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Copper-Mediated Chelation-Assisted *Ortho* Nitration of (Hetero)arenes

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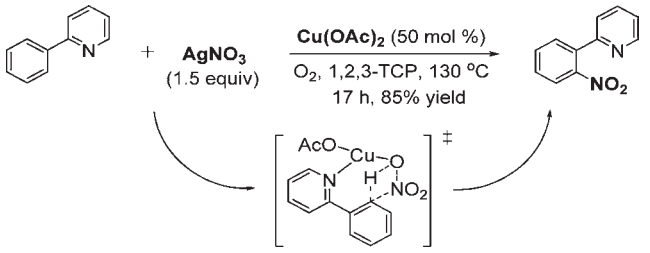
ABSTRACT



A novel copper-mediated chelation-assisted *ortho* C−H nitration of (hetero)arenes has been developed for the first time, which used dioxygen as terminal oxidant and 1,2,3-TCP as solvent, leading to the synthesis of nitroaromatics with excellent regioselectivity and in good yields. Mechanistic investigations indicate a mechanism involving a four-centered transition state, with simultaneous cleavage of an *ortho* C−H bond and a N−O bond of the nitrate anion on the 2-arylpyridine-coordinated copper(II) complex.

Regioselective nitration of the aromatics represents a long-term challenge.[1] Even though the regioselective issue encountered in the traditional electrophilic aromatic substitution has been evaded by the strategic transformation of the functional groups into the nitro group,[2] the development of new strategy for the direct C−H nitration is still highly desirable. Recently, the chelation-assisted C−H bond functionalization processes, in particular using 2-pyridyl as a directing group, have received substantial attention, and currently most functional groups can be introduced onto specific positions of arenes by this method.[3] However, to our knowledge, only one procedure, reported by Liu and co-workers, describes the first palladium-catalyzed chelation-assisted *ortho* nitration of aromatic C−H bonds aided by a Lewis base group (Figure 1, path a). Unfortunately, this protocol suffers from a number of limitations, most notably of which is the lack of selectivity

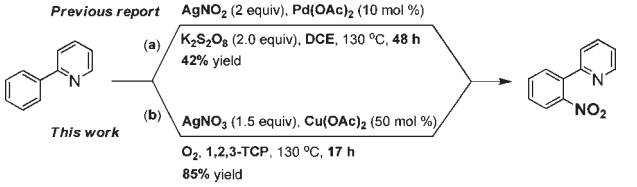


Figure 1. Chelation-assisted *ortho* C−H nitration of arenes.

for the unsymmetrical aromatic rings and the use of expensive palladium salt as catalyst.[4] In a seminal work, Yu and co-workers reported Cu(II)-mediated *ortho* functionalizations of 2-arylpyridines using various nucleophiles, but again their protocol did not account for nitration.[5] As part of our continuing interest in the development of copper-catalyzed C−H activation/functionalization,[6] herein we report the

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(1) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; VCH: Weinheim, 1989.
(2) (a) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898. (b) Prakash, G. K. S.; Mathew, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1726 and references therein.
(3) For a leading review on "chelation-directed C−H functionalization", see: Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
(4) Liu, Y.-K.; Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Chem.—Eur. J.* **2010**, *16*, 13590.
(5) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.
(6) Xiong, T.; Li, Y.; Bi, X.; Lv, Y.; Zhang, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 7140.

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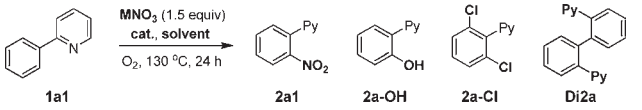
first copper-mediated directed *ortho* C−H nitration of (hetero)arenes using 1,2,3-trichloropropane (1,2,3-TCP) as solvent and dioxygen as terminal oxidant (Figure 1, path b). One of the novel findings is the necessity of 1,2,3-TCP as solvent to achieve high conversion in the nitration. In this paper, a mechanism involving a four-centered transition state based on results of the kinetic isotope effect (KIE) studies and designed experiments is proposed to interpret the *ortho* regioselectivity and the source of nitro group. This finding represents a new approach to regioselective aromatic nitration.

