* could oxidize Pd^{II} to Pd^{IV}, and the subsequent reductive elimination may enable the C−H

Scheme 1. Strategies for Palladium-Catalyzed C−H Functionalization



Received: December 31, 2014
Revised: February 8, 2015
Published: February 12, 2015

DOI: 10.1021/cs502126n
ACS Catal. 2015, 5, 1956−1963

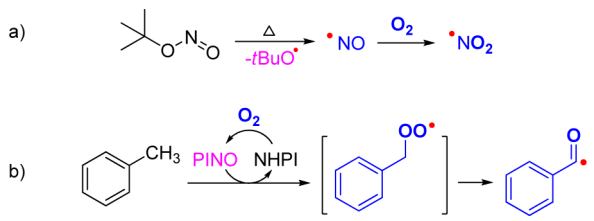
functionalization with this radical precursors, providing new strategy for aryl C−H functionalization (Scheme 1c).

Herein, we report an efficient $Pd(OAc)_2$-catalyzed aerobic oxidative C−H nitration and acylation of arenes via a radical pathway (Scheme 1d). The following characteristics exist in this chemistry: (1) A radical process is reasonably involved in this aerobic catalytic cycle between Pd^{II} and Pd^{IV} species; (2) Simple and commercial available TBN and toluene are employed, respectively, as the radical precursors in these novel aerobic oxidative C−H nitration and acylation reactions; (3) Many kinds of directing groups (e.g., pyridine, pyrimidine, pyrazole, pyridol, pyridylketone, oxime, and azo groups) can be used in this direct transformation with broad substrate scope under mild conditions; (4) Environmentally benign molecular oxygen is employed as both oxidant and reagent.

RESULTS AND DISCUSSION

According to this hypothesis, it is a prerequisite to find an aerobic oxidative pathway to generate active radicals and will be very attractive to start from simple starting materials via dioxygen activation,[3,4] which would enable the direct oxygenation process using molecular oxygen as the oxygen source. It is known that the commercial available TBN can decompose into the NO radical and *t*BuO radical by heating, and then the NO radical could be directly oxidized by O_2 to generate NO_2 radical (Scheme 2a).[11] On the other hand, on the basis of NHPI (*N*-hydroxyphthalimide)-catalyzed aerobic oxygenation reactions,[12] we envisioned that PINO (phthalimido-*N*-oxyl) radical could be smoothly generated with molecular oxygen, and the benzoyl radical can be produced from very simple toluene via SET processes (Scheme 2b). If the above proposed active N-radical and C-radical could be successfully generated in Pd^{II}-catalysis, the following relay of oxidation of Pd^{II}-intermediate to Pd^{IV} species and reductive elimination would occur to afford new C−N and C−C bonds. In these cases, Pd-catalyzed *ortho* nitration and acylation of arenes with dioxygen as the terminal oxidant could be realized.

Scheme 2. (a) Aerobic Oxidative Generation of *t*BuO Radical and NO_2 Radical; (b) Aerobic Oxidative Generation of PINO Radical and Benzoyl Radical

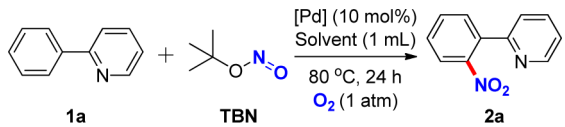


Aromatic nitro compounds are important synthetic intermediates for the generation of pharmaceuticals, dyes, explosives, and materials.[13] The classical electrophilic nitration of arenes[14,15] is widely used for the synthesis of nitroarenes. Evidently, these methods suffer from some disadvantages of poor regioselectivity and limited functional group tolerance under harsh conditions such as strong acidic systems. In order to prepare nitroarenes at the specific position, transition-metal-catalyzed coupling type nitration of aryl halides,[16] aryl boronic acids,[17] and other prefunctionalized arenes[18] have been developed. Alternatively, inspired by the development of directed C−H bond functionalization with a directing group, the synthesis of nitroarenes via direct C−H bond nitration has been an attractive topic.[19] Despite the significances on the specific nitration position of these methodologies, the employment of expensive nitrite salts such as $AgNO_2$ as the nitro source and the additional stoichiometric oxidants such as peroxides, hypervalent iodine oxidants and toxic metal salts, limited their application.

More recently, simple and readily available nitro source has been employed in the synthesis of nitroarenes.[20,21] Buchwald and co-workers developed an elegant protocol for the regioselective nitration of prefunctionalized aryl chlorides, triflates, and nonaflates with $NaNO_2$ as a simple nitro source.[20] Alternatively, Li et al. reported a significant Rh-catalyzed C−H nitration of arenes with $NaNO_2$ assisted by an expensive hypervalent iodine oxidant.[21a] Therefore, although many nitration approaches have been developed in the past decades,[16−21] it is still very attractive to develop better methodologies with (1) environmentally benign oxidant, such as molecular oxygen and (2) a broad scope of directing groups in the C−H bond nitration reaction.

On the basis of the above hypothesis, we initiated our investigation by exploring the nitration of 2-phenylpyridine **1a** with simple, readily available TBN[22] and O_2 as nitro source using $Pd(OAc)_2$ as catalyst. When the reaction was conducted in DCE at 80 °C, the *ortho*-nitration product **2a** was indeed isolated in 31% yield (entry 1, Table 1). Solvent screening showed that PhCl is a very suitable solvent for this transformation providing the product **2a** in 74% yield (entry 6). Whereas the reactions in other solvents such as CH_3CN, *t*Amyl−OH, CH_3NO_2 and toluene showed low efficiency (entries 2−5). The reaction catalyzed by $PdCl_2$ or $PdTFA_2$ gave lower yield than that catalyzed by $Pd(OAc)_2$ (entries 7−8). The reaction under air instead of pure molecular oxygen performed well but produced **2a** with a slightly lower yield (entry 9). However, the yield of **2a** declined dramatically when

Table 1. Optimization of the Reaction Conditions[a]



