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Palladium-Catalyzed Chelation-Assisted Aromatic C−H Nitration: Regiospecific Synthesis of Nitroarenes Free from the Effect of the Orientation Rules

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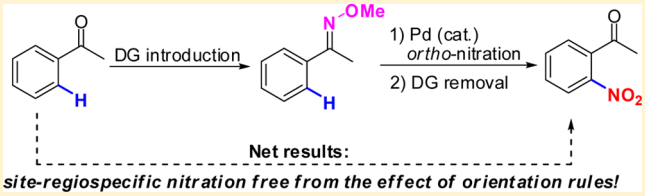
Supporting Information

ABSTRACT: A palladium-catalyzed chelation-assisted *ortho*-nitration of aryl C−H bond is described. A range of azaarenes such as 2-arylquinoxalines, pyridines, quinoline, and pyrazoles were nitrated with excellent chemo- and regioselectivity. Using the *O*-methyl oximyl group as a removable directing group, the regiospecific synthesis of a variety of *o*-nitro aryl ketones was achieved starting from aryl ketones via a three-step process involving the Pd-catalyzed *ipso*-nitration of C−H bond as a key step. Mechanistic investigations support a silver-mediated radical mechanism involving Pd((II/III) and/or Pd(II/IV) catalytic cycles under oxidizing conditions.



INTRODUCTION

Aromatic nitro compounds are important synthetic precursors in the chemical industry as well as in academic research.[1] Since Mitscherlich[2] reported the first nitration of benzene with fuming nitric acid in 1834, the nitrating agent-involved electrophilic aromatic substitution has long been the predominant synthetic approach for the preparation of nitroarenes.[3] However, the traditional electrophilic nitration processes are usually associated with several persistent disadvantages including poor regioselectivity, poor chemoselectivity arising from overnitration, imperfect functional group and/or substrate compatibility under acidic conditions, nitration sites significantly depending on the orientation effect of different functional groups, and the use of environmentally harmful acid reagents.[3] Therefore, it is still highly desirable to develop new nitration methods that can overcome the above-mentioned problems.

Until now, several new strategies, most focusing on regiospecific synthesis of nitroarenes, have been developed.[4,5] For example, *ipso*-oxidation of an amino[6] or an azide[7] to a nitro group provides an indirect nitration protocol to introduce the nitro group in regiospecific manner. Recently, *ipso*-nitration protocol[4] has received attention as a more attractive method for the regiospecific synthesis of nitroarenes which can be achieved via nitrodemetalation of an organometallic reagents (M = B, Li)[5,8,9] or via nitrodecarboxylation of an aryl carboxylic acid,[10] or via transition-metal-catalyzed (Cu or Pd) *ipso*-nitration of aryl halides, pseudohalides, or aryl boronic acids.[11] Despite the promising prospects of these methods for the regiospecific synthesis of nitroarenes, they all suffer from the use of prefunctionalized starting materials.

In the last decades, transition-metal-catalyzed chelation-assisted C−H functionalization has emerged as a powerful tool for the regioselective construction of carbon−carbon and carbon−heteroatom bonds.[12] The excellent regioselectivity achieved in these C−H functionalizations led us to envision a regioselective and environmentally benign direct C−H nitration of arenes that can avoid the prefunctionalized steps.[8−11] In this context, we have recently communicated the first palladium-catalyzed chelation-assisted *ortho*-specific nitration of aromatic C−H bonds mainly using *N*-heterocycles as the directing groups which are difficult to be removed.[13,14] For practical purposes, we envision that using a removable or modifiable directing group[15] has more advantages because it not only expands the scope of substrates and products but also enables a site-regiospecific introduction of the nitro group to the target functional groups free from the effect of orientation rules which is difficult to pursue via traditional methods. Herein, we detail our recent efforts in developing palladium-catalyzed chelation-assisted site-regiospecific nitration of aromatic C−H bonds, the practical synthesis of *o*-nitro aryl ketones using removable directing groups, and mechanistic studies.

RESULTS AND DISCUSSION

We commenced the study with the direct *ortho*-nitration of aromatic C−H bonds using the quinoxaline moiety as the directing group[16] due to the potential utilities of quinoxaline derivatives in materials science, chemical, and pharmaceutical fields.[17] 2-Phenylquinoxaline **1a** was selected as a model substrate for optimizing the reaction conditions, and the results are listed in Table 1. First, several palladium catalysts were surveyed using $AgNO_2$ (2 equiv) as a nitro source and $K_2S_2O_8$ (2 equiv) as an oxidant in DCE at 130 °C for 48 h. It was found that

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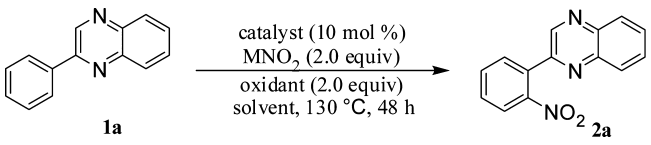
Table 1. Optimization of Reaction Conditions for *Ortho*-Nitration of 1a[a]



entry	catalyst	oxidant	MNO_2	solvent	yield[b] (%)
1	$PdCl_2$	$K_2S_2O_8$	$AgNO_2$	DCE	45
2	$Pd(PPh_3)_2Cl_2$	$K_2S_2O_8$	$AgNO_2$	DCE	74
3	**$Pd(OAc)_2$**	**$K_2S_2O_8$**	**$AgNO_2$**	**DCE**	**91 (86[c])**
4	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_2$	DCE	82[d], 41[e]
5	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_2$	DCE	80[f], 48[g],
6	$Pd(OAc)_2$/2,2′-bipyridyl[h]	$K_2S_2O_8$	$AgNO_2$	DCE	<5
7	$Pd(OAc)_2$	$K_2S_2O_8$	$NaNO_2$	DCE	31
8	$Pd(OAc)_2$	$K_2S_2O_8$/Ag_2O/PivOH[i]	$NaNO_2$	DCE	42
9	$Pd(OAc)_2$	$K_2S_2O_8$	KNO_2/18-crown-6[j]	DCE	<5
10	$Pd(OAc)_2$	$K_2S_2O_8$	$(TBA)NO_2$	DCE	<5
11	$Pd(OAc)_2$	BQ[k]	$AgNO_2$	DCE	0
12	$Pd(OAc)_2$	Oxone	$AgNO_2$	DCE	88
13	$Pd(OAc)_2$	CAN[l]	$AgNO_2$	DCE	76
14	$Pd(OAc)_2$	$PhI(OAc)_2$	$AgNO_2$	DCE	trace
15	$Pd(OAc)_2$	DDQ[m]	$AgNO_2$	DCE	0
16	$Pd(OAc)_2$	$Cu(OAc)_2$	$AgNO_2$	DCE	24
17	$Pd(OAc)_2$	$CuCl_2$	$AgNO_2$	DCE	0
18	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_2$	1,4-dioxane	0
19	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_2$	DMF	0
20	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_2$	toluene	0
21	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_2$	$MeNO_2$	0
22	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_2$	MeCN	0
23	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_2$	CH_2Cl_2	86
24	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_2$	MeOH	0
25		$K_2S_2O_8$	$AgNO_2$	DCE	0

[a]Reaction conditions: **1a** (0.3 mmol), [Pd] (0.03 mmol), MNO_2 (0.06 mmol), oxidant (0.06 mmol) in 3.5 mL of solvent at 130 °C for 48 h unless otherwise noted. [b]GC yields using phenanthrene as an internal standard. [c]Isolated yields. [d]The reaction temperature is 110 °C. [e]The reaction temperature is 90 °C. [f]5 mol % of $Pd(OAc)_2$ was used. [g]In the presence of $AgNO_2$ (1 equiv) and $K_2S_2O_8$ (1 equiv). [h]0.036 mmol of 2,2′-bipyridyl. [i]2 equiv of Ag_2O/PivOH. [j]18-Crown-6 (0.6 mmol) was added as a phase-transfer catalyst (PTC). [k]BQ = benzoquinone. [l]CAN = cerium ammonium nitrate. [m]DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

$Pd(OAc)_2$ was superior to other palladium sources including $PdCl_2$ and $Pd(PPh_3)_2Cl_2$, affording the desired nitroarene **2a** in 91% GC yield and 86% isolated yield, respectively (entries 1−3, Table 1). Decreasing the reaction temperature did not favor the nitration (Table 1, entry 4). The reaction gave inferior results when the catalyst loading (5 mol %) and the amount of $AgNO_2$/$K_2S_2O_8$ (1 equiv), respectively, were decreased (entry 5, Table 1). A combination of $Pd(OAc)_2$ and 2,2′-bipyridyl (0.12 equiv) gave trace amount of **2a** (entry 6, Table 1). No reaction took place in the absence of a palladium catalyst (entry 25, Table 1). Then, a series of nitrites were surveyed, and $AgNO_2$ was proven to be the best choice (entries 7−10 vs 3, Table 1). Finally, the effects of oxidants and solvents were examined. It was found that Oxone and CAN could give moderate yields of **2a** (entries 12, 13, Table 1) while other oxidants (BQ, $PhI(OAc)_2$), DDQ, $Cu(OAc)_2$, and $CuCl_2$) showed low efficiency (entries 11, 14−17, Table 1). Among several solvents so far surveyed, DCE was found to be the best choice (entries 18−24, Table 1).

Under the established reaction conditions, the scope of the Pd-catalyzed *ortho*-nitration of quinoxaline derivatives **1** with $AgNO_2$ was investigated (Table 2). A variety of quinoxaline derivatives **1** could be smoothly *ortho*-nitrated to furnish the desired nitration products **2** in moderate to good yields (35−93%, entries 1−18 except 13 and 15, Table 2). Substrates **1** bearing electron-rich aryl rings generally afforded the desired product in moderate to good yields (76−93%, entries 1−7, Table 2). The protocol also enabled *ortho*-nitration of electron-deficient aryl rings albeit with lower yields (35−51%, entries 8−10 and 12, Table 2). A thiophene-yl ring tethered with the quinoxaline directing group could also be *ortho*-nitrated in 35% yield (entry 14, Table 2). When quinoxaline derivatives **1m** or **1o** was employed as a substrate, the reaction failed to furnish the desired product while the starting substrate was recovered quantitatively (entries 13, 15, Table 2). Note that the neutral conditions could tolerate a series of functional groups, such as methoxy, hydroxyl, acetoxy, and thiophene-yl groups (entries, 3−5, 6, 12, and 14, Table 2). Interestingly, a bromo substituent survived under the palladium-catalyzed conditions and could be further decorated (entry 10, Table 2). For the more challenging nitrations of 2,3-diphenylquinoxalines **1q** and **1r**, double-centered C−H nitration directed by each proximal nitrogen donor in the quinoxaline ring was also achieved in high chemoselectivity (entries 17 and 18, Table 2). The *ortho*-regiochemistry of the nitrating reaction was unambiguously established on the basis of the spectral analyses, which was further confirmed by the X-ray crystallography of **2c** (see the Supporting Information).

Next, the generality of this protocol for other *N*-heterocycle-assisted C−H nitration was examined. To our delight, the 2-pyridyl group could be equally employed as a directing group for the C−H nitration of both electron-rich and electron-deficient arenes, albeit with lower yields compared with the cases of 2-quinoxalinyl group (**4a**−**g**, Figure 1). When 2-(naphthalen-2-yl)pyridine **3g** was tested, regioisomers **4g** and **4g′** were obtained in a total yield of 45% with a ratio of 1:1 (Figure 1). Under the standard reaction conditions, it was found that benzo[*h*]quinoline **3h** and 1-phenyl-1*H*-pyrazole **3i** gave only trace amounts of the desired nitroarenes and the starting substrates were recovered. However, when the oxidant was switched to CAN, the *ortho*-nitration of **3h** and **3i** proceeded smoothly and the desired products were obtained in 61% and 55% yield, respectively (Figure 1, **4h** and **4i**).