Initially, a survey on the reaction parameters, including catalyst, nitrating agent, and solvent, was conducted under dioxygen atmosphere at fixed temperature (130 °C) and reaction time (24 h), using the nitration of 2-phenylpyridine **1a1** as a model (Table 1). Metal catalysts were first screened using $AgNO_3$ as a nitrating agent and 1,2,3-TCP as solvent. With $Cu(OAc)_2$ as catalyst, at least 50 mol % $Cu(OAc)_2$ was found to be essential for an efficient conversion affording **2a1** in 85% yield within 17 h (entries 1−3). Also worthy of note is the cuprous salt CuOAc, which, like $Cu(OAc)_2$, is similarly effective, albeit with the need for slightly longer reaction time (24 h) (entry 4). As a control, no reaction occurred without $Cu(OAc)_2$ under otherwise identical conditions (entry 5). Instead of $Cu(OAc)_2$, other cupric salts such as $Cu(OTf)_2$ and CuF_2 resulted in only a slight conversion with the recovery of a bulk of substrate **1a1** (entries 6 and 7), thus asserting the importance of the acetate ion. Under similar conditions as for $Cu(OAc)_2$, $Pd(OAc)_2$ (10 mol %) also demonstrated comparable efficiency but with a lower conversion (entry 8). Other metal salts such as $Mn(OAc)_3$ (a single-electron oxidant) and $Sc(OTf)_3$ (a strong Lewis acid) proved ineffective for this reaction (entries 9 and 10). Furthermore, investigations on the nitrating agents disclosed that except for $AgNO_2$, which produced **2a1** with almost identical efficiency as $AgNO_3$, no reaction occurred with $Fe(NO_3)_3 \cdot 9H_2O$ (entries 11, 12). With $NaNO_3$, an *ortho* hydroxylated **2a-OH** was obtained as the major product[7] (entry 13). Eventually, different solvents were screened, and among them 1,2,3-TCP exhibited unmatched efficacy for the nitration. The halogenated alkanes with high boiling point such as 1,3-dichloropropane (DCP) gave **2a-Cl** as the major product along with a trace amount of **2a1** (entry 14). In addition, 1,4-dioxane, DMSO, and pentanediol all proved to be unsuitable solvents (entries 15−17). The importance of dioxygen for a clean and single conversion was confirmed, since a mixture of **1a1**, **2a1**, and **2a-OH** was obtained in nearly equal amount under nitrogen atmosphere (entry 18). Consequently, the reaction conditions in entry 3 were endorsed as optimal and subjected to further investigations. Obviously, 1,2,3-TCP played a crucial role in the reaction.[8]

Table 1. Condition Screening[a]



1a1 2a1 2a-OH 2a-Cl Di2a

entry	cat.	amt (mol %)	MNO_3	solvent	yield[b] (%) of **2a1**
1[c]	$Cu(OAc)_2$	10	$AgNO_3$	1,2,3-TCP	7.5 (92.5)
2[c]	$Cu(OAc)_2$	30	$AgNO_3$	1,2,3-TCP	45 (55)
3[d]	$Cu(OAc)_2$	50	$AgNO_3$	1,2,3-TCP	85
4	CuOAc	50	$AgNO_3$	1,2,3-TCP	67
5			$AgNO_3$	1,2,3-TCP	0
6[c]	$Cu(OTf)_2$	50	$AgNO_3$	1,2,3-TCP	18 (82)
7[c]	CuF_2	50	$AgNO_3$	1,2,3-TCP	17 (83)
8[c]	$Pd(OAc)_2$	10	$AgNO_3$	1,2,3-TCP	23 (77)
9	$Mn(OAc)_3$	50	$AgNO_3$	1,2,3-TCP	0
10	$Sc(OTf)_3$	50	$AgNO_3$	1,2,3-TCP	0
11	$Cu(OAc)_2$	50	$AgNO_2$	1,2,3-TCP	75
12[e]	$Cu(OAc)_2$	50	$Fe(NO_3)_3$	1,2,3-TCP	0
13	$Cu(OAc)_2$	50	$NaNO_3$	1,2,3-TCP	**2a**−**OH** 62
14[g]	$Cu(OAc)_2$	50	$AgNO_3$	DCP[f]	**2a-Cl** 78
15	$Cu(OAc)_2$	50	$AgNO_3$	1,4-dioxane	0
16	$Cu(OAc)_2$	50	$AgNO_3$	DMSO	trace
17	$Cu(OAc)_2$	50	$AgNO_3$	pentanediol	**Di2a** 15
18[h]	$Cu(OAc)_2$	50	$AgNO_3$	1,2,3-TCP	1:1:1[i]