1a TBN 2a

entry	[Pd] (10 mol %)	solvent	yield (%)[b]
1	$Pd(OAc)_2$	DCE	31
2	$Pd(OAc)_2$	CH_3CN	26
3	$Pd(OAc)_2$	*t*-Amyl−OH	5
4	$Pd(OAc)_2$	CH_3NO_2	18
5	$Pd(OAc)_2$	toluene	49
6	**$Pd(OAc)_2$**	**PhCl**	**74**
7	$PdCl_2$	PhCl	40
8	$PdTFA_2$	PhCl	70
9[c]	$Pd(OAc)_2$	PhCl	53
10[d]	$Pd(OAc)_2$	PhCl	10
11[e]	$Pd(OAc)_2$	PhCl	74
12	-	PhCl	0
13[f]	$Pd(OAc)_2$	PhCl	0
14[g]	$Pd(OAc)_2$	PhCl	trace

[a]Reaction conditions: **1a** (0.3 mmol), catalyst (10 mol %), TBN (2.0 equiv), solvent (1 mL), stirred at 80 °C under O_2 (1 atm) for 24 h. [b]Isolated yields. [c]The reaction was carried out under air (1 atm). [d]The reaction was carried out at 60 °C. [e]The reaction was carried out in the dark. [f]$NaNO_3$ or $NaNO_2$ was used as nitro source instead of TBN. [g]NO_2 gas was used as nitro source instead of TBN.

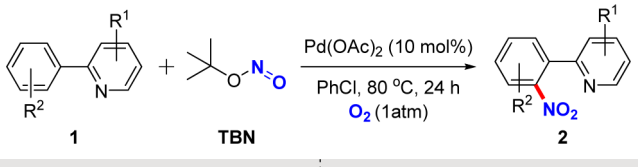
DOI: 10.1021/cs502126n
ACS Catal. 2015, 5, 1956−1963

the reaction temperature decreased to 60 °C (entry 10). The reaction proceeded well in the dark, which indicated that the nitration is not initiated by photoirradiation (entry 11). As a control, no product **2a** was detected in the absence of $Pd(OAc)_2$ catalyst (entry 12). When $NaNO_2$, $NaNO_3$, and NO_2 gas were used, respectively, as nitro source instead of TBN, the nitration product was not obviously obtained (entries 13−14).

As shown in Table 2, a range of 2-arylpyridines underwent this *ortho*-nitration very well with TBN and dioxygen. It was found that either an electron-donating group, such as alkyl, alkoxy, phenyl, or electron-withdrawing group, such as halogen, trifluoromethyl, ethoxycarbonyl, nitro, at the 4-position (**2b**−**2j**), 2-position (**2k**−**2m**), or 3-position (**2n**−**2p**) of the phenyl ring, was compatible in this procedure, leading to the corresponding nitration products in moderate to good yields. Consistent with previous Pd-catalyzed C−H functionalization studies,[2] the nitration of *meta*-substituted 2-arylpyridines occurred selectively at the less-hindered position of the aromatic ring (**2n**−**2p**).

It is noteworthy that pyrimidine and pyrazole rings were also effective directing groups in this transformation (**4a**−**4f**, Table 3). Moreover, phenyl(pyridin-2-yl)methanone was also tolerant to provide the nitration product **4g** in moderate yield.

Table 2. Substrate Scope of Nitration of 2-Arylpyridines with TBN and Dioxygen[a]

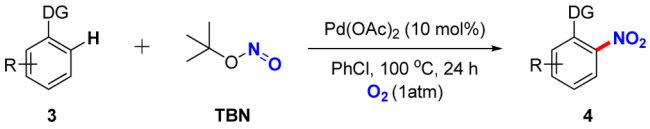


1 TBN 2

entry	product	yield
1	R = H	**2a** (74%)
2	R = CH_3	**2b** (78%)
3	R = Ph	**2c** (63%)
4[b]	R = OCH_3	**2d** (66%)
5[b]	R = OEt	**2e** (63%)
6[b]	R = Cl	**2f** (68%)
7[b]	R = F	**2g** (70%)
8[b]	R = CF_3	**2h** (70%)
9[b]	R = $COOCH_3$	**2i** (62%)
10[b]	R = NO_2	**2j** (60%)
11	R = CH_3	**2k** (66%)
12	R = OCH_3	**2l** (55%)
13[b]	R = Cl	**2m** (55%)
14	R = CH_3	**2n** (62%)
15	R = Cl	**2o** (76%)
16[b]	R = COOEt	**2p** (69%)
17	R = 3-CH_3	**2q** (79%)
18	R = 4-CH_3	**2r** (51%)
19	R = 5-CH_3	**2s** (73%)
20	R = 3,5-dimethyl	**2t** (74%)
21		**2u** (72%)
22		**2v** (50%)
23[b]		**2w** (73%)
24		**2x** (54%)

[a]Standard conditions: **1** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), TBN (2.0 equiv), PhCl (1 mL), at 80 °C under O_2 (1 atm) for 24 h. Isolated yields. [b]3.0 equiv of TBN was employed at 100 °C.

Table 3. Substrate Scope of Nitration with TBN and Dioxygen Directed by Other Pyridine Groups[a]



3 TBN 4

entry	product	yield
1	R = H	**4a** (79%)
2	R = 2-CH_3	**4b** (63%)
3	R = 3-OCH_3	**4c** (58%)
4	R = 3-CH_3	**4d** (55%)
5		**4e** (78%)
6		**4f** (61%)
7		**4g** (69%)
8[a]		**4h** (56%)
9	R^1 = H, R^2 = H	**4i** (75%)
10	R^1 = H, R^2 = 4-CH_3	**4j** (57%)
11	R^1 = H, R^2 = 4-OCH_3	**4k** (68%)
12	R^1 = H, R^2 = 4-I	**4l** (56%)
13	R^1 = H, R^2 = 3-CH_3	**4m** (57%)
14	R^1 = H, R^2 = 2-CH_3	**4n** (69%)
15	R^1 = 5-CH_3, R^2 = H	**4o** (73%)
16	R^1 = 3-CH_3, R^2 = H	**4p** (59%)
17		**4q** (69%)

[a]Standard conditions: **3** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), TBN (3.0 equiv), PhCl (1 mL), at 100 °C under O_2 (1 atm) for 24 h. Isolated yields. [b]1.0 equiv of TBN was employed at 80 °C.