After realizing *ortho*-nitration of aromatic C−H bonds assisted by *N*-heterocycles which are difficult to be removed from the final products, we further attempted to employ the present strategy in the regioselective nitration of removable *N*-donor tethered aromatics. Thus acetophenone *O*-methyl oxime **5a** was selected as a target substrate. We envision that the *ortho*-nitration of **5a** followed by removal of the *O*-methyl oximyl group[18] of the resulting nitrated product would open a novel access to regiospecifically synthesize *o*-nitro acetophenone **7a**, which is a useful building block in synthetic organic chemistry.[19] Owing to the orientation effect of the carbonyl group,[3] it is infeasible that acetophenone itself regiospecifically transforms to **7a** via traditional electrophilic nitration processes.[20]

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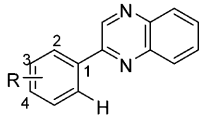
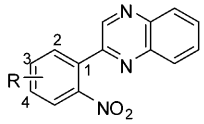
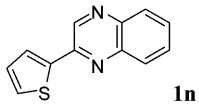
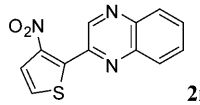
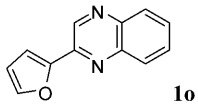
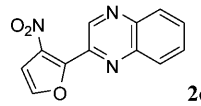
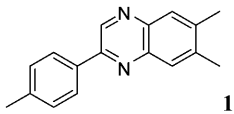
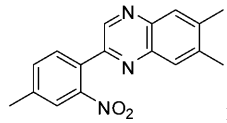
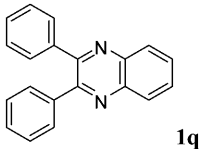
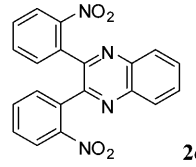
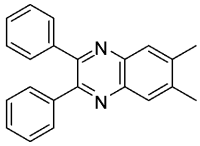
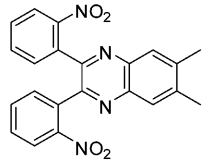
Table 2. Pd-Catalyzed *Ortho*-Nitration of Quinoxaline Derivatives 1.[a]

entry	substrate (**1**)	product (**2**)	yield (%)[b]
			
	(**1a–m**)	(**2a–m**)	
1	**1a**: R = H	**2a**	86
2	**1b**: R = 4-Me	**2b**	76
3	**1c**: R = 4-OMe	**2c**	88
4	**1d**: R = 2-OMe	**2d**	93
5	**1e**: R = 3-OMe	**2e**	82
6	**1f**: R = 4-OH	**2f**	81[c]
7	**1g**: R = 4-Ph	**2g**	87
8	**1h**: R = 4-F	**2h**	35
9	**1i**: R = 4-Cl	**2i**	44
10	**1j**: R = 4-Br	**2j**	50
11	**1k**: R = 4-CN	**2k**	0
12	**1l**: R = 2-OAc	**2l**	51
13	**1m**: R = 3,4-OCH_2O	**2m**	0
14	 **1n**	 **2n**	35
15	 **1o**	 **2o**	0
16	 **1p**	 **2p**	46
17	 **1q**	 **2q**	60[d]
18	 **1r**	 **2r**	55[d]

[a]Reaction conditions: **1** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $AgNO_2$ (0.6 mmol), $K_2S_2O_8$ (0.6 mmol) in 3.5 mL of DCE at 130 °C for 48 h. [b]Isolated yields. [c]$AgNO_2$ (0.3 mmol) and $K_2S_2O_8$ (0.3 mmol) were used. [d]$AgNO_2$ (0.9 mmol), $K_2S_2O_8$ (0.9 mmol), and $Pd(OAc)_2$ (0.045 mmol) were used.

When acetophenone *O*-methyl oxime **5a** was subjected to the above-mentioned conditions, 2-nitrated product **6a** was indeed obtained in 51% isolated yield (entry 1, Table 3). Through carefully screening a series of parameters including palladium

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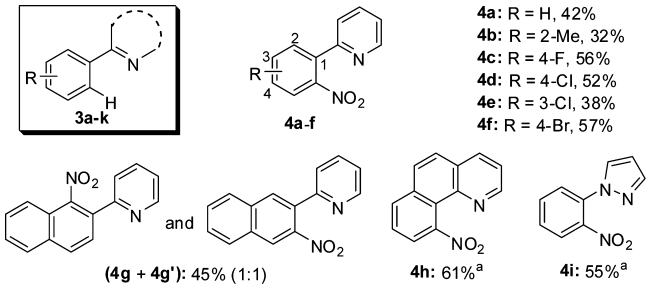
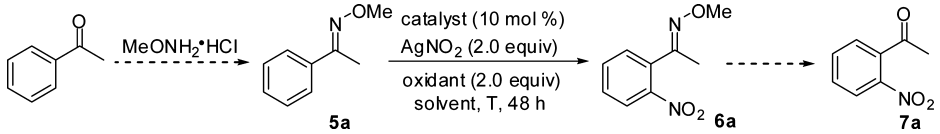


Figure 1. Pd-catalyzed *ortho*-nitration of aromatic C−H bond in **3** directed by other *N*-heterocycle directing groups. Conditions: **3** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $AgNO_2$ (0.6 mmol), $K_2S_2O_8$ (0.6 mmol) in 3.5 mL of DCE at 130 °C for 48 h. [a]CAN (0.6 mmol) was used as the oxidant.

sources, oxidants, solvents, and temperatures (Table 3), we finally found that $Pd(OCOCF_3)_2$ (10 mol %) was a better catalyst and 110 °C was a more suitable temperature for the C−H nitration of **5a**, in which case the desired product **6a** could be obtained in 83% isolated yield with $AgNO_2$ (2 equiv) as the nitro source, $K_2S_2O_8$ (2 equiv) as the oxidant, and DCE as the solvent for 48 h (entry 4, Table 3).

To investigate the scope of the reaction, a variety of aryl ketone *O*-methyl oximes **5** were subjected to the optimal reaction conditions (Table 4). In the participation of electron-rich aryl rings, the reaction proceeded smoothly to furnish the desired nitroarenes in moderate to good yields (50−85%, entries 1−8, Table 4). Surprisingly, when electron-deficient aryl rings were employed, the reaction proceeded even more cleanly to furnish the corresponding nitroarenes in moderate to excellent yields (72−91%, entries 9−18 except 13, Table 4) which was opposite to that case of quinoxaline substrates (Table 2, vide supra). For example, a series of fluoro-, chloro-, bromo-, iodo-, cyano-, methylsulfonyl-, or even nitro-*para*-substituted phenyl rings could be well *ortho*-nitrated to furnish the target products in good to excellent yields (72−91%, entries, 9, 10, 12, 14−16, and 18, Table 4), while low (substituted with *p*-halo groups, entries 8−10, Table 2) or negligible (substituted with CN group) yields were obtained in the case of quinoxaline substrates. We speculated that such a difference may arise from the different C−H activation mechanisms between quinoxaline and *O*-methyl oxime substrates. The former substrate may involve the electrophilic aromatic substitution mechanism (S_EAr),[21] namely electrophilic metalation.[22] In this mechanism, electron-rich arenes usually undergo C−H functionalization more smoothly;[23] the latter substrate may involve in the concerted metalation deprotonation mechanism (CMD)[24] in which electron-deficient arenes usually undergo C−H functionalization more smoothly due to enhanced acidity.[25] Note that substrates bearing a methoxy- or nitro-*meta*-substituted phenyl ring could exclusively afford a regioisomer in which the nitro group was introduced to the *para*-position to the already present substituent (entries, 6, 17, **6f** and **6q**, Table 4). We speculated that such regioselectivity was generally governed by the steric effect upon the formation of the related palladacycle intermediate leading to the cleavage of the less sterically hindered *o*-C−H bond (see Scheme 3, vide infra).[25a,26] When substrates other than acetophenone *O*-methyl oximes were used, the reaction still proceeded smoothly to give the desired products in moderate to good yields (55−83%, entries 19−23, Table 4). Besides the excellent regioselectivity, the present reaction also showed excellent chemoselectivity as most reactions gave mononitration products predominantly (>95%).

Table 3. Optimization of Reaction Conditions for *Ortho*-Nitration of 5a[a]



entry	catalyst	oxidant	temp (°C)	solvent	yield[b] (%)
1	$Pd(OAc)_2$	$K_2S_2O_8$	130	DCE	56 (51[c])
2	$Pd(OAc)_2$	$K_2S_2O_8$	110	DCE	77
3	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	130	DCE	64
4	**$Pd(OCOCF_3)_2$**	**$K_2S_2O_8$**	**110**	**DCE**	**88 (83[c])**
5	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	90	DCE	67
6	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	60	DCE	42
7	$PdCl_2$	$K_2S_2O_8$	110	DCE	66
8	$Pd(PPh_3)_2Cl_2$	$K_2S_2O_8$	110	DCE	15
9	$Cu(OAc)_2$	$K_2S_2O_8$	110	DCE	0
10	--	$K_2S_2O_8$	110	DCE	0
11	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	MeCN	30
12	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	MeOH	<5
13	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	1,4-dioxane	10
14	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	$MeNO_2$	32
15	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	Et_2O	7
16	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	THF	0
17	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	toluene	40
18	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	DMF	0
19	$Pd(OCOCF_3)_2$	$Cu(OAc)_2$	110	DCE	0
20	$Pd(OCOCF_3)_2$	$PhI(OAc)_2$	110	DCE	0

[a]Reaction conditions: **5a** (0.3 mmol), catalyst (0.03 mmol), $AgNO_2$ (0.06 mmol), $K_2S_2O_8$ (0.06 mmol) in 3.5 mL of solvent for 48 h unless otherwise noted. [b]GC yields using phenanthrene as an internal standard. [c]Isolated yields.

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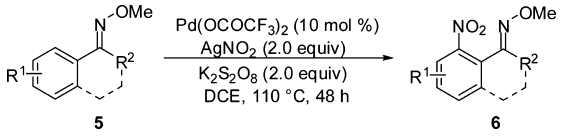
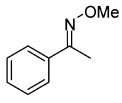
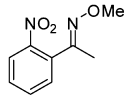
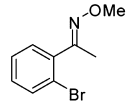
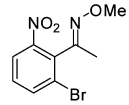
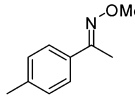
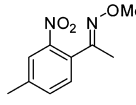
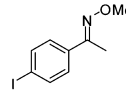
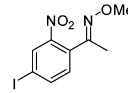
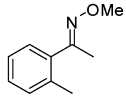
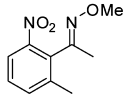
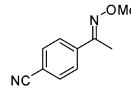
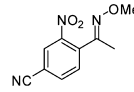
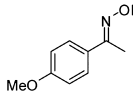
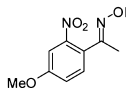
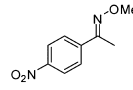
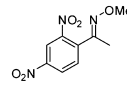
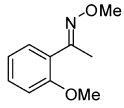
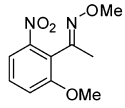
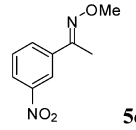
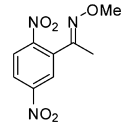
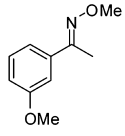
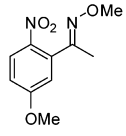
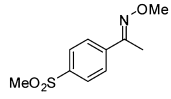
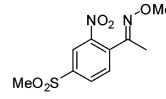
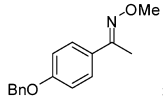
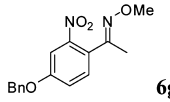
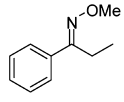
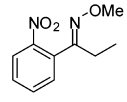
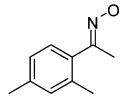
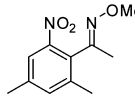
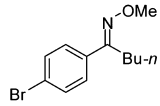
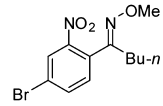
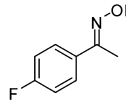
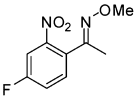
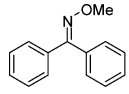
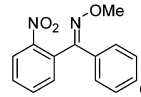
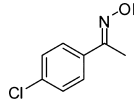
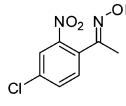
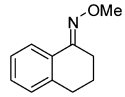
Table 4. Pd-Catalyzed *Ortho*-Nitration of Aryl Ketone *O*-Methyl Oximes 5[a]



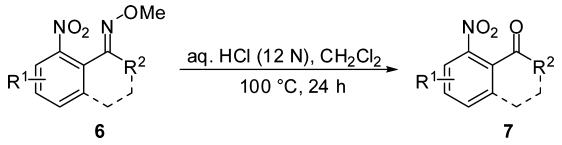
5 6

entry	substrate (**5**)	product (**6**)	yield (%)[b]	entry	substrate (**5**)	product (**6**)	yield (%)[b]
1	 **5a**	 **6a**	83	13	 **5m**	 **6m**	42
2	 **5b**	 **6b**	70	14	 **5n**	 **6n**	80
3	 **5c**	 **6c**	75	15	 **5o**	 **6o**	90
4	 **5d**	 **6d**	72	16	 **5p**	 **6p**	72
5	 **5e**	 **6e**	85	17	 **5q**	 **6q**	81
6	 **5f**	 **6f**	71	18	 **5r**	 **6r**	91
7	 **5g**	 **6g**	50	19	 **5s**	 **6s**	83
8	 **5h**	 **6h**	72	20	 **5t**	 **6t**	68
9	 **5i**	 **6i**	83	21	 **5u**	 **6u**	83
10	 **5j**	 **6j**	82	22	 **5v**	**6v**	55
11	**5k**	**6k**	85	23	**5w**	**6w**	78
12	**5l**	**6l**	77				