[a] Reactions were performed on 1.0 mmol scale, at 0.5 M (with respect to 2-phenylpyridine **1a1**). [b] Isolated yields. [c] Ratio of **2a1** to the recovered **1a1** (in parentheses) was determined by ^1H NMR analysis of crude product. [d] Reaction was complete in 17 h. [e] $Fe(NO_3)_3 \cdot 9H_2O$ was used. [f] 1,3-Dichloropropane. [g] Trace amount of **2a1** was detected by TLC. [h] Under nitrogen atmosphere. [i] The ratio of **2a1**/**2a-OH**/**1a1** was determined by ^1H NMR analysis of crude product.

As summarized in Scheme 1, substrates **1b** with different directing groups were subjected to the optimal conditions (Table 1, entry 3). The chelating group appeared to be essential for the nitration because no reaction was observed for 3- and 4-phenylpyridine (**2b1** and **2b2**). Clearly, a suitable directing group was necessary to achieve both high reaction efficiency and high yields for *ortho* C−H nitration of arenes. For instance, other common directing groups, including pyrimidine, thiazole, and pyrazole, could be equally employed to direct *ortho* C−H nitration, but relatively lower yields and longer reaction times are expected in comparison with the 2-pyridyl group (**2b3**−**2b5**). In addition, *o*-methyloxime completely failed as a directing group (**2b6**). These results are consistent with the capability of coordination of these directing groups.[9] Using quinoline as the directing group, it was found that benzo[*h*]quinoline exclusively gave the desired product **2b7** in 75% yield, whereas 8-methylquinoline was unreactive (**2b8**).

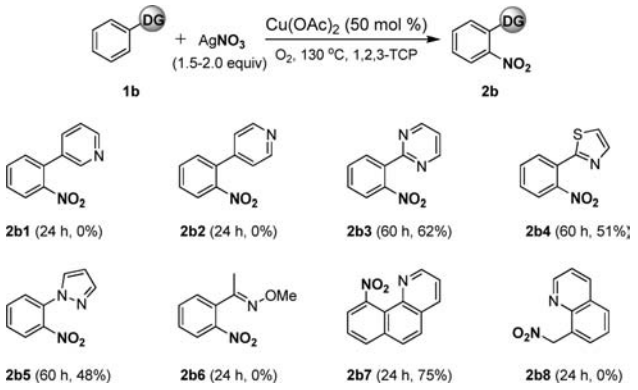
With a reliable protocol in hand, the scope of the direct *ortho* nitration of 2-(hetero)arylpyridines **1a** was investigated (Table 2). Under the optimal conditions (Table 1, entry 3), a variety of 2-(2-nitroaryl)pyridines, bearing either an electron-donating or electron-withdrawing group at the 2-position (**2a2**−**2a5**), 4-position (**2a6**−**2a13**), or 3-position

(7) For *ortho*-hydroxylation of 2-arylpyridines, see: Kim, S. H.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 5863.

(8) 1,2,3-TCP may act as an oxidant or proton donor like other chlorinated alkanes: (a) Jin, L.; Xin, J.; Huang, Z.; He, J.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 9607. (b) Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 7672.

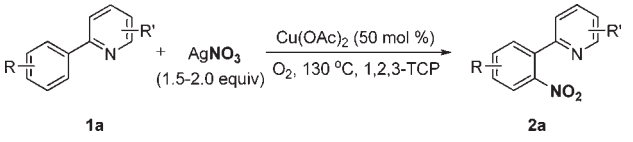
(9) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285.