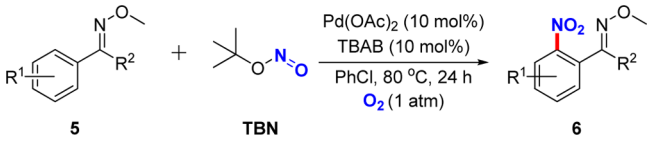
Significantly, the sp^3 C−H bond of 8-methylquinoline reacted with 1.0 equiv of TBN and afforded benzyl nitro compound **4h** in moderate yield. Interestingly, the reaction conditions were equally applicable to 2-aryloxypyridine substrates (**4i**−**4q**).

To investigate the scope of other directing groups in this C−H nitration reaction, we next examined several different arenes containing oxime groups (Table 4). When acetophenone *O*-methyl oxime **5a** was tested under the standard nitration conditions, *ortho*-nitrated product **6a** was isolated in 44% yield. The yield could be improved to 65% when 10 mol % of tetrabutyl ammonium bromide (TBAB) was added as an additive into the reaction.[23] Acetophenoneoximes bearing both electron-donating (Me, OMe, *t*Bu) and electron-withdrawing (Br, F) substitutents were successfully converted into the corresponding *ortho*-nitrated products (**6b**−**6g**). An *ortho*-methyl-substituted aryloxime was also tolerant in this transformation to afford the nitration product (**6h**). Additionally, when alkylphenone, benzaldehyde, and diarylketone *O*-methyl oximes were examined, the transformation still proceeded well to afford the desired products (**6i**−**6p**).

The scope of the reaction with regard to azoarenes was then explored (Table 5).[24] The azoarenes with electron-donating groups proceeded faster than those with electron-withdrawing groups (**8a**−**8j**). When the reaction was performed with 3.0 equiv of TBN at 100 °C, the electron-deficient azoarenes can produce the desired products in moderate to excellent yields (**8d**−**8f**, **8h**, **8i**). Furthermore, we also examined the electronic effect of substitutents on the regioselectivity of the *ortho*-

DOI: 10.1021/cs502126n
ACS Catal. 2015, 5, 1956−1963

Table 4. C−H Bond Nitration with TBN and Dioxygen Directed by a Oxime Group[a]



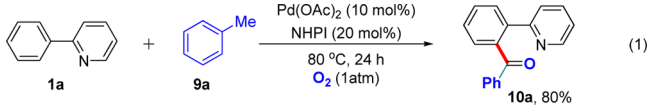
5 TBN 6

entry	product	yield	entry	product	yield
1	R = H	**6a** (65%)	10		**6j** (55%)
2	R = CH_3	**6b** (58%)	11		**6k** (40%)
3	R = OCH_3	**6c** (44%)			
4	R = *t*Bu	**6d** (61%)			
5[b]	R = Br	**6e** (48%)			
6[b]	R = F	**6f** (58%)	12	R = H	**6l** (71%)
7	R = Br	**6g** (70%)	13	R = CH_3	**6m** (53%)
8[b]		**6h** (47%)	14	R = OCH_3	**6n** (50%)
			15[b]	R = F	**6o** (81%)
9		**6i** (64%)	16		**6p** (63%)

[a]Standard conditions: **5** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), TBAB (10 mol %), TBN (1.5 equiv), PhCl (1 mL) at 80 °C under O_2 (1 atm) for 24 h. Isolated yields. [b]The reaction was carried out with 3.0 equiv of TBN at 100 °C.

nitration of unsymmetrical azoarenes. The results indicated that the *ortho*-nitration reactions occurred mainly on the electron-rich aryl rings (**8k**, **8l**).

Hence, our hypothesis was proved reasonable by these positive results. Encouraged by this successful radical nitration reaction, then we carried out the aerobic oxidative radical acylation project (Scheme 1d and Scheme 2b). As expected, under 1 atm of O_2, the reaction of **1a** with toluene (**9a**) as both the acylation reagent and solvent using 10 mol % $Pd(OAc)_2$ and 20 mol % NHPI as cocatalyst at 80 °C gave the acylation product aryl ketone (**10a**) in 80% yield with trace amount of dibenzoylated product formation (eq 1).[25] Aryl ketones are

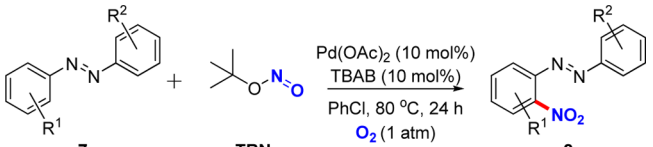


1a 9a **10a**, 80% (1)

important structural units and synthetic precursors in natural products, pharmaceutical compounds, and functional materials.[26] The present acylation reaction provides a simple route for *ortho* acylation of arenes with molecular oxygen as the terminal oxidant and oxygen source to afford aryl ketones. Therefore, the aerobic oxidative nitration and acylation of arenes via dioxygen activation are successfully achieved through the proposed active radical oxidation strategy.