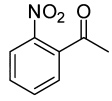
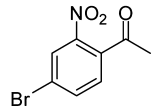
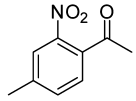
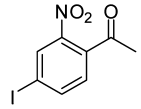
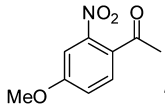
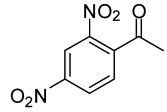
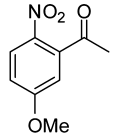
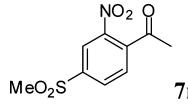
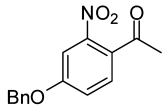
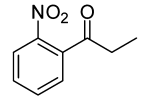
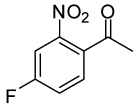
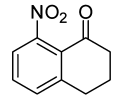
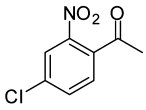
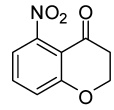
[a]Reaction conditions: **5** (0.3 mmol), $Pd(OCOCF_3)_2$ (0.03 mmol), $AgNO_2$ (0.6 mmol), $K_2S_2O_8$ (0.6 mmol) in 3.5 mL of DCE at 110 °C for 48 h. [b]Isolated yields.

dx.doi.org/10.1021/jo400594j | *J. Org. Chem.* 2013, 78, 5932−5948

Table 5. Conversion of 6 to 7 via Removal of the *O*-Methyl Oximyl Group[a]



6 7

entry	substrate (**6**)	product (**7**)	yield (%)[b]	entry	substrate (**6**)	product (**7**)	yield (%)[b]
1	**6a**	 **7a**	85	8	**6l**	 **7l**	78
2	**6b**	 **7b**	75	9	**6n**	 **7n**	40
3	**6d**	 **7d**	90	10	**6p**	 **7p**	42
4	**6f**	 **7f**	50	11	**6r**	 **7r**	88
5	**6g**	 **7g**	40	12	**6s**	 **7s**	98
6	**6i**	 **7i**	71	13	**6v**	 **7v**	95
7	**6j**	 **7j**	77	14	**6w**	 **7w**	78

[a]Reaction conditions: **6** (0.2 mmol), aq HCl (12 N, 1.0 mL), CH_2Cl_2 (1.0 mL) in a sealed tube in 100 °C for 24 h. [b]Isolated yields.

The removal of the *O*-methyl oximyl directing group in **6** was readily achieved via treatment of **6** with aq HCl (12 N) in CH_2Cl_2 at 100 °C for 24 h in a sealed tube according to a modified procedure reported by Sanford.[18a] Selected examples of transformation of **6** to **7** were listed in Table 5. Generally, *o*-nitro aryl ketones **7** could be selectively obtained in moderate to good yields (40−98%, entries 1−14, Table 5). Starting from aryl ketones, we have realized a regiospecific transformation of aryl ketones to *o*-nitroaryl ketones via an overall three-step process involving the Pd-catalyzed chelation-assisted *ipso*-nitration of C−H bond as the key step.

Several experiments were done to gain a mechanistic insight into the Pd-catalyzed C−H nitration. First, a binuclear palladacycle **8** was prepared from the stoichiometric reaction of **3a** with $Pd(OAc)_2$.[27] It was found that **8** was also a suitable catalyst for the nitration of **3a** to give the desired product **4a** in 67% GC yield (eq 1, Scheme 1). For acetophenone *O*-methyl oxime **5a**, we could not get the binuclear palladacycle **9** (eq 2, Scheme 1). We then prepared mononuclear palladacycle **10** via a stoichiometric reaction of **5a** with $Pd(OAc)_2$ and Ag_2O in TFA according to a previous literature reported by Cheng.[28] Employing **10** (10 mol %) as a catalyst, **5a** could also give the target product **6a** in 75% yield under otherwise identical conditions as the optimal (eq 3, Scheme 1).

Then, the kinetic isotope effects (k_H/k_D) for the C−H nitration were determined. The intramolecular k_H/k_D for substrate **1a**-d_4 was 5.3 ± 0.2, based on the ^1H NMR spectroscopic analyses (eq 1, Scheme 2); the intermolecular k_H/k_D of **1a** to **1a**-d_5 was determined to be 4.6 ± 0.2 (eq 2, Scheme 2); and the intermolecular k_H/k_D of **5a** to **5a**-d_5 was 2.3 ± 0.2 (eq 3, Scheme 2). These results suggested a rate-determining cyclopalladation step. Finally, with the reaction proceeding, the formation and gradually consumption of a brown gas, which should be assigned to NO_2 gas,[29] were observed in the sealed tube. The nitration of **1a** under

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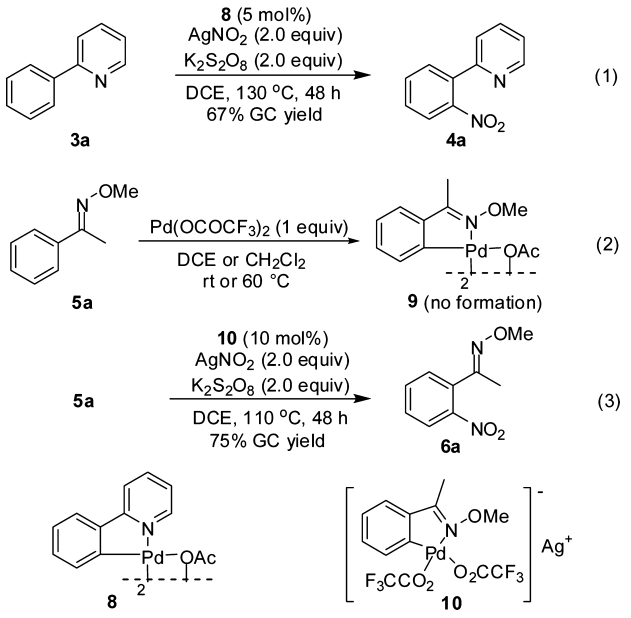
Scheme 1. Studies on the Catalytic Species



the standard conditions gave a decreased yield of **2a** (14%) in the presence of 0.5 equiv of TEMPO and failed to give **2a** by using 2 equiv of TEMPO (eq 4, Scheme 2), demonstrating that the reaction may involve a radical process.[30]

On the basis of the mechanistic experiments described above, a proposed mechanism for the Pd-catalyzed chelation-assisted C−H nitration was proposed in Scheme 3. For substrates **1** or **3**, the reaction may proceed via a silver-mediated radical mechanism[29,31,32] involving a binuclear palladacycle species through the Pd^{II}/Pd^{III}[27a,33] and/or Pd^{II}/Pd^{IV}[34,35] catalytic cycles; while for substrate **5**, a mechanism involving a mononuclear palladacycle species through the Pd^{II}/Pd^{IV} catalytic cycle is more likely.[28,36]

CONCLUSION

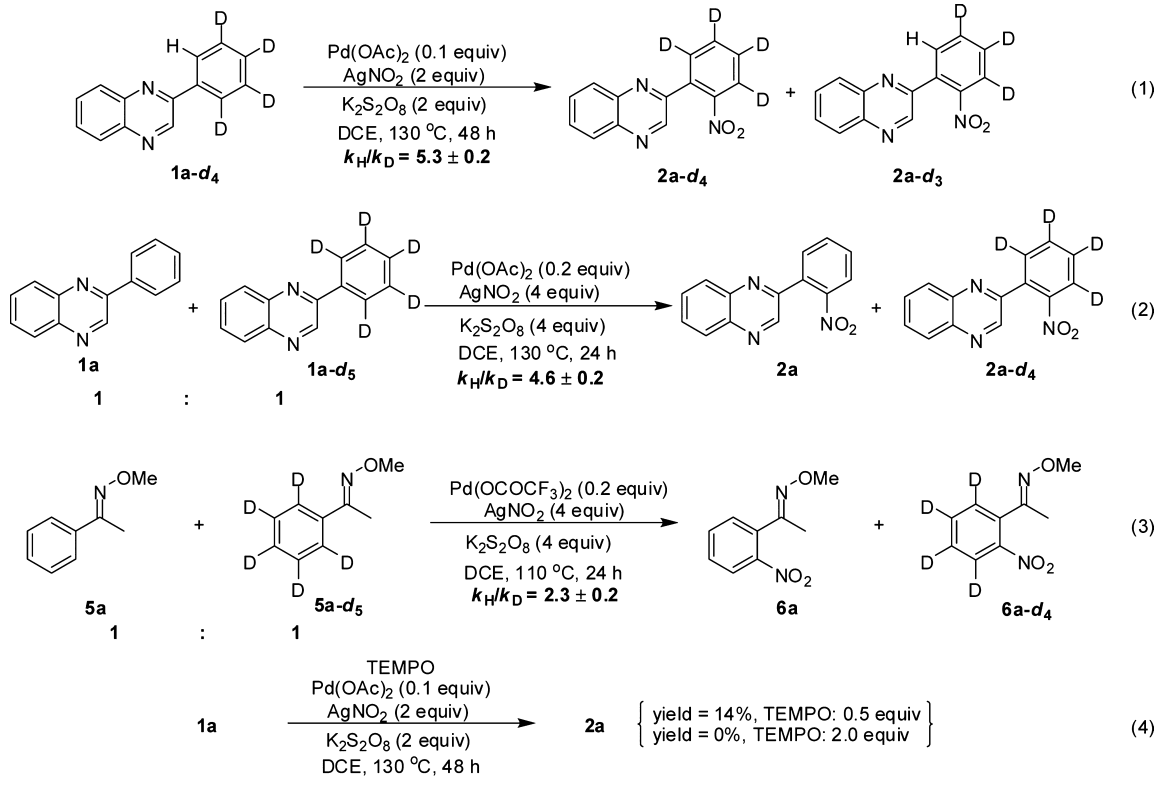
In summary, we have developed a regiospecific synthesis of nitroarenes via palladium-catalyzed chelation-assisted C−H nitration. The present protocol has also been successfully applied in the regiospecific synthesis of *o*-nitroaryl ketones from aryl ketones via a three-step process involving directing group introduction, *ortho*-nitration of C−H bond, and directing group removal. The present strategy for the *ipso*-nitration of C−H bond has several characteristic advantages including site-regiospecific nitration of C−H bond free from the effect of the orientation rules, excellent mononitration selectivity, broad functional group and substrate tolerance under neutral conditions, and no need for prefunctionalization of C−H bonds.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without purifications. All solvents for reactions were dried and distilled prior to use according to standard methods. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a spectrometer at 25 °C in $CDCl_3$ at 500 and 125 MHz, respectively, with TMS as internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants J are given in Hz. The IR spectra were recorded on an FT-IR spectrometer. GC−MS experiments were performed with EI source, high resolution mass spectra (HRMS) were obtained on a TOF MS instrument with EI or ESI source.