Scheme 1. C−H Bond Nitration with Varied Directing Groups[a,b]

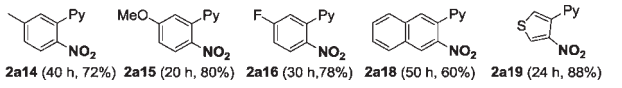


[a] Reactions were performed on 1.0 mmol scale, at 0.5 M. [b] Isolated yields.

Table 2. Synthesis of Nitroaromatics **2a**[a,b]



entry	R	R'	time (h)	**2a**	yield (%)[b]
1	2-Me	H	36	**2a2**	63
2	2-BnO	H	12	**2a3**	87
3	2-F	H	15	**2a4**	82
4	2-Br	H	48	**2a5**	47
5	4-Me	H	20	**2a6**	88
6	4-MeO	H	13	**2a7**	81
7	4-F	H	17	**2a8**	86
8	4-Ph	H	17	**2a9**	80
9	4-MeS	H	30	**2a10**	72
10	4-CF_3	H	60	**2a11**	43
11	4-CN	H	60	**2a12**	39
12	4-BnO	H	28	**2a13**	71
13	2,4-diMe	H	48	**2a17**	46
14	2-thienyl	H	48	**2a20**	84
15	H	3-Me	48	**2a21**	75



[a] Reactions were performed on 1.0 mmol scale, at 0.5 M (with respect to 2-(hetero)arylpyridines). [b] Isolated yields.

(**2a14**−**2a16**) of the phenyl ring, were prepared in good to high yields. Clearly, the electronic nature of the R group of **1a** has a significant influence on the nitration from the observation that the reaction rate was accelerated by an electron-donating group on the phenyl ring. Furthermore, the efficiency of the reaction was confirmed by the successful nitration of disubstituted, fused, and heteroaromatic rings (**2a17**−**2a20**). The longer reaction time needed for **2a21** as opposed to **2a1** might be due to the steric hindrance of the 3-methyl group on pyridyl ring. It is also noteworthy that the regioselective formation of nitrated products **2a14**−**2a16**, **2a18**, and **2a19** was achieved with unsymmetrical substrates, and the nitration occurred exclusively at the least hindered position. We therefore provide an easy access to various *ortho*-nitrobiaryl compounds with heteroaryl component, such as **2a** and **2b**, under Pd-free conditions.[4]

To unravel the reasons for the directed *ortho* C−H nitration of arenes, we carried out mechanistic investigations and obtained a number of valuable insights (Scheme 2). First, a large kinetic isotope effect (KIE) (K_H/K_D = 6.5 ± 0.5) was observed in an intramolecular competition experiment using deuterated substrate **1a1-*d*** (Scheme 2, eq 1).[10] This result clearly indicated that the *ortho* C−H bond cleavage of 2-phenylpyridine was involved in the rate-determining step of the nitration, thus ruling out the possibility of an electrophilic aromatic substitution (S_EAr) pathway.[11] In addition, the nitration reaction appeared to proceed through a different mechanism from Yu's report because no KIEs were observed in their kinetic isotope labeling experiment.[5] The failure in the nitration of 3-methyl-2-*o*-tolylpyridine **1a22** implied that the proximity of *ortho* C−H of the aromatic ring to the pyridyl-coordinated copper(II) species was necessary for the nitration (Scheme 2, eq 2). A search for the source of nitro group disclosed that nitronium ion could be first excluded as the reacting NO_2 species because no **2a1** was detected using nitronium tetrafluorborate (NO_2BF_4), a typical nitronium salt;[12] instead, a mixture of *meta*- and *para*-nitrated products was obtained in a ratio of about 1 to 1 (Scheme 2, eq 3). Next, a continuous nitrogen dioxide flow was used,[17b] and unexpectedly, **2a-Cl** was exclusively produced in 85% yield (Scheme 2, eq 4). This proved that the free NO_2 dispersed in the reaction mixture could not be the source of nitro group, thus excluding the possible reaction pathway that $AgNO_3$ first decomposed to produce NO_2 free radical which then reacted with the *ortho* C−H of 2-arylpyridines.[4] However, the result that $Cu(NO_3)_2\cdot 3H_2O$ alone acted as an efficient nitrating agent provided an important clue to the reaction mechanism because the in situ decomposition of coordinated $CuNO_3X$ (X may be nitrate ion or other anions) could be the pathway producing the reacting NO_2 species and then initiated the *ortho* C−H nitration (Scheme 2, eq 5).[13] This mechanistic speculation was further supported by the applicability of HNO_3 in the nitration reaction (Scheme 2, eq 6), since anion exchange could occur between $Cu(OAc)_2$ and HNO_3, leading to the incorporation