Followed these results, the acylation reaction by combination of toluene and molecular oxygen (eq 1) was also expanded to

Table 5. C−H Bond Nitration with TBN and Dioxygen Directed by a Azo Group[a]



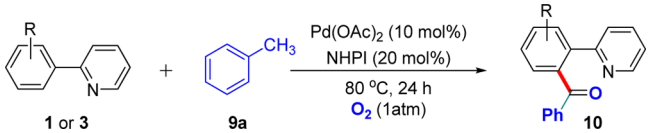
7 TBN 8

entry	product	yield	entry	product	yield
1	R = H	**8a** (72%)	10		**8j** (80%)
2	R = CH_3	**8b** (60%)	11		**8k** (64%)
3	R = OCH_3	**8c** (42%)			
4[b]	R = Cl	**8d** (72%)			
5[b]	R = CF_3	**8e** (89%)			
6[b]	R = OCF_3	**8f** (82%)			
7	R = CH_3	**8g** (72%)	12		**8l + 8l'**, (75%) (1.5:1)
8[b]	R = F	**8h** (41%)			
9[b]		**8i** (45%)			

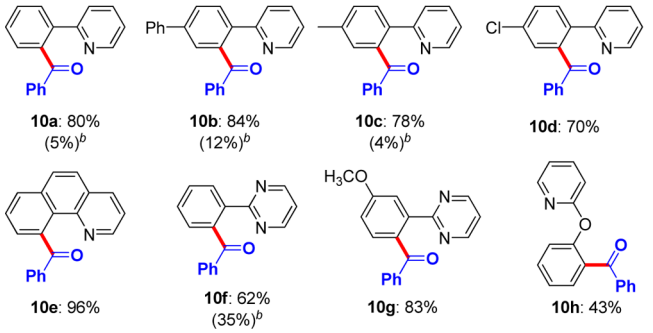
[a]Standard conditions: **7** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), TBAB (10 mol %), TBN (1.5 equiv), PhCl (1 mL) at 80 °C under O_2 (1 atm) for 24 h. Isolated yields. [b]The reaction was carried out with 3.0 equiv of TBN at 100 °C.

2-arylpyridines and other arenes with different directing groups (Tables 6−8). For the 2-arylpyridines substrates (Table 6), the benzene rings with electron-donating and electron-withdrawing groups proceeded smoothly to give **10a**−**10d** in good to excellent yields. The reaction of benzo[*h*]quinoline and 2-arylpyrimidine were also examined and the excellent yields of

Table 6. Acylation Reaction with Pyridine Groups[a]



1 or 3 9a **10**



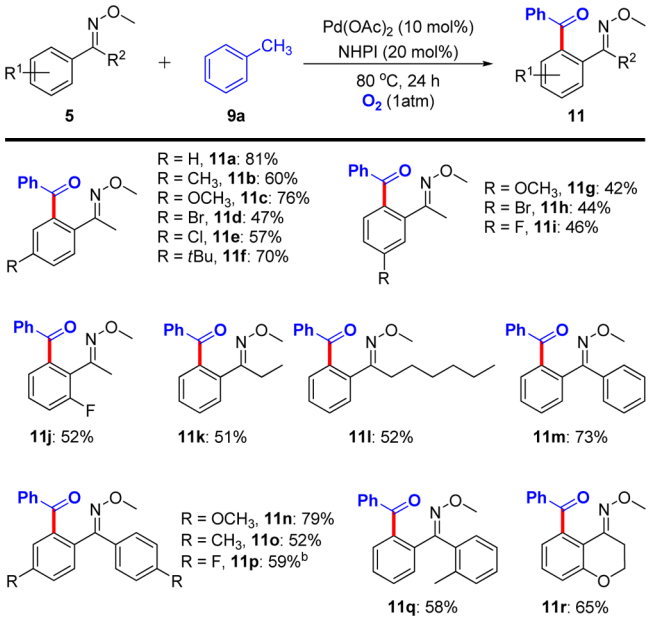
[a]Standard conditions: **1** or **3** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), NHPI (20 mol %), toluene **9a** (1 mL) at 80 °C under O_2 (1 atm) for 24 h. Isolated yields. [b]In some cases, diacylation occurred. The number in the parentheses is the yield of diacylation product.

DOI: 10.1021/cs502126n
ACS Catal. 2015, 5, 1956−1963

products **10e**−**10g** were obtained. 2-Phenoxypyridine could be benzoylated to generate **10h** in moderate yield (Table 6).

Subsequently, the acylation reaction of *O*-methyl oximes was investigated (Table 7). Under the optimized acylation reaction

Table 7. Acylation Reaction of *O*-methyl Oximes with Toluene[a]



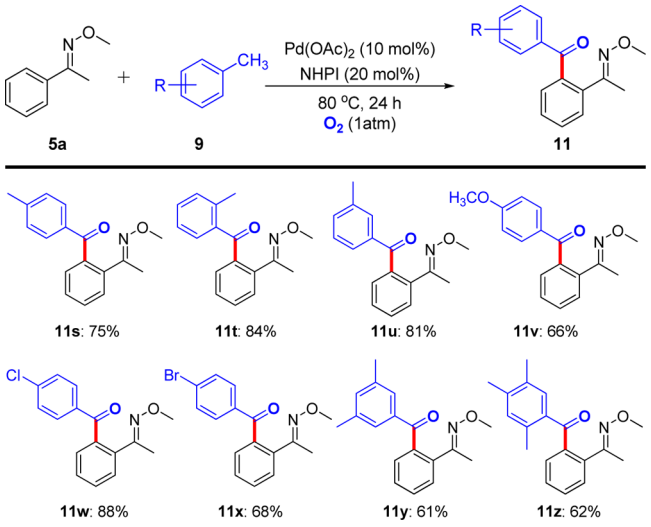
[a]Standard conditions: **5** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), NHPI (20 mol %), toluene **9a** (1 mL) at 80 °C under O_2 (1 atm) for 24 h. Isolated yields. [b]At 100 °C.

conditions (see the Supporting Information), various substitutents at the *para*-position of the aryl ring were tolerated well to provide the products **11a**−**11f** in moderate to good yields. The electron-rich substrates generally provided superior efficiencies to electron-deficient substrates. The acylation of *meta*-substituted acetophenone *O*-methyl oximes were favored at the less hindered *ortho*-position, to produce the corresponding products **11g**−**11i**. An *ortho*-fluorine-substituted acetophenone *O*-methyl oxime gave the product in moderate yield (**11j**). Moreover, *O*-methyl oximes which derived from alkylphenone and diarylketone were also converted to the corresponding products (**11k**−**11q**). 4-Chromanone *O*-methyl oxime, with a bicyclic scaffold, reacted smoothly (**11r**). It is noted that the reaction of **5a** in 20 mmol scale afforded **11a** in 78% yield, which demonstrates the potential application in synthesis.