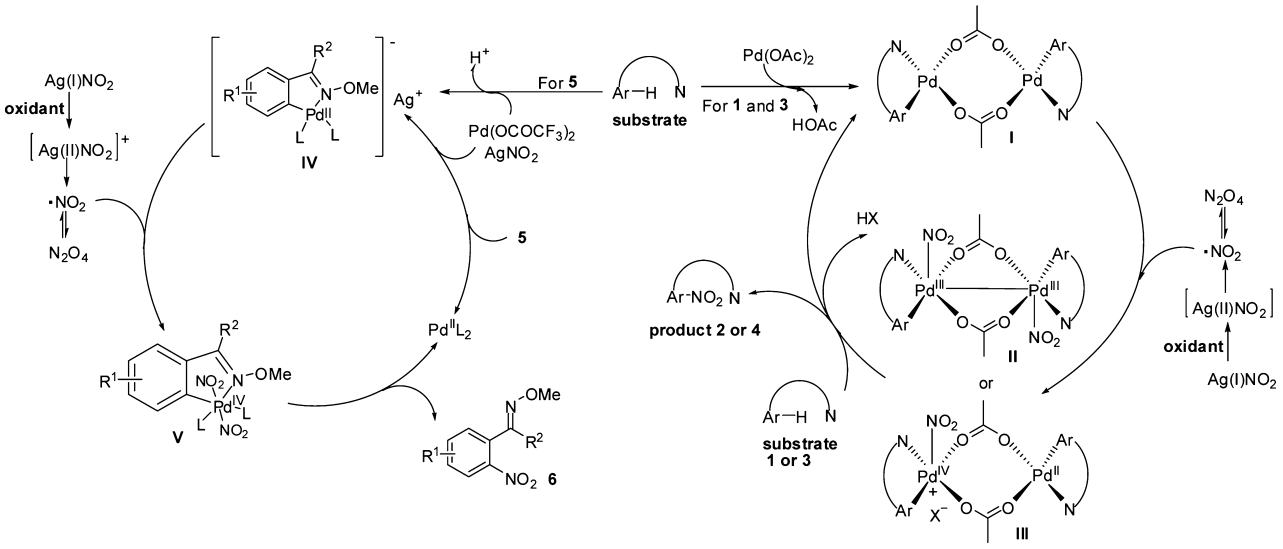
Starting Materials. Starting materials 2-arylquinoxalines (**1a−r**),[37,38] 2-arylpyridines (**3a−g**),[39] 2-phenylpyrazole **3i**,[40] and *O*-methyl oximes (**5a−w**)[41] were synthesized according to the literature procedures.

Scheme 2. Investigation on the Effects of Kinetic Isotope and Radical Scavenger TEMPO



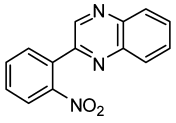
dx.doi.org/10.1021/jo400594j | J. Org. Chem. 2013, 78, 5932−5948

Scheme 3. Proposed Mechanism



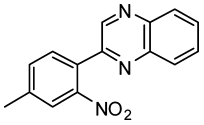
Typical Experimental Procedure for Synthesis of Nitroarenes 2 and 4. Compound **1** or **3** (0.3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $AgNO_2$ (92.3 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol) or CAN (329.0 mg, 0.6 mmol, for **3h**, **3i**), and anhydrous DCE (3.5 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 130 °C for 48 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100−200 mesh) using cyclohexane−EtOAc as eluent (3:1, V/V) to give desired product **2** or **4**.

*2-(2-Nitrophenyl)quinoxaline (**2a**):*[42]



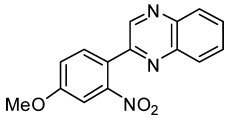
pale yellow solid (64.8 mg, 86%); mp 114−115 °C (lit.[42] mp 116−118 °C); IR (KBr) ν = 1531 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.97 (s, 1H), 8.18−8.10 (m, 3H), 7.83−7.68 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.1, 148.8, 144.3, 141.8, 141.6, 133.3, 133.0, 131.9, 130.6, 130.4, 130.3, 129.6, 129.3, 125.0; MS (EI, 70 eV) m/z = 251 (83) [M^+], 221(100); HRMS (EI) for $C_{14}H_9N_3O_2$ calcd 251.0695, found 251.0690.

*2-(4-Methyl-2-nitrophenyl)quinoxaline (**2b**):*



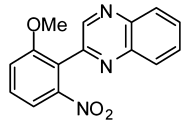
pale yellow solid (60.5 mg, 76%); mp 153−154 °C; IR (KBr) ν = 1531 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.94 (s, 1H), 8.17−8.15 (m, 1H), 8.11−8.09 (m, 1H), 7.92 (s, 1H), 7.82−7.80 (m, 2H), 7.64 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 7.5, 1H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.1, 148.6, 144.4, 141.9, 141.5, 141.3, 133.9, 131.7, 130.5, 130.3, 130.1, 129.6 129.3 125.3, 21.2 MS (EI, 70 eV) m/z = 265 (79) [M^+], 235 (100); HRMS (EI) for $C_{15}H_{11}N_3O_2$ calcd 265.0851, found 265.0851.

*2-(4-Methoxy-2-nitrophenyl)quinoxaline (**2c**):*



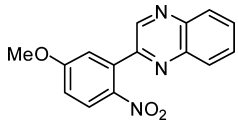
yellow solid (74.3 mg, 88%); mp 157−158 °C; IR (KBr) ν = 1531 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.92 (s, 1H), 8.16−8.14 (m, 1H), 8.10−8.09 (m, 1H), 7.81−7.79 (m, 2H), 7.68 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 2.5 Hz, 1H), 7.29 (dd, J_1 = 8.5, J_2 = 2.5 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.8, 150.9, 149.6, 144.5, 141.9, 141.3, 132.9, 130.4, 130.1, 129.5, 129.2, 125.0, 119.2, 110.1, 56.1; MS (EI, 70 eV) m/z = 281 (100) [M^+], 251 (89); HRMS (EI) for $C_{15}H_{11}N_3O_3$ calcd 281.0800, found 281.0786.

*2-(2-Methoxy-6-nitrophenyl)quinoxaline (**2d**):*



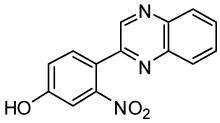
pale yellow solid (78.5 mg, 93%); mp 144−145 °C; IR (KBr) ν = 1533 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.98 (s, 1H), 8.18−8.16 (m, 1H), 8.06−8.04 (m, 1H), 7.81−7.75 (m, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.3, 150.4, 149.0, 146.4, 142.2, 141.3, 130.9, 130.09, 130.06, 129.5, 129.3, 122.2, 116.7, 115.7, 56.6; MS (EI, 70 eV) m/z = 281 (42) [M^+], 263 (42), 233 (100); HRMS (EI) for $C_{15}H_{11}N_3O_3$ calcd 281.0800, found 281.0817.

*2-(5-Methoxy-2-nitrophenyl)quinoxaline (**2e**):*



pale yellow solid (69.2 mg, 82%); mp 178−179 °C; IR (KBr) ν = 1575 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.89 (s, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.19−8.11 (m, 2H), 7.83−7.81 (m, 2H), 7.13−7.09 (m, 2H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.4, 152.0, 144.7, 141.8, 141.5, 141.1, 136.0, 130.5, 130.3, 129.5, 129.3, 127.7, 117.1, 115.1, 56.2; MS (EI, 70 eV) m/z = 281 (60) [M^+], 251 (100); HRMS (EI) for $C_{15}H_{11}N_3O_3$ calcd 281.0800, found 281.0793.

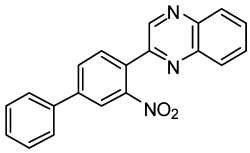
*3-Nitro-4-(quinoxalin-2-yl)phenol (**2f**):*



yellow solid (64.9 mg, 81%); mp 184−185 °C; IR (KBr) ν = 1537 (NO_2), 3201 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.80 (s, 1H), 9.32 (s, 1H), 8.98 (d, J = 2.5 Hz, 1H), 8.51 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 8.15−8.12 (m, 2H), 7.83−7.77 (m, 2H), 7.36 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.3, 148.7, 142.08, 142.04, 141.7, 136.0, 134.0, 130.7, 130.0, 129.5, 129.4, 129.2, 123.9, 121.0; MS (EI, 70 eV) m/z = 267 (100) [M^+], 221 (53); HRMS (EI) for $C_{14}H_9N_3O_3$ calcd 267.0644, found 267.0656.

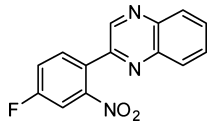
dx.doi.org/10.1021/jo400594j | J. Org. Chem. 2013, 78, 5932−5948

*2-(4-Phenyl-2-nitrophenyl)quinoxaline (**2g**):*



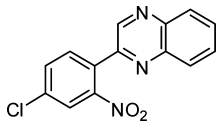
yellow solid (85.4 mg, 87%); mp 150−151 °C; IR (KBr) ν = 1537 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.01 (s, 1H), 8.32 (d, J = 1.5 Hz, 1H), 8.19−8.11 (m, 2H), 7.99 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.84−7.80 (m, 3H), 7.68 (d, J = 8.0 Hz, 2H), 7.55−7.46 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.8, 149.2, 144.3, 143.8, 141.9, 141.6, 137.9, 132.3, 131.4, 131.3, 130.6, 130.4, 129.6, 129.3, 129.0, 127.2, 123.4; MS (EI, 70 eV) m/z = 327 (92), 297 (100); HRMS (EI) for $C_{20}H_{13}N_3O_2$ calcd 327.1008, found 327.1017.

*2-(4-Fluoro-2-nitrophenyl)quinoxaline (**2h**):*



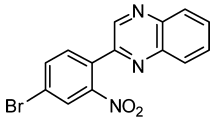
pale yellow solid (28.3 mg, 35%); mp 147−148 °C; IR (KBr) ν = 1540 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.94 (s, 1H), 8.19−8.17 (m, 1H), 8.11−8.09 (m, 1H), 7.89−7.76 (m, 4H), 7.54−7.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.6 (d, J = 253.8 Hz), 150.1, 149.4 (d, J = 8.8 Hz), 144.1, 141.8, 141.6, 133.6 (d, J = 8.8 Hz), 130.7, 130.6, 129.6, 129.3, 129.2, 120.6 (d, J = 21.3 Hz), 112.9 (d, J = 27.5 Hz); MS (EI, 70 eV) m/z = 269 (78) [M^+], 239 (100); HRMS (EI) for $C_{14}H_8FN_3O_2$ calcd 269.0601, found 269.0605.

*2-(4-Chloro-2-nitrophenyl)quinoxaline (**2i**):*[43]



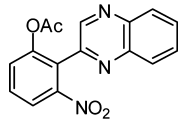
yellow solid (37.7 mg, 44%); mp 193−194 °C; IR (KBr) ν = 1527 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.95 (s, 1H), 8.19−8.17 (m, 1H), 8.11−8.09 (m, 2H), 7.85−7.81 (m, 2H), 7.78−7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.9, 149.2, 144.0, 141.8, 141.7, 136.4, 133.3, 132.9, 131.3, 130.8, 130.7, 129.6, 129.3, 125.2; MS (EI, 70 eV) m/z = 285.0 (88) [M^+], 255.0 (100); HRMS (EI) for $C_{14}H_8ClN_3O_2$ calcd 285.0305, found 285.0309.

*2-(4-Bromo-2-nitrophenyl)quinoxaline (**2j**):*



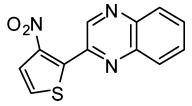
white solid (49.5 mg, 50%); mp 193−194 °C; IR (KBr) ν = 1531 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.95 (s, 1H), 8.26 (d, J = 2.0 Hz, 1H), 8.19−8.17m, 1H), 8.11−8.09 (m, 1H), 7.93 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.85−7.83 (m, 2H), 7.66 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.9, 149.1, 143.8, 141.8, 141.6 136.3 133.1, 131.6, 130.8, 130.7, 129.6, 129.3, 128.0, 123.9; MS (EI, 70 eV) m/z = 331 (91) [M^+], 301 (63), 220 (100); HRMS (EI) for $C_{14}H_8BrN_3O_2$ calcd 328.9800, found 328.9803.

*3-Nitro-2-(quinoxalin-2-yl)phenyl acetate (**2l**):*



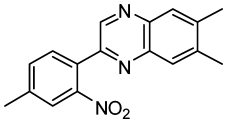
yellow solid (47.3 mg, 51%); mp 106−107 °C; IR (KBr) ν = 1531 (NO_2), 1774 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.91 (s, 1H), 8.20−8.18 (m, 1H), 8.10−8.07 (m, 2H), 7.87−7.80 (m, 2H), 7.70 (t, J = 8.5, 1H), 7.58 (dd, J_1 = 8.5 Hz, J_1 = 1.0 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 149.74, 149.69, 147.9, 145.0, 142.0, 141.4, 130.6, 130.53, 130.51, 129.5, 129.3, 128.4, 126.7, 122.5, 20.4; MS (EI, 70 eV) m/z = 309 (3) [M^+], 267 (57), 237 (18); HRMS (EI) for $C_{16}H_{11}N_3O_4$ calcd 309.0750, found 309.0753.