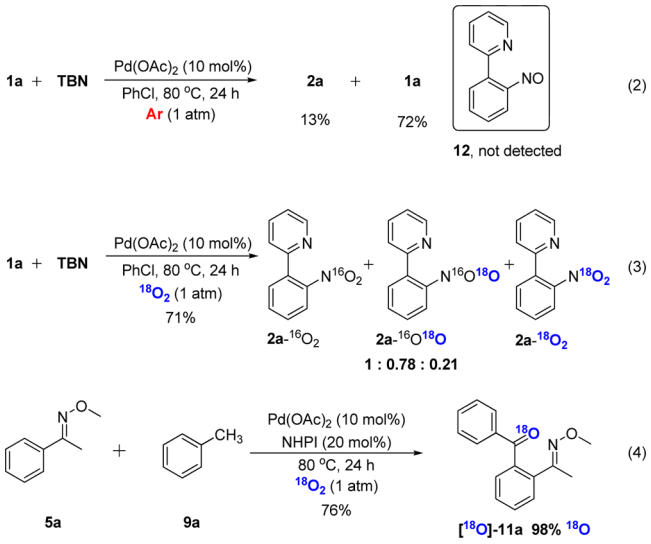
We next tested the scope of the toluene derivatives as the simple acyl source (Table 8). *p*-Xylene, *o*-xylene, and *m*-xylene reacted well to generate the products **11s**−**11u** in good yields. The reaction only occurred on one methyl group, with the other methyl group remaining intact. Electron-donating 4-methoxy-toluene gave slightly lower yield (**11v**). Furthermore, halo groups (Cl, Br) on aromatic rings were compatible (**11w**−**11x**), offering versatile synthetic functionality for further transformation. Multiple substituted toluenes smoothly executed this reaction with moderate yields (**11y**, **11z**).

To obtain mechanistic insights into the present direct C−H nitration reaction, a series of experiments for mechanistic study were carried out. The reaction of **1a** under Ar atmosphere only produced **2a** in 13% yield with 72% of **1a** recovered (eq 2). The

Table 8. Scope of Toluene Derivatives as the Source of Acyl[a]

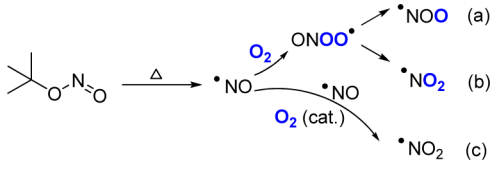


[a]Standard conditions: **5a** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), NHPI (20 mol %), toluene derivatives **9** (1 mL) at 80 °C under O_2 (1 atm) for 24 h. Isolated yields.



2-(2-nitrosophenyl)pyridine **12** was not detected by GC-MS and in situ NMR in this reaction (eq 2), which illustrated that **12** is not the intermediate of this nitration. When the reaction was performed under $^{18}O_2$ atmosphere, three products were obtained (**2a**-$^{16}O_2$, **2a**-$^{18}O^{16}O$, **2a**-$^{18}O_2$, with the ratio of 1:0.78:0.21) (eq 3), which demonstrated that the NO_2 radical might be generated from NO radical through different processes under O_2 (Scheme 3). It is known that NO radical could be directly oxidized by O_2 to afford NO_2 radical (Scheme

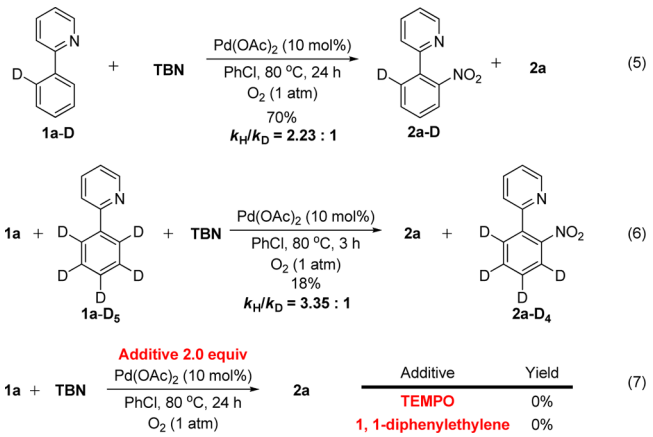
Scheme 3. (a), (b) Generation of NO_2 Radical through the Direct Oxidation of NO Radical with O_2; (c) Generation of NO_2 Radical through the Disproportionation of NO Radical



DOI: 10.1021/cs502126n
ACS Catal. 2015, 5, 1956−1963

3a,b) just as our design for this reaction (Scheme 2a).[11] Alternatively, the disproportionation reaction of NO radical catalyzed by O_2 occurs to give NO_2 radical (Scheme 3c).[22i,27] Clearly, the oxygen atom of the generated carbonyl group originates from molecular oxygen in the aerobic acylation reaction proved by the ^{18}O-labeling experiment (eq 4).

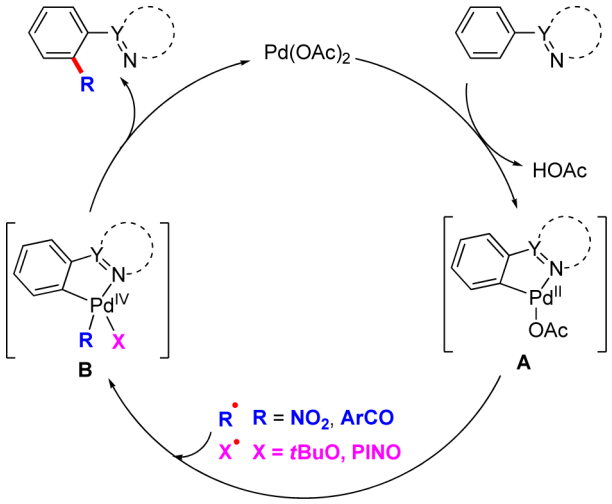
Furthermore, a kinetic isotopic effect (KIE) study was also conducted. The intramolecular k_H/k_D of **1a** was determined to be 2.23 (eq 5), and the intermolecular k_H/k_D was 3.35 (eq 6),



which suggested that the C−H activation should be irreversible. Moreover, the reactions were completely inhibited in the presence of a radical scavenger such as TEMPO or 1,1-diphenylethylene (eq 7), which indicated that a radical process might be involved in this transformation.