*2-(3-Nitrothiophene-2-yl)quinoxaline (**2n**):*



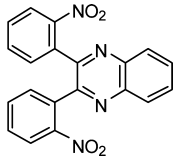
yellow solid (27.0 mg, 35%); mp 247−248 °C; IR (KBr) ν = 1537 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.29 (s, 1H), 8.15−8.12 (m, 2H), 8.00 (d, J = 4.5 Hz, 1H), 7.86−7.80 (m, 2H), 7.77 (d, J = 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.9, 145.2, 142.5, 142.0, 141.1, 131.2, 130.8, 129.6, 129.4, 129.2, 124.9; MS (EI, 70 eV) m/z = 257 (4) [M^+]; HRMS (EI) for $C_{12}H_7N_3O_2S$ calcd 257.0259, found 257.0253.

*6,7-Dimethyl-2-(4-methyl-2-nitrophenyl)quinoxaline (**2p**):*



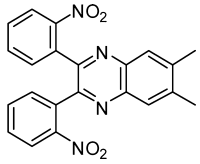
pale yellow solid (40.5 mg, 46%); mp 189−190 °C; IR (KBr) ν = 1529 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.84 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.84 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 2.54 (s, 3H), 2.53 (s, 3H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.0, 148.9, 143.3, 141.3, 141.1, 141.0, 140.9, 140.5, 133.7, 131.6, 130.4, 128.6, 128.3, 125.3, 21.2, 20.5, 20.4; MS (EI, 70 eV) m/z = 293 (78) [M^+], 263 (100); HRMS (EI) for $C_{17}H_{15}N_3O_2$ calcd 293.1164, found 293.1180.

*2,3-Bis(2-nitrophenyl)quinoxaline (**2q**):*



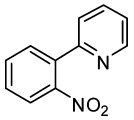
yellow solid (67.0 mg, 60%); mp 207−208 °C; IR (KBr) ν = 1528 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.18 (dd, J_1 = 6.5 Hz, J_2 = 3.5 Hz, 2H), 7.95 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 2H), 7.86 (dd, J_1 = 6.5 Hz, J_2 = 3.5 Hz, 2H), 7.68−7.60 (m, 4H), 7.54−7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.1, 147.7, 141.0, 134.0, 133.4, 132.8, 130.7, 130.1, 129.3, 124.3; MS (EI, 70 eV) m/z = 372 (48) [M^+], 342 (59); HRMS (EI) for $C_{20}H_{12}N_4O_4$ calcd 372.0859, found 372.0876.

*6,7-Dimethyl-2,3-bis(2-nitrophenyl)quinoxaline (**2r**):*



yellow solid (66.1 mg, 55%); mp 211−212 °C; IR (KBr) ν = 1528 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.94−7.91 (m, 4H), 7.64−7.57 (m, 4H), 7.52 −7.48 (m, 2H), 2.54 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.8, 147.9, 141.4, 140.0, 133.8, 133.7, 132.7, 129.8, 128.3, 124.3, 20.4; MS (EI, 70 eV) m/z = 400 (41) [M^+], 370 (7); HRMS (EI) for $C_{22}H_{16}N_4O_4$ calcd 400.1172, found 400.1174.

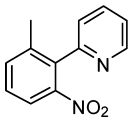
*2-(2-Nitrophenyl)pyridine (**4a**):*[44]



orange oil (25.2 mg, 42%); IR (neat) ν = 1524 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.65 (d, J = 4.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.81−7.78 (m, 1H), 7.68−7.47 (m, 4H), 7.33−7.30 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.4, 149.6, 149.3, 136.8, 135.2, 132.3, 131.2, 129.2, 124.3, 122.9, 122.6; MS (EI, 70 eV) m/z = 200 (20) [M^+], 170 (100); HRMS (EI) for $C_{11}H_8N_2O_2$ calcd 200.0586, found 200.0591.

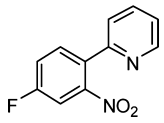
dx.doi.org/10.1021/jo400594j | J. Org. Chem. 2013, 78, 5932−5948

*2-(2-Methyl-6-nitrophenyl)pyridine (**4b**):*



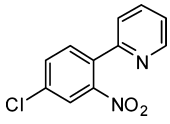
brown oil (20.6 mg, 32%); IR (neat) ν = 1527 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.69 (d, J = 4.5 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.81−7.77 (m, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.33−7.30 (m, 2H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.6, 149.8, 149.5, 139.1, 136.5, 134.9, 134.8, 128.6, 123.9, 122.6, 121.9, 20.1; MS (EI, 70 eV) m/z = 213 (100) [M^+], 167 (81); HRMS (EI) for $C_{12}H_9N_2O_2$ $(M - H)^+$ calcd 213.0664, found 213.0668.

*2-(4-Fluoro-2-nitrophenyl)pyridine (**4c**):*



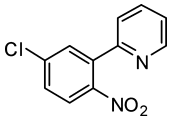
pale yellow solid (36.7 mg, 56%); mp 104−105 °C; IR (KBr) ν = 1539 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.64 (d, J = 4.5 Hz, 1H), 7.82−7.78 (m, 1H), 7.65−7.61 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.41−7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.9 (d, J = 252.5 Hz), 154.5, 149.7, 137.0, 132.9 (d, J = 8.8 Hz), 131.52, 131.49, 123.1, 122.7, 119.6 (d, J = 21.3 Hz), 112.3 (d, J = 26.3 Hz); MS (EI, 70 eV) m/z = 218 (32) [M^+], 188 (100); HRMS (EI) for $C_{11}H_7FN_2O_2$ calcd 218.0492, found 218.0486.

*2-(4-Chloro-2-nitrophenyl)pyridine (**4d**):*[45]



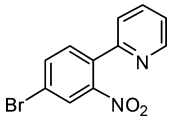
pale yellow solid (36.6 mg, 52%); mp 106−107 °C; IR (KBr) ν = 1531 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.65 (d, J = 4.5 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.82−7.79 (m, 1H), 7.64 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.34−7.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.3, 149.8, 149.5, 137.0, 135.0, 133.6 132.4, 132.3, 124.6, 123.2, 122.6; MS (EI, 70 eV) m/z = 234 (27) [M^+], 204 (100); HRMS (EI) for $C_{11}H_7ClN_2O_2$ calcd 234.0196, found 234.0189.

*2-(5-Chloro-2-nitrophenyl)pyridine (**4e**):*



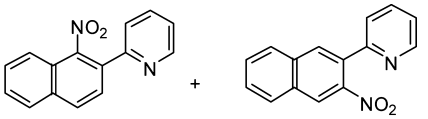
pale yellow oil (26.7 mg, 38%); IR (neat) ν = 1529 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.67 (d, J = 4.5 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.84−7.80 (m, 1H), 7.62 (d, J = 2.5 Hz, 1H), 7.52 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.37−7.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.3, 149.8, 147.4, 138.6, 137.0, 136.9, 131.3, 129.1, 125.8, 123.3, 122.7; MS (EI, 70 eV) m/z = 234 (17) [M^+], 204 (100); HRMS (EI) for $C_{11}H_7ClN_2O_2$ calcd 234.0196, found 234.0200.

*2-(4-Bromo-2-nitrophenyl)pyridine (**4f**):*



yellow oil (47.7 mg, 57%); IR (neat) ν = 1534 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.65−8.64 (m, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.82−7.78 (m, 2H), 7.51 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.34−7.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.4 149.8, 149.6, 137.0, 135.4, 134.0, 132.5, 127.4, 123.2, 122.6, 122.5; MS (EI, 70 eV) m/z = 278 (18) [M^+], 248 (43), 169 (100); HRMS (EI) for $C_{11}H_7BrN_2O_2$ calcd 277.9691, found 277.9692.

*2-(1-Nitronaphthalen-2-yl)pyridine and 2-(3-nitronaphthalen-2-yl)pyridine (**4g** + **4g′**):*

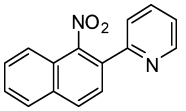


4g **4g'**

1 : **1**

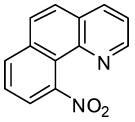
yellow oil (33.8 mg, 45%); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.74 (d, J = 5 Hz, 1H), 8.69 (d, J = 4.5 Hz, 1H), 8.47 (s, 1H), 8.09−7.60 (m, 14H), 7.55−7.53 (m, 1H), 7.36−7.32 (m, 2H).

*2-(1-Nitronaphthalen-2-yl)pyridine (**4g**, recrystallization from mixture of **4g** and **4g′**):*



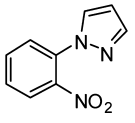
colorless solid (9.5 mg, recrystallization yield 56%); mp 149−150 °C; IR (KBr) ν = 1534 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.73 (d, J = 1.0 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.84−7.79 (m, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.70−7.62 (m, 3H), 7.36−7.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.5, 150.0, 147.0, 137.1, 133.6, 130.8, 129.9, 128.9, 128.0, 127.8, 126.3, 124.8, 123.2, 123.0, 122.2; MS (EI, 70 eV) m/z = 250 (42) [M^+], 220 (100); HRMS (EI) for $C_{15}H_{10}N_2O_2$ calcd 250.0742, found 250.0742.

*10-Nitrobenzo[h]quinoline (**4h**):*[46]



pale yellow solid (41.0 mg, 61%); mp 158−159 °C (lit.[46] 168−169); IR (KBr) ν = 1528 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.92 (dd, J_1 = 4.3 Hz, J_2 = 1.7 Hz, 1H), 8.19 (dd, J_1 = 8.1 Hz, J_1 = 1.7 Hz, 1H), 8.04 (dd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 7.85−7.68 (m, 4H), 7.55 (dd, J_1 = 8.1 Hz, J_2 = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.8, 143.4, 137.5, 136.7, 134.9, 130.4, 127.4, 127.3, 127.2, 127.0, 122.8, 121.7, 121.4; MS (EI, 70 eV) m/z = 224 (47) [M^+], 194 (25); HRMS (EI) for $C_{13}H_8N_2O_2$ calcd 224.0586, found 224.0592.

*1-(2-Nitrophenyl)-1H-pyrazole (**4i**):*[47]

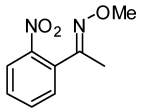


pale yellow solid (31.2 mg, 55%); mp 87−88 °C (lit.[47] mp 87−88 °C); IR (KBr) ν = 1535 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.87 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.75 (d, J = 1.5 Hz, 1H), 7.72 (d, J = 2.5 Hz, 1H), 7.70−7.68 (m, 1H), 7.59 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.54−7.50 (m, 1H), 6.50 (t, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.7, 142.3, 133.5, 133.0, 129.7, 128.3, 126.3, 125.0, 108.2; MS (EI, 70 eV) m/z = 189 (100) [M^+], 143 (35); HRMS (EI) for $C_9H_7N_3O_2$ calcd 189.0538, found 189.0543.

General Procedure for the Synthesis of *o*-Nitro Aryl Ketone *O*-Methyl Oximes 6. Aryl ketone *O*-methyl oximes **5** (0.3 mmol), $Pd(OCOCF_3)_2$ (10 mg, 0.03 mmol), $AgNO_2$ (92.3 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), and anhydrous DCE (3.5 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 48 h. Upon completion, the reaction mixture was cooled to rt and diluted with CH_2Cl_2 (10 mL) and filtered through Celite. The solvent was then removed under reduce pressure and the residue was purified by flash column chromatography on silica gel with cyclohexane−EtOAc (3:1, V/V) as the eluent.

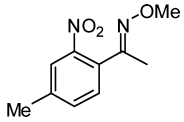
dx.doi.org/10.1021/jo400594j | J. Org. Chem. 2013, 78, 5932−5948

*(E)-1-(2-Nitrophenyl)ethanone O-methyl oxime (**6a**):*[48]



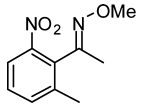
yellow oil (48.4 mg, 83%); IR (neat) ν = 1527 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.01 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.66−7.63 (m, 1H), 7.55−7.52 (m, 1H), 7.47 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H), 3.98 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.1, 148.0, 133.24, 133.16, 130.6, 129.5, 124.6, 62.0, 15.9; MS (EI, 70 eV) m/z = 194 (31) [M^+], 149 (44); HRMS (EI) for $C_9H_{10}N_2O_3$ calcd 194.0691, found 194.0685.

*(E)-1-(4-Methyl-2-nitrophenyl)ethanone O-methyl oxime (**6b**):*



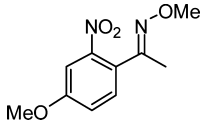
white solid (43.7 mg, 70%); mp 45−46 °C; IR (KBr) ν = 1525 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.82 (s, 1H), 7.44 (d, J = 8.5 Hz), 7.34 (d, J = 8.5 Hz,1H), 3.96 (s, 3H), 2.46 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.1, 147.9, 140.2, 133.8, 130.4, 128.4, 124.9, 62.0, 21.0, 15.9; MS (EI, 70 eV) m/z = 208 (43) [M^+], 163 (51); HRMS (EI) for $C_{10}H_{12}N_2O_3$ calcd 208.0848, found 208.0845.

*(E)-1-(6-Methyl-2-nitrophenyl)ethanone O-methyl oxime (**6c**):*



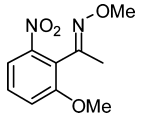
yellow oil (46.8 mg, 75%); IR (neat) ν = 1531 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 3.93 (s, 3H), 2.37 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.9, 148.8, 139.1, 135.2, 132.2, 128.8, 122.0, 61.9, 19.4, 16.4; MS (EI, 70 eV) m/z = 208 (68) [M^+], 163 (40); HRMS (EI) for $C_{10}H_{12}N_2O_3$ calcd 208.0848, found 208.0850.

*(E)-1-(4-Methoxy-2-nitrophenyl)ethanone O-methyl oxime (**6d**):*



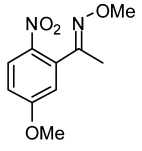
white solid (48.4 mg, 72%); mp 54−55 °C; IR (KBr) ν = 1534 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.50 (d, J = 2.5 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 7.15 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz,1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.1, 153.8, 148.7, 131.5, 125.5, 119.3, 109.5, 61.9, 56.0, 16.0; MS (EI, 70 eV) m/z = 224 (88) [M^+], 179 (61); HRMS (EI) for $C_{10}H_{12}N_2O_4$ calcd 224.0797, found 224.0792.

*(E)-1-(6-Methoxy-2-nitrophenyl)ethanone O-methyl oxime (**6e**):*



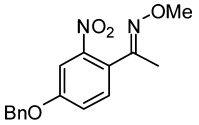
white solid (57.2 mg, 85%); mp 74−75 °C; IR (KBr) ν = 1525 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.52 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 7.45 (t, J = 8.5 Hz, 1H), 7.16 (dd, J_1 = 8.0 Hz, J_2 = 0.5 Hz,1H), 3.895 (s, 3H), 3.893 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.5, 152.2, 149.8, 129.9, 122.0, 115.9, 115.3, 61.8, 56.4, 16.0; MS (EI, 70 eV) m/z = 224 (31) [M^+], 178 (100); HRMS (EI) for $C_{10}H_{12}N_2O_4$ calcd 224.0797, found 224.0795.

*(E)-1-(5-Methoxy-2-nitrophenyl)ethanone O-methyl oxime (**6f**):*



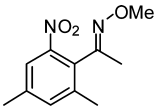
white solid (47.8 mg, 71%); mp 58−59 °C; IR (KBr) ν = 1508 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.13 (d, J = 9.5 Hz, 1H), 6.97 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1H), 6.87 (d, J = 3.0 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 155.2, 140.5, 136.1, 127.4, 115.8, 114.4, 62.0, 56.1, 16.3; MS (EI, 70 eV) m/z = 224 (91) [M^+], 179 (76); HRMS (EI) for $C_{10}H_{12}N_2O_4$ calcd 224.0797, found 224.0801.

*(E)-1-(4-Benzyloxy-2-nitrophenyl)ethanone O-methyl oxime (**6g**):*



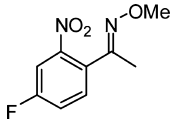
yellow oil (45.0 mg, 50%); IR (neat) ν = 1538 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, J = 2.5 Hz, 1H), 7.44−7.36 (m, 6H), 7.21 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 5.16 (s, 2H), 3.96 (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2 154.0, 148.7, 135.6, 131.6, 128.8, 128.5, 127.5, 125.8, 120.1, 110.7, 70.8, 61.9, 16.0; MS (EI, 70 eV) m/z = 300 (13) [M^+], 91(100); HRMS (EI) for $C_{16}H_{16}N_2O_4$ calcd 300.1110, found 300.1113.

*(E)-1-(4,6-Dimethyl- 2-nitrophenyl)ethanone O-methyl oxime (**6h**):*



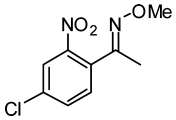
brown oil (48.0 mg, 72%); IR (neat) ν = 1532 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.68 (s, 1H), 7.31 (s, 1H), 3.92 (s, 3H), 2.41 (s, 3H), 2.32 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.0, 148.8, 139.2, 138.7, 135.9, 129.6, 122.4, 61.8, 20.9, 19.4, 16.5; MS (EI, 70 eV) m/z = 222 (57) [M^+], 177 (42); HRMS (EI) for $C_{11}H_{14}N_2O_3$ calcd 222.1004, found 222.1008

*(E)-1-(4-Fluoro-2-nitrophenyl)ethanone O-methyl oxime (**6i**):*



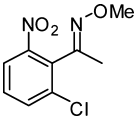
brown oil (52.8 mg, 83%); IR (neat) ν = 1540 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.73 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H), 7.47 (dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz, 1H), 7.39−7.35 (m, 1H), 3.97 (s, 3H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.0 (d, $^1J_{F-C}$ = 251.3 Hz), 153.2, 148.7, 132.3 (d, $^3J_{F-C}$ = 8.8 Hz), 129.4 (d, $^4J_{F-C}$ = 3.8 Hz), 120.4 (d, $^2J_{F-C}$ = 21.3 Hz), 112.3 (d, $^2J_{F-C}$ = 26.3 Hz), 62.1, 15.9; MS (EI, 70 eV) m/z = 212 (48) [M^+], 167 (59); HRMS (EI) for $C_9H_9FN_2O_3$ calcd 212.0597, found 212.0591.

*(E)-1-(4-Chloro-2-nitrophenyl)ethanone O-methyl oxime (**6j**):*



pale yellow oil (56.2 mg, 82%); IR (neat) ν = 1536 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, J = 1.5 Hz, 1H), 7.61 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 3.96 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 148.5, 135.4, 133.2, 131.7, 131.5, 124.8, 62.2, 15.7; MS (EI, 70 eV) m/z = 228 (43) [M^+], 183 (71); HRMS (EI) for $C_9H_9ClN_2O_3$ calcd 228.0302, found 228.0305.

*(E)-1-(6-Chloro-2-nitrophenyl)ethanone O-methyl oxime (**6k**):*

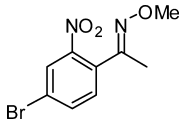


white solid (58.3 mg, 85%); mp 57−58 °C; IR (KBr) ν = 1534 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.91(dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.69 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 3.93 (s, 3H), 2.28 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.4, 150.0, 135.6, 134.3, 131.9, 129.8, 122.7, 62.2, 16.1; MS (EI, 70 eV) m/z = 228

dx.doi.org/10.1021/jo400594j | J. Org. Chem. 2013, 78, 5932−5948

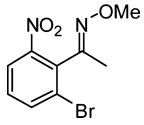
(28) [M$^+$], 183 (75); HRMS (EI) for $C_9H_9ClN_2O_3$ calcd 228.0302, found 228.0307.

*(E)-1-(4-Bromo-2-nitrophenyl)ethanone O-methyl oxime (**6l**):*



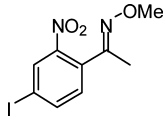
pale yellow solid (63.1 mg, 77%); mp 77−78 °C; IR (KBr) ν = 1534 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (d, J = 2.0 Hz, 1H), 7.77 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 3.97 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 148.5, 136.1, 131.94, 131.88, 127.6, 122.8, 62.2, 15.7; MS (EI, 70 eV) m/z = 272 (19) [M$^+$], 227 (41); HRMS (EI) for $C_9H_9BrN_2O_3$ calcd 271.9797, found 271.9807.

*(E)-1-(6-Bromo-2-nitrophenyl)ethanone O-methyl oxime (**6m**):*



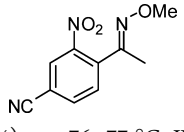
yellow solid (34.4 mg, 42%); mp 62−63 °C; IR (KBr) ν = 1534 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 3.93 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.7, 150.0, 137.5, 133.6, 130.0, 124.8, 123.3, 62.1, 16.2; MS (EI, 70 eV) m/z = 272 (12) [M$^+$], 212 (56); HRMS (EI) for $C_9H_9BrN_2O_3$ calcd 271.9797, found 271.9802.

*(E)-1-(4-Iodo-2-nitrophenyl)ethanone O-methyl oxime (**6n**):*



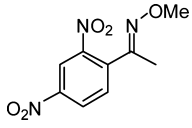
white solid (76.8 mg, 80%); mp 72−73 °C; IR (KBr) ν = 1524 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 (d, J = 2.0 Hz, 1H), 7.96 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.20 (d, J = 3.0 Hz, 1H), 3.96 (s, 3H), 2.14 (s, 3H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.1, 148.3, 142.1, 133.2, 132.5, 131.8, 93.3, 62.2, 15.6; MS (EI, 70 eV) m/z = 320 (100) [M$^+$], 275 (71); HRMS (EI) for $C_9H_9IN_2O_3$ calcd 319.9658, found 319.9654.

*(E)-1-(4-Cyano-2-nitrophenyl)ethanone O-methyl oxime (**6o**):*



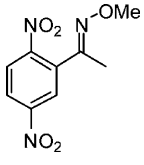
white solid (59.2 mg, 90%); mp 76−77 °C; IR (KBr) ν = 1533 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (d, J = 1.5 Hz, 1H), 7.91 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 3.98 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.1, 148.4, 137.0, 136.0, 131.8, 128.1, 116.2, 113.7, 62.5, 15.; MS (EI, 70 eV) m/z = 219 (14) [M$^+$], 174 (25); HRMS (EI) for $C_{10}H_9N_3O_3$ calcd 219.0644, found 219.0638.

*(E)-1-(2,4-Binitrophenyl)ethanone O-methyl oxime (**6p**):*



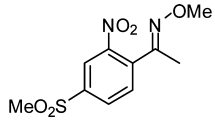
white solid (51.7 mg, 72%); mp 65−66 °C; IR (KBr) ν = 1534 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.80 (d, J = 2.0 Hz, 1H), 8.47 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 4.00 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.9, 148.4, 147.7, 138.4, 132.0, 127.1, 120.0, 62.5, 15.4; MS (EI, 70 eV) m/z = 239 (14) [M$^+$], 194 (31); HRMS (EI) for $C_9H_9N_3O_5$ calcd 239.0542, found 239.0544.

*(E)-1-(5-Nitro-2-nitrophenyl)ethanone O-methyl oxime (**6q**):*



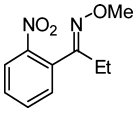
white solid (58.1 mg, 81%); mp 102−104 °C; IR (KBr) ν = 1534 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.37−8.35 (m, 2H), 8.07 (d, J = 9.5 Hz, 1H), 4.00 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.42, 151.37, 149.4, 134.3, 125.8, 125.7, 124.4, 62.5, 15.2; MS (EI, 70 eV) m/z = 239 (43) [M$^+$], 194 (76); HRMS (EI) for $C_9H_9N_3O_5$ calcd 239.0542, found 239.0539.

*(E)-1-(4-Methylsulfonyl-2-nitrophenyl)ethanone O-methyl oxime (**6r**):*



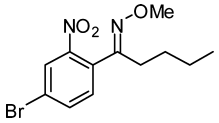
white solid (74.3 mg, 91%); mp 123−124 °C; IR (KBr) ν = 1533 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (d, J = 1.5 Hz, 1H), 8.19 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 3.98 (s, 3H), 3.13 (s, 3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.2, 148.5, 142.0, 137.7, 132.1, 131.3, 123.9, 62.4, 44.3, 15.4; MS (EI, 70 eV) m/z = 272 (42) [M$^+$], 227 (89); HRMS (EI) for $C_{10}H_{12}N_2O_5S$ calcd 272.0467, found 272.0461.

*(E)-1-(2-Nitrophenyl)propionyl O-methyl oxime (**6s**):*



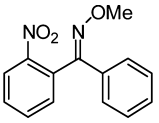
yellow oil (51.8 mg, 83%); IR (neat) ν = 1534 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$,500 MHz) δ 8.05 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 7.67 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 7.64−7.42 (m, 2H), 3.94 (s, 3H), 2.72 (q, J = 7.5 Hz, 2H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.4, 148.2, 133.1, 132.0, 131.1, 129.4, 124.6, 62.0, 22.9, 10.1; MS (EI, 70 eV) m/z = 208 (20) [M$^+$], 163 (12); HRMS (EI) for $C_{10}H_{12}N_2O_3$ calcd 208.0848, found 208.0844.