On the basis of the above studies and reported literature,[7a,9a] a catalytic cycle of this Pd-catalyzed C−H nitration or acylation is illustrated in Scheme 4. The transformation occurs probably

Scheme 4. Proposed Mechanism



involving (1) the formation of palladacycle intermediate **A** by directing group assisted *ortho*-selective cyclometalation on the benzene ring of the substrate with $Pd(OAc)_2$; (2) oxidative addition of active radicals (NO_2 and *t*-BuO radiacls for nitration, ArCO and PINO radicals for acylation) to **A** provides Pd^{IV} intermediate[28,29] **B**; (3) C−N or C−C bond formation through reductive elimination affords the corresponding products along with the regeneration of the Pd^{II} species.

CONCLUSION

In conclusion, we have developed Pd-catalyzed aerobic oxidative direct regioselective C−H nitration and acylation reactions with simple, inexpensive, and readily available *tert*-butyl nitrite (TBN) and toluene as the radical precursors. Molecular oxygen is employed as the terminal oxidant and oxygen source to initiate the active radical reactants. Many different directing groups such as pyridine, pyrimidine, pyrazole, pyridol, pyridylketone, oxime, and azo can be employed in these novel C−H nitration and acylation transformations. The reaction proceeds under mild conditions and shows a broad substrate scope. These reactions may proceed via a Pd-mediated radical mechanism through the Pd^{II}/Pd^{IV} catalytic cycle. Further studies to elucidate the detailed reaction mechanism are ongoing in our group and we hope to disclose it in the near future.

ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs502126n.

Experimental procedures, analytical data for products, NMR spectra of products (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: jiaoning@pku.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from National Basic Research Program of China (973 Program) (grant no. 2015CB856600) and National Natural Science Foundation of China (nos. 21325206, 21172006), and National Young Top-notch Talent Support Program are greatly appreciated. We thank Wujie Zou for reproducing the results of **4i** and **6k**.

REFERENCES

(1) (a) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley and Sons: Hoboken, NJ, 2002. (b) van Leeuwen, P. W. N. M. *Homogeneous Catalysis: Understanding the Art*; Kluwer Academic Publishers: Dordrecht, 2004.

(2) For recent reviews on C-H functionalization, see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (c) Daugulis, O.; Do, H.-Q.; Shabashow, D. *Acc. Chem. Res.* **2009**, *42*, 1074−1086. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624−655. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (f) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890−931. (g) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212−11222. (h) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866−4877. (i) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761. (j) Lu, H.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899−1909. (k) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215−1292. (l) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315−1345. (m) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083. (n) McMurry, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885−1898. (o) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678. (p) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588−5598. (q) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788−802. (r) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.*

DOI: 10.1021/cs502126n
ACS Catal. 2015, 5, 1956−1963

2012, *51*, 8960−9009. (s) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879−5918. (t) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936−946. (u) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369−375. (v) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281−295. (w) Zheng, Q.-Z.; Jiao, N. *Tetrahedron Lett.* **2014**, *55*, 1121−1126. (x) Wang, T.; Jiao, N. *Acc. Chem. Res.* **2014**, *47*, 1137−1145. (y) Topczewski, J. J.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70−76.

(3) For recent reviews of reactions using molecular oxygen as an oxidant, see: (a) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362−367. (b) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329−2364. (c) Gligorich, M. K.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612−6615. (d) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221−229. (e) Muzart, J. *Chem.—Asian J.* **2006**, *1*, 508−515. (f) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318−5365. (g) Piera, J.; Bäckvall, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506−3523. (h) Stahl, S. S. *Science* **2005**, *309*, 1824−1826. (i) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227−8241. (j) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062−11087. (k) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381−3430. (l) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736−1748. (m) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234−6458. (n) Ryland, B. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 8824−8838.

(4) For reviews on Pd-catalyzed aerobic oxidative, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (b) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854−3867. (c) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851−863.

(5) For recent examples, see: (a) Yan, Z.-L.; Chen, W.-L.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Wang, Y.-Q. *Adv. Synth. Catal.* **2014**, *356*, 1085−1092. (b) Jiang, H.; Yang, W.; Chen, H.; Li, J.; Wu, W. *Chem. Commun.* **2014**, *50*, 7202−7204. (c) Ji, X.; Huang, H.; Wu, W.; Jiang, H. *J. Am. Chem. Soc.* **2013**, *135*, 5286−5289. (d) Ling, F.; Li, Z.; Zheng, C.; Liu, X.; Ma, C. *J. Am. Chem. Soc.* **2014**, *136*, 10914−10917. (e) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209−213. (f) Diao, T.; Pun, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 8205−8212. (g) Liu, B.; Jiang, H.-Z.; Shi, B.-F. *J. Org. Chem.* **2014**, *79*, 1521−1526. (h) Wu, G.; Su, W. *Org. Lett.* **2013**, *15*, 5278−5281. (i) Ye, X.; Shi, X. *Org. Lett.* **2014**, *16*, 4448−4451. (j) Cong, X.; You, J.; Gao, G.; Lan, J. *Chem. Commun.* **2013**, *49*, 662−664.

(6) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods: Fundamentals and Applications*, 2nd ed.; John Wiley and Sons: New York, 2001.

(7) (a) Weinstein, A. B.; Stahl, S. S. *Catal. Sci. Technol.* **2014**, *4*, 4301−4307. (b) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560−14561. (c) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603−7610.

(8) Khusnutdinova, J. R.; Rath, N. P.; Mirica, L. M. *J. Am. Chem. Soc.* **2012**, *134*, 2414−2422.

(9) (a) Stowers, K. J.; Kubota, A.; Sanford, M. S. *Chem. Sci.* **2012**, *3*, 3192−3195. (b) Zhang, Y. H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654−14655. (c) Zhang, J.; Khaskin, E.; Anderson, N. P.; Zavalij, P. Y.; Vedernikov, A. N. *Chem. Commun.* **2008**, 3625−3627. (d) Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 1760−1762. (e) Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846−3847. (f) Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 6284−6285. (g) Ref 12h..