*(E)-1-(4-Bromo-2-nitrophenyl)valeryl O-methyl oxime (**6t**):*



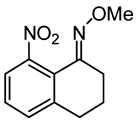
brown oil (64.3 mg, 68%); IR (neat) ν = 1537 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.16 (d, J = 2.0 Hz, 1H), 7.77 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 3.93 (s, 3H), 2.64 (t, J = 7.5 Hz, 2H), 1.40−1.32 (m, 4H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3, 148.7, 136.0, 132.2, 131.2, 127.7, 122.7, 61.2, 29.1, 27.8, 22.9, 13.7; MS (EI, 70 eV) m/z = 315(10) [M$^+$], 270 (70); HRMS (EI) for $C_{12}H_{15}BrN_2O_3$ calcd 314.0266, found 314.0270.

*(E)- (2-Nitrophenyl)phenyl methanone O-methyl oxime (**6u**):*



yellow oil (63.8 mg, 83%); IR (neat) ν = 1530 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.67 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 7.65−7.51 (m, 4H), 7.38−7.37 (m, 2H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.2, 149.2, 132.7, 132.4, 132.2, 131.7, 129.8, 129.72, 129.68, 128.0, 124.5, 62.7; MS (EI, 70 eV) m/z = 256 (94) [M$^+$], 211 (14); HRMS (EI) for $C_{14}H_{12}N_2O_3$ calcd 256.0848, found 256.0843.

*(E)-8-Nitro-3,4-dihydro-1(2H)naphthalenone O-methyl oxime (**6v**):*

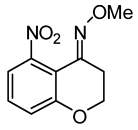


yellow solid (36.3 mg, 55%); mp 73−74 °C; IR (KBr) ν = 1536 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.30 (m, 3H), 3.92 (s, 3H), 2.78−2.75 (m, 4H), 1.90−1.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.8, 149.1, 142.8, 130.6, 128.4, 123.2, 121.7, 62.3, 30.2, 24.2, 20.7;

dx.doi.org/10.1021/jo400594j | J. Org. Chem. 2013, 78, 5932−5948

MS (EI, 70 eV) m/z = 220 (16) [M^+], 159 (100); HRMS (EI) for $C_{11}H_{12}N_2O_3$ calcd 220.0848, found 220.0851.

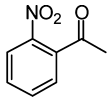
*(E)-5-Nitro-2,3-dihydro-4H-1-benzopyran-4-one O-methyl oxime (**6w**):*



yellow solid (52.0 mg, 78%); mp 121−123 °C; IR (KBr) ν = 1535 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30 (t, J = 8.0 Hz, 1H), 7.06−7.03 (m, 2H), 4.27 (t, J = 6.0 Hz, 2H), 3.93 (s, 3H), 2.95 (t, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.6, 148.5, 144.2, 130.0, 120.3, 116.4, 110.9, 65.3, 62.5, 30.9; MS (EI, 70 eV) m/z = 222 (40) [M^+], 161 (100); HRMS (EI) for $C_{10}H_{10}N_2O_4$ calcd 222.0641, found 222.0648.

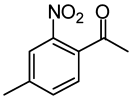
General Procedure for the Synthesis of 2-Nitrated Aryl Ketones. *o*-Nitro aryl ketone *O*-methyl oximes **6** (0.2 mmol), 12 N HCl (1 mL), and CH_2Cl_2 (1 mL) were added to a 25 mL sealed tube. Then the mixture was stirred at 100 °C for 24 h. Upon completion, the reaction mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The solvent was then removed under reduce pressure and the residue was purified by flash column chromatography on silica gel (100−200 mesh) with petroleum ether/EtOAc (3:1, v/v) as the eluent.

*1-(2-Nitrophenyl)ethanone (**7a**):*[49]



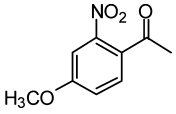
yellow oil (28.1 mg, 85%); IR (neat) ν = 1531 (NO_2), 1706 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.11 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 7.75 (dd, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 7.73−7.44 (m, 2H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.7, 145.8, 138.0, 134.1, 130.6, 127.3, 124.3, 30.1; MS (EI, 70 eV) m/z =165 (1) [M^+], 150 (100); HRMS (EI) for $C_8H_7NO_3$ calcd 165.0426, found 165.0431.

*1-(4-Methyl-2-nitrophenyl)ethanone (**7b**):*[50]



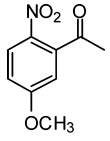
white solid (26.9 mg, 75%); mp 39−40 °C; IR (KBr) ν = 1534 (NO_2), 1687 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.86 (s, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 2.54 (s, 3H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.5, 146.3, 141.9, 134.9, 134.5, 127.5, 124.6, 30.0, 21.1; MS (EI, 70 eV) m/z = 179(2) [M^+], 164(100); HRMS (EI) for $C_9H_9NO_3$ calcd 179.0582, found 179.0585.

*1-(4-Methoxy-2-nitrophenyl)ethanone (**7d**):*[51]



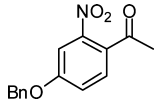
white solid (35.1 mg, 90%); mp 50−51 °C (lit.[51] mp 49−50 °C); IR (KBr) ν = 1539 (NO_2), 1692 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.17 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 3.92 (s, 3H), 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.1, 161.5, 148.3, 129.6, 128.8, 118.9, 109.4, 56.2, 29.5 ; MS (EI, 70 eV) m/z = 195(2) [M^+], 180(100); HRMS (EI) for $C_9H_9NO_4$ calcd 195.0532, found 195.0527.

*1-(5-Methoxy-2-nitrophenyl)ethanone (**7f**):*[51]



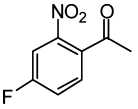
white solid (19.5 mg, 50%); mp 70−71 °C (lit.[51] 69−70 °C); IR (KBr) ν = 1508 (NO_2), 1705 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.16 (d, J = 9.5 Hz, 1H), 7.01 (dd, J_1 = 9.0 Hz, J_2 = 1.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 3.93 (s, 3H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.0, 164.4, 141.3, 138.2, 127.0, 114.9, 111.9, 56.2, 30.3; MS (EI, 70 eV) m/z = 195(38) [M^+], 180(100); HRMS (EI) for $C_9H_9NO_4$ calcd 195.0532, found 195.0528.

*1-(4-Benzyloxy-2-nitrophenyl)ethanone (**7g**):*



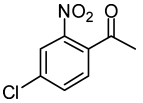
white solid (21.7 mg, 40%); mp 67−68 °C; IR (KBr) ν = 1528 (NO_2), 1680 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.54−7.22 (m, 8H), 5.18 (s, 2H), 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.2, 160.5, 148.1, 135.2, 129.6, 129.2, 128.9, 128.7, 127.6, 119.8, 110.4, 71.0, 29.5; MS (EI, 70 eV) m/z = 271(2) [M^+], 91(100); HRMS (EI) for $C_{15}H_{13}NO_4$ calcd 271.0845, found 271.0849.

*1-(4-Fluoro-2-nitrophenyl)ethanone (**7i**):*



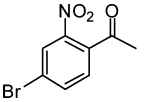
yellow oil (26.0 mg, 71%); IR (neat) ν = 1531 (NO_2), 1706 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.77 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 1H), 7.52−7.42 (m, 2H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.2, 162.7 (d, $^1J_{F-C}$ = 255.0 Hz), 147.3, 133.7 (d, $^4J_{F-C}$ = 3.8 Hz), 129.6 (d, $^3J_{F-C}$ = 8.8 Hz), 121.1 (d, $^2J_{F-C}$ = 21.3 Hz), 112.2 (d, $^2J_{F-C}$ = 26.3 Hz), 29.9; MS (EI, 70 eV) m/z =183(1) [M^+], 168(100); HRMS (EI) for $C_8H_6FNO_3$ calcd 183.0332, found 183.0337.

*1-(4-Chloro-2-nitrophenyl)ethanone (**7j**):*[52]



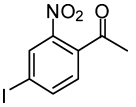
white solid (30.7 mg, 77%); mp 56−57 °C (lit.[52] mp 55−56 °C); IR (KBr) ν = 1537 (NO_2), 1707 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.08 (d, J = 2.0 Hz, 1H), 7.70 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.3, 146.6, 136.8, 135.9, 134.1, 128.7, 124.6, 29.9; MS (EI, 70 eV) m/z = 199 (1) [M^+], 184 (100); HRMS (EI) for $C_8H_6ClNO_3$ calcd 199.0036, found 199.0044.

*1-(4-Bromo-2-nitrophenyl)ethanone (**7l**):*[53]



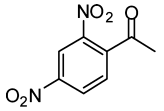
yellow solid (38.1 mg, 78%); mp 67−68 °C (lit.[53] mp 70 °C); IR (KBr) ν = 1533 (NO_2), 1706 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.23 (d, J = 2.0 Hz, 1H), 7.86 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.4, 146.5, 137.1, 136.3, 128.8, 127.4, 124.3, 28.9; MS (EI, 70 eV) m/z = 243 (2) [M^+], 228 (100); HRMS (EI) for $C_8H_6BrNO_3$ calcd 242.9531, found 242.9527.

*1-(4-Iodo-2-nitrophenyl)ethanone (**7n**):*[53]



white solid (23.3 mg, 40%); mp 37−38 °C; IR (KBr) ν = 1523 (NO_2), 1689 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.41 (d, J = 1.5 Hz, 1H), 8.06 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.6, 146.2, 143.0, 136.9, 133.1, 128.7, 95.0, 29.9; MS (EI, 70 eV) m/z = 291(2) [M^+], 176(100); HRMS (EI) for $C_8H_6INO_3$ calcd 290.9392, found 290.9387.

*1-(4-Nitro-2-nitrophenyl)ethanone (**7p**):*[54]

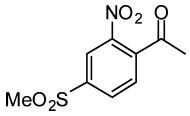


white solid (17.7 mg, 42%); mp 46−47 °C (lit.[54] mp 41−42 °C); IR (KBr) ν = 1535 (NO_2), 1717 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$,

dx.doi.org/10.1021/jo400594j | J. Org. Chem. 2013, 78, 5932−5948

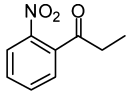
500 MHz) δ 8.97 (d, J = 2.0 Hz, 1H), 8.59 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.6, 148.4, 146.0, 142.9, 128.8, 128.7, 120.1, 30.1; MS (EI, 70 eV) m/z = 210(2) [M^+], 195(100); HRMS (EI) for $C_8H_6N_2O_5$ calcd 210.0277, found 210.0284.

*1-(4-Methylsulfonyl-2-nitrophenyl)ethanone (**7r**):*



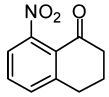
white solid (42.8 mg, 88%); mp 149−150 °C; IR (KBr) ν = 1536 (NO_2), 1708 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.70 (d, J = 1.5 Hz, 1H), 8.31 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 3.16 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.1, 145.9, 143.3, 142.5, 133.0, 128.8, 124.0, 44.3, 30.1; MS (EI, 70 eV) m/z = 243(2) [M^+], 228(100); HRMS (EI) for $C_9H_9NO_5S$ calcd 243.0201, found 243.0204.

*1-(2-Nitrophenyl)propanone (**7s**):*



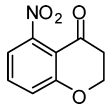
yellow oil (35.1 mg, 98%); IR (neat) ν = 1529 (NO_2), 1706 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.75−7.72 (m, 1H), 7.63−7.59 (m, 1H), 7.39 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 2.81 (q, J = 7.5 Hz, 2H), 1.28 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.2, 145.7, 138.3, 134.2, 130.3, 127.2, 124.4, 36.4, 8.2; MS (EI, 70 eV) m/z = 179(2) [M^+], 150(100); HRMS (EI) for $C_9H_9NO_3$ calcd 179.0582, found 179.0584.

*8-Nitro-3,4-dihydro-1(2H)naphthalenone (**7v**):*[55]



yellow solid (36.3 mg, 95%); mp 150−151 °C (lit.[55] mp 147−150 °C); IR (KBr) ν = 1540 (NO_2), 1688 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 3.04 (t, J = 6.0 Hz, 2H), 2.73 (t, J = 6.5 Hz, 2H), 2.22−2.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.4, 149.9, 146.5, 133.2, 131.4, 124.7, 121.3, 39.0, 29.7, 22.6; MS (EI, 70 eV) m/z = 191(24) [M^+], 147 (31); HRMS (EI) for $C_{10}H_9NO_3$ calcd 191.0582, found 191.0587.

*5-Nitro-2,3-dihydro-4H-1-benzopyran-4-one (**7w**):*



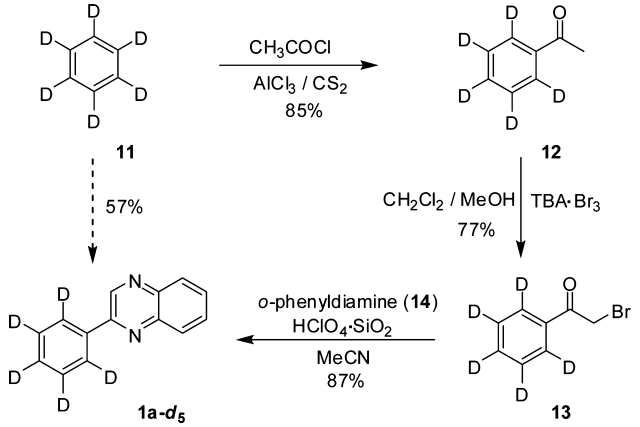
white solid (30.1 mg, 78%); mp 149−150 °C; IR (KBr) ν = 1539 (NO_2), 1693 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (dd, J_1 = 8.5 Hz, J_2 = 3.0 Hz, 1H), 7.18 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 7.06 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 4.63 (t, J = 6.5 Hz, 2H), 2.89 (t, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.5, 162.2, 149.3, 135.3, 121.2, 115.7, 113.0, 67.2, 37.6; MS (EI, 70 eV) m/z = 193(50) [M^+], 165(100); HRMS (EI) for $C_9H_7NO_4$ calcd 193.0375, found 193.0379.

Mechanistic Studies. *Nitration of 2-phenylpyridine (**3a**) Catalyzed by Complex **8**.* Complex **8** was prepared according to the literature procedure.[27] The analytical data were in accordance with the reported ones.[27]

The procedure for using **8** as a catalyst for nitration of **3a**: **3a** (46.6 mg, 0.3 mmol), **8** (9.6 mg, 0.015 mmol), $AgNO_2$ (92.3 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), phenanthrene (21.4 mg, 0.12 mmol, internal standard), and anhydrous DCE (3.5 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 130 °C for 48 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. Sample was taken for GC analysis, and 67% yield of **4a** was determined.

*Nitration of Acetophenone O-Methyl Oxime **5a** Catalyzed by Complex **10**.* Complex **10** was prepared according to the literature procedure.[28] The procedure for using **10** as a catalyst for the nitration of **5a**: **5a** (44.8 mg, 0.3 mmol), **10** (17.7 mg, 0.03 mmol), $AgNO_2$ (92.3 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), phenanthrene (21.4 mg, 0.12 mmol, internal standard), and anhydrous DCE (3.5 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 110 °C for 48 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. A sample was taken for GC analysis, and 75% yield of **6a** was determined.

*Preparation of 2-Phenyl-d_5-quinoxaline (**1a-d_5**).*



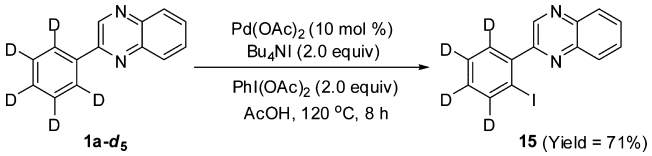
Compound **12** was synthesized via a modified procedure according to a previous report.[56] Benzene-d_6 (0.6 mL, 6.4 mmol), $AlCl_3$ (1.07 g, 8.0 mmol), and anhydrous CS_2 (1.5 mL) were added to a 10-mL flask under argon atmosphere. To the mixture was dropwise added a solution of acetyl chloride (0.628 g, 8.05 mmol) in anhydrous CS_2 (2.5 mL) at 5 °C. The resulting mixture was allowed to warm to room temperature and stirred for 5 h. Then the mixture was heated to reflux for 3 h. After being cooled to room temperature, the resulting mixture was poured out to ice water and extracted with CH_2Cl_2 (3 × 30 mL). The orgnic layer was washed with saturated aqueous Na_2CO_3 (20 mL) and brine (20 mL) and then dried over Na_2SO_4. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100−200 mesh) using petroleum ether−EtOAc (15:1) as eluent to give **12** (0.68 g, 85%) as a colorless oil: MS (EI, 70 eV) m/z = 125 (27) [M^+].

Compound **13** was synthesized according to the literature procedure.[57] The obtained **12** (0.375 g, 3.0 mmol), CH_2Cl_2 (15 mL), CH_3OH (6 mL), and TBA·Br_3[57] were added to a 50-mL flask. The mixture was stirred at 30 °C for 2 h until it turned light yellow. Then the solvent was removed under vacuum, and the residue was diuted with water (10 mL) and extracted with ether (3 × 20 mL). The orgnic layer was then dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography on silica gel (100−200 mesh) using petroleum ether-EtOAc (10:1) as eluent to give **13** (0.47 g, 77%): MS (EI, 70 eV) m/z = 203 (2) [M^+], 205 (2) [M^++2].

Compound **1a-d_5** was synthesized according to the literature procedure.[37] To a suspension of **13** (0.41 g, 2.0 mmol) and $HClO_4$·SiO_2[58] (0.2 g) in CH_3CN (10 mL) was dropwise added a solution of *o*-phenyldiamine **14** (0.26 g, 2.4 mmol) in CH_3CN (2 mL), and the mixture was stirred at room temperature for 5 h. After completion (monitored by TLC), the reaction mixture was filtered and washed with CH_2Cl_2 (20 mL). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (100−200 mesh) using petroleum ether−EtOAc (6:1, V/V) as eluent to obtain pure 2-phenyl-d_5-quinoxaline (**1a-d_5**) as a yellow solid (0.37 g, 87%): mp 151−152 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.33 (s, 1H), 8.16 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 8.12 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 7.80−7.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.8, 143.3, 142.3, 141.6, 136.6, 130.2, 130.0−129.7 (m, 1C), 129.6, 129.5, 129.1, 128.9−128.4 (m, 2C), 127.4−126.9 (m, 2C); MS (EI, 70 eV) m/z = 211 (100) [M^+], 184 (33); HRMS (EI) for $C_{14}H_5D_5N_2$ calcd 211.1158, found 211.1165.

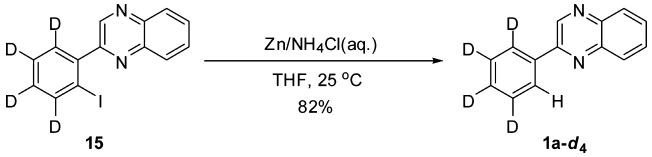
dx.doi.org/10.1021/jo400594j | J. Org. Chem. 2013, 78, 5932−5948

*Preparation of 2-(2-Iodophenyl-d_4)quinoxaline (**15**).*



Compound **15** was synthesized via a modified procedure according to previous report.[59] To a 25-mL flask were added 2-phenyl-d_5-quinoxaline (**1a-d_5**) (211.0 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), Bu_4NI (738.0 mg, 2.0 mmol), $PhI(OAc)_2$ (644.0 mg, 2.0 mmol), and AcOH (6.0 mL). The mixture was stirred and heated to reflux for 8 h (monitored by TLC). Upon completion, it was treated with saturated aqueous Na_2CO_3 (10 mL) and CH_2Cl_2 (20 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined orgnic layer was then dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (100−200 mesh) using petroleum ether−EtOAc (4:1, v/v) as eluent to give pure **15** (238.0 mg, 71%) as pale yellow solid: R_f = 0.56 (cyclohexane-EtOAc, 3:1); mp 153−154 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.14 (s, 1H), 8.19−8.17 (m, 2H), 7.85−7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.7, 146.0, 142.1, 141.8, 141.5, 139.9−139.3 (m, 1C), 130.8−130.5 (m, 2C), 130.4, 130.2, 129.6, 129.3, 128.5−128.0 (m, 1C), 96.3; MS (EI, 70 eV) m/z = 336 (100) [M^+], 209 (81); HRMS (EI) for $C_{14}H_5D_4IN_2$ calcd 336.0062, found 336.0056.

*Preparation of 2-Phenyl-1,2,3,4-d_4-quinoxaline (**1a-d_4**).*



Compound **1a-d_4** was synthesized according to the literature procedure.[60] A solution of 2-(2-iodophenyl-d_4)-quinoxaline (**15**) (0.22 g, 0.65 mmol), zinc powder (0.169 g, 2.6 mmol) in saturated aqueous NH_4Cl (3.0 mL), and THF (1.5 mL) was stirred at 25 °C overnight. After completion (monitored by TLC), THF was removed in vacuo, and the residue was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were concentrated in vacuo. The residue was purified by column chromatography on silica gel (100−200 mesh) using petroleum ether−EtOAc (4:1, v/v) as eluent to give desired product **1a-d_4** (111.9 mg, 82%) as a yellow solid: R_f = 0.51 (cyclohexane-EtOAc, 3:1); mp 148−149 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.34 (s, 1H), 8.21 (s, 1H), 8.17 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 8.13 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.81−7.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.8, 143.3, 142.3, 141.6, 136.7, 130.2, 130.0−129.7 (m, 1C), 129.6, 129.5, 129.1, 129.0−128.4 (m, 2C), 127.4, 127.5−126.9 (m, 1C); MS (EI, 70 eV) m/z = 210 (100) [M^+], 183 (39); HRMS (EI) for $C_{14}H_6D_4N_2$ calcd 210.1095, found 210.1096.

*Determination of Intramolecular Kinetic Isotope Effect of **1a-d_4**.* To a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal were sequentially added 2-phenyl-1,2,3,4-*d4*-quinoxaline **1a-d_4** (63.0 mg, 0.3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $AgNO_2$ (92.4 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), and anhydrous DCE (3.5 mL). Then the flask was sealed and heated to 130 °C for 48 h. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100−200 mesh) using petroleum ether−EtOAc (4:1, V/V) as eluent to give the mixture of **2a-d_3** and **2a-d_4**. Based on the ^{1}H NMR spectral analyses, the kinetic isotope effect is calculated to be k_H/k_D = 5.3 ± 0.2.

*Determination of Intermolecular Kinetic Isotope Effect between **1a** and **1a-d_5**.* To a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal were sequentially added 2-phenyl-d_5-quinoxaline (**1a-d_5**) (31.7 mg, 0.15 mmol), 2-phenylquinoxaline (**1a**) (30.1 mg, 0.15 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $AgNO_2$ (92.4 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), and anhydrous DCE (3.5 mL). The flask was sealed and heated to 130 °C for 24 h. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100−200 mesh) using petroleum ether−EtOAc (4:1, V/V) as eluent. A mixture of **2a-d_4** and **2a** was determined on the basis of ^{1}H NMR spectral analysis. Based on the integrations related to different hydrogen resonances, the kinetic isotope effect is calculated to be k_H/k_D = 4.6 ± 0.2.

*Determination of Intermolecular Kinetic Isotope Effect between **5a** and **5a-d_5**.* Compound **5a-d_5** was prepared according to the reported procedure.[61] Procedure for determination of intermolecular isotope effect: To a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal were sequentially added acetophenone *O*-methyl oxime **5a** (22.4 mg, 0.15 mmol), **5a-d_5** (23.1 mg, 0.15 mmol), $Pd(OCOCF_3)_2$ (10.0 mg, 0.03 mmol), $AgNO_2$ (92.4 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), and anhydrous DCE (3.5 mL). The flask was sealed and heated to 110 °C for 24 h. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100−200 mesh) using petroleum ether−EtOAc (4:1, V/V) as eluent. A mixture of **6a-d_4** and **6a** was determined on the basis of ^{1}H NMR spectral analyses. Based on the integrations related to different hydrogen resonances, the kinetic isotope effect is calculated to be k_H/k_D = 2.3 ± 0.2.

Effect of Radical Scavenger TEMPO on the Reaction. Compound **1a** (61.9 mg, 0.3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $AgNO_2$ (92.3 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), TEMPO (0.15 or 0.6 mmol), phenanthrene (21.4 mg, 0.12 mmol, internal standard), and anhydrous DCE (3.5 mL) were sequentially added to a 25-mL Schlenk flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the flask was sealed and stirred at 130 °C for 48 h. Upon completion, the resulting mixture was analyzed by GC (14% of **2a**, TEMPO = 0.5 equiv; 0% of **2a**, TEMPO = 2 equiv).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray structural data (CIF) of compound **2c**, charts for mechanistic studies, as well as copies of ^{1}H NMR and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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