(10) For some recent examples of aerobic oxidation reactions in our group, see: (a) Huang, X.; Li, X.; Zou, M.; Song, S.; Tang, C.; Yuan, Y.; Jiao, N. *J. Am. Chem. Soc.* **2014**, *136*, 14858−14865. (b) Tang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 6528−6532. (c) Liang, Y.-F.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 548−552. (d) Zhang, C.; Jiao, N. *Org. Chem. Front.* **2014**, *1*, 109−112. (e) Shen, T.; Yuan, Y.; Song, S.; Jiao, N. *Chem. Commun.* **2014**, *50*, 4115−4118. (f) Zhang, C.; Feng, P.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 15257−15262. (g) Wang, T.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 11692−11695. (h) Su, Y.; Sun, X.; Wu, G.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 9808−9812. (i) Shi, Z.; Zhang, B.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4036−4041. (j) Zhang, B.; Xiang, S.-K.; Zhang, L.-H.; Cui, Y.; Jiao, N. *Org. Lett.* **2011**, *13*, 5212−5215.

(11) (a) Koley, D.; Colón, O. C.; Savinov, S. N. *Org. Lett.* **2009**, *11*, 4172−4175. (b) Taniguchi, T.; Yajima, A.; Ishibashi, H. *Adv. Synth. Catal.* **2011**, *353*, 2643−2647. (c) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384−3387. (d) Manna, S.; Jana, S.; Saboo, T.; Maji, A.; Maiti, D. *Chem. Commun.* **2013**, *49*, 5286−5288. (e) Taniguchi, T.; Sugiura, Y.; Hatta, T.; Yajima, A.; Ishibashi, H. *Chem. Commun.* **2013**, *49*, 2198−2200. (f) Kilpatrick, B.; Heller, M.; Arns, S. *Chem. Commun.* **2013**, *49*, 514−516.

(12) For reviews on NHPI as catalyst, see: (a) Wertz, S.; Studer, A. *Green Chem.* **2013**, *15*, 3116−3134. (b) Coseri, S. *Catal. Rev.* **2009**, *51*, 218−292. (c) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800−3842. (d) Minisci, F.; Punta, C.; Recupero, F. *J. Mol. Catal. A: Chem.* **2006**, *251*, 129−149. (e) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051−1071. (f) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393−427. For examples that NIPI as catalyst in our group, see: (g) Lin, R.; Chen, F.; Jiao, N. *Org. Lett.* **2012**, *14*, 4158−4161. (h) Yan, Y.; Feng, P.; Zheng, Q.-Z.; Liang, Y.-F.; Lu, J.-F.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5827−5831.

(13) (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Feuer, H.; Nielson, A. T. *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; Wiley-VCH: Weinheim, 1990.

(14) For reviews, see: (a) Yan, G.; Yang, M. *Org. Biomol. Chem.* **2013**, *11*, 2554−2566. (b) Prakash, G. K. S.; Mathew, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1726−1728. (c) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; Wiley-VCH: New York, 1989. (d) Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*, 4th ed.; Wiley-VCH: Weinheim, 2003.

(15) For some examples on electrophilic nitration of arenes, see: (a) Samajdar, S.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2000**, *41*, 8017−8020. (b) Rajagopal, R.; Srinivasan, K. V. *Synth. Commun.* **2003**, *33*, 961−966. (c) Yang, X.; Xi, C.; Jiang, Y. *Tetrahedron Lett.* **2005**, *46*, 8781−8783. (d) Lu, Y.; Li, Y.; Zhang, R.; Jin, K.; Duan, C. *Tetrahedron* **2013**, *69*, 9422−9427. (e) Hernando, E.; Castillo, R. R.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem.—Eur. J.* **2014**, *20*, 13854−13859.

(16) (a) Saito, S.; Koizumi, Y. *Tetrahedron Lett.* **2005**, *46*, 4715−4719. (b) LaBeaume, P.; Placzek, M.; Daniels, M.; Kendrick, I.; Ng, P.; McNeel, M.; Afroze, R.; Alexander, A.; Thomas, R.; Kallmerten, A. E.; Jones, G. B. *Tetrahedron Lett.* **2010**, *51*, 1906−1910. (c) Joseph, P. J. A.; Priyadarshini, S.; Kantam, M. L.; Maheswaran, H. *Tetrahedron Lett.* **2012**, *53*, 1511−1513.

(17) (a) Stefan, S.; Jurgen, S.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **2000**, 1485−1487. (b) Prakash, G. K. S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2004**, *6*, 2205−2207. (c) Wu, X.-F.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Commun.* **2011**, *47*, 12462−12463. (d) Yang, H. J.; Li, Y.; Jiang, M.; Wang, J. M.; Fu, H. *Chem.—Eur. J.* **2011**, *17*, 5652−5660. (e) Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maiti, D. *Org. Lett.* **2012**, *14*, 1736−1739. (f) Yan, G.; Zhang, L.; Yu, J. *Lett. Org. Chem.* **2012**, *9*, 133−137. (g) Yadav, R. R.; Vishwakarma, R. A.; Bharate, S. B. *Tetrahedron Lett.* **2012**, *53*, 5958−5960. (h) Wang, S.; Shu, C.; Wang, T.; Yu, J.; Yan, G. *Chin. Chem. Lett.* **2012**, *23*, 643−646.

(18) (a) Das, J. P.; Sinha, P.; Roy, S. *Org. Lett.* **2002**, *4*, 3055−3058. (b) Tani, K.; Lukin, K.; Eaton, P. E. *J. Am. Chem. Soc.* **1997**, *119*, 1476−1477. (c) Fargeas, V.; Favresse, F.; Mathieu, D.; Beaudet, I.; Charrue, P.; Lebret, B.; Piteau, M.; Quintard, J.-P. *Eur. J. Org. Chem.* **2003**, 1711−1719. (d) Emmons, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 5528−5530. (e) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, L. *Adv. Synth. Catal.* **2009**, *351*, 93−96. (f) Corey, E. J.; Samuelsson, B.; Luzzio, F. A. *J. Am. Chem. Soc.* **1984**, *106*, 3682−3683. (g) Rozen, S.; Carmeli, M. *J. Am. Chem. Soc.* **2003**, *125*, 8118−8119.

(19) (a) Liu, Y.-K.; Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Chem.—Eur. J.* **2010**, *16*, 13590−13593. (b) Zhang, L.; Liu, Z.; Li, H.; Fang, G.; Barry, B.-D.; Belay, T. A.; Bi, X.; Liu, Q. *Org. Lett.* **2011**, *13*, 6536−6539. (c) Zhang, W.; Lou, S.; Liu, Y.; Xu, Z. *J. Org. Chem.* **2013**, *78*, 5932−

DOI: 10.1021/cs502126n
ACS Catal. 2015, 5, 1956−1963

5948. (d) Katayev, D.; Pfister, K. F.; Wendling, T.; Goossen, L. J. *Chem.—Eur. J.* **2014**, *20*, 9902−9905. (e) Zhang, W.; Wu, D.; Zhang, J.; Liu, Y. *Eur. J. Org. Chem.* **2014**, 5827−5835. (f) Zhang, W.; Zhang, J.; Ren, S.; Liu, Y. *J. Org. Chem.* **2014**, *79*, 11508−11516. For nitration of *N*,1-diaryl-5-aminotetrazoles and *N*,4-diaryl-3-amino-1,2,4-triazoles, see: (g) Sadhu, P.; Alla, S. K.; Punniyamurthy, T. *J. Org. Chem.* **2014**, *79*, 8541−8549.

(20) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898−12899.

(21) (a) Xie, F.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 11862−11866. (b) For an elegant $Cu(OTf)_2$ (1.5 equiv) mediated C-H nitration with KNO_2 as the nitro source, see: Zhang, H.; Zhao, L.; Wang, D.-X.; Wang, M.-X. *Org. Lett.* **2013**, *15*, 3836−3839.

(22) For some recent examples of TBN as the reagent, see: (a) Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10573−10576. (b) Dannoun, G.; Bayarmagnai, B.; Grünberg, M. F.; Goossen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7972−7975. (c) Wang, X.; Xu, Y.; Mo, F.; Ji, G.; Qiu, D.; Feng, J.; Ye, Y.; Zhang, S.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2013**, *135*, 10330−10333. (d) Qiu, D.; Meng, H.; Jin, L.; Wang, S.; Tang, S.; Wang, X.; Mo, F.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 11581−11584. (e) Ohkubo, K.; Fujimoto, A.; Fukuzumi, S. *J. Am. Chem. Soc.* **2013**, *135*, 5368−5371. (f) Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8436−8439. (g) Crisóstomo, F. P.; Martín, T.; Carrillo, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2181−2185. (h) Liu, Y.; Zhang, J.-L.; Song, R.-J.; Qian, P.-C.; Li, J.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9017−9020. (i) Shen, T.; Yuan, Y.; Jiao, N. *Chem. Commun.* **2014**, *50*, 554−556.

(23) For an example that TBAB improved the efficiency of the reaction of TBN, see: Chen, F.; Huang, X.; Li, X.; Shen, T.; Zou, M.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 10495−10499.

(24) During the preparation of this manuscript, the nitration of azoarenes was reported: (a) Dong, J.; Jin, B.; Sun, P. *Org. Lett.* **2014**, *16*, 4540−4542. (b) Majhi, B.; Kundu, D.; Ahammed, S.; Ranu, B. C. *Chem.—Eur. J.* **2014**, *20*, 9862−9866.

(25) It should be noted that in our previous work (ref 12h), the hydroxylation took place under the conditions of $PdCl_2$/NHPI/toluene/100 °C, where as the described acylation occurred instead of hydroxylation under the similar conditions of $Pd(OAc)_2$/NHPI/toluene/80 °C. The anion or ligand in catalyst may have a crucial influence on the chemselectivity between the hydroxylation and the acylation. The reaction temperature and the concentration of reactants are also influential. Definitely, the mechanism is unclear yet. Further experimental and calculational studies are underway in our group for the deep understanding of these aerobic oxidation reactions.

(26) (a) Franck, H. G. *Industrial Aromatic Chemistry*; Springer: Berlin, 1988. (b) Horsley, J. A. *CHEMTECH* **1997**, *10*, 45−49. (c) Surburg, H.; Panten, J. *Common Fragrance and Flavor Materials*, 5th ed.; Wiley-VCH: Weinheim, 2006.

(27) Jovel, I.; Prateeptongkum, S.; Jackstell, R.; Vogl, N.; Weckbecker, C.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2493−2497.

(28) For mononuclear Pd^{IV} intermediate, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301. (b) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046−4048. (c) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234−11241. (d) Ye, Y.; Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 14682−14687. (e) Zhao, X.; Dong, V. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 932−34. For reviews, see: (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (h) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412−9423. (i) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712−733. (j) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177−185.

(29) For binuclear Pd^{III} intermediate, see: (a) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050−17051. (b) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302−309. (c) Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14092−14103. (d) Powers, D. C.; Lee, E.; Ariafard, A.; Sanford, M. S.; Yates, B. F.; Canty, A. J.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 12002−12009. (e) Cotton, F. A.; Gu, J.; Murillo, C. A.; Timmons, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 13280−13281. (f) Cotton, F. A.; Koshevoy, I. O.; Lahuerta, P.; Murillo, C. A.; Sanaú, M.; Ubeda, M. A.; Zhao, Q. *J. Am. Chem. Soc.* **2006**, *128*, 13674−13675. (g) Power, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14530−14536. (h) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2012**, *45*, 840−850. (i) Nielsen, M. C.; Lyngvi, E.; Schoenebeck, F. *J. Am. Chem. Soc.* **2013**, *135*, 1978−1985.

DOI: 10.1021/cs502126n
ACS Catal. 2015, 5, 1956−1963