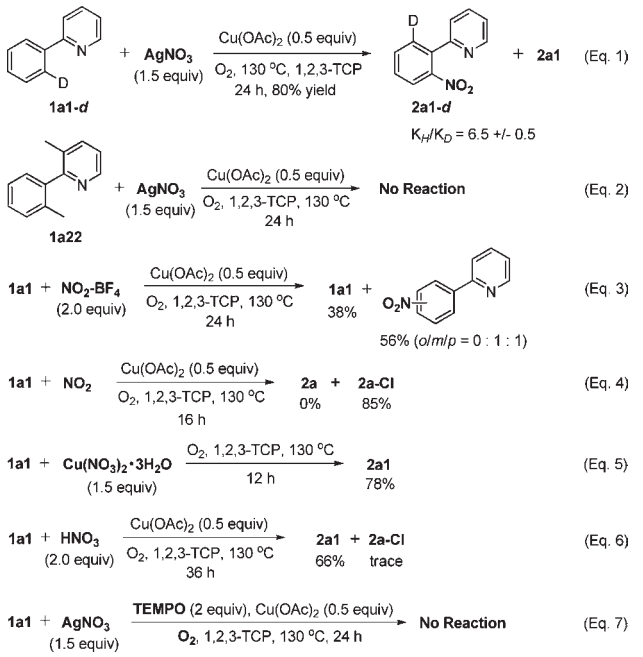
(10) For a review on "kinetic isotope effects in the study of organometallic reaction mechanisms", see: (a) Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev.* **2011**, *111*, 4857. Large KIE values have been reported in C−H hydroxylations catalyzed by bis(μ-oxo)dicopper or bis(μ-oxo)-diiron complexes, in which a free radical mechanism was proposed; see: (b) Kim, C.; Dong, Y.; Que, L., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 3635.

(11) A small secondary reverse isotope effect was often observed in electrophilic aromatic nitration; see: Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4571.

(12) Olah, G. A.; Laali, K. K.; Sandford, G. *Proc. Nati. Acad. Sci. U.S.A.* **1992**, *89*, 6670.

(13) Compared with other nitrates, the thermal decomposition of $Cu(NO_3)_2\cdot 3H_2O$ released nitrogen dioxide at a lower temperature (ca. 200 °C); see: Morozov, I. V.; Znamenkov, K. O.; Korenev, Y. M.; Shlyakhtin, O. A. *Thermochim. Acta* **2003**, *403*, 173.

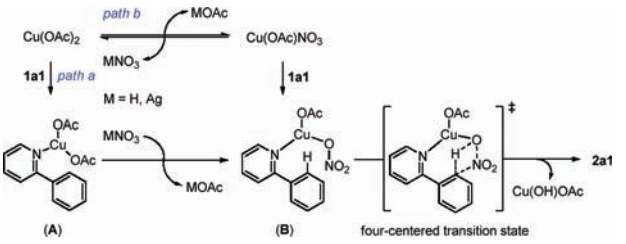
Scheme 2. Investigation on Reaction Mechanism



of nitrate ions into copper(II) moiety. This gives an advantage to nitric acid as a nitrating agent by making the nitration process much more practical and economical. Finally, inhibition of the nitration by a free radical scavenger TEMPO indicated that the reaction proceeded through a radical mechanism (Scheme 2, eq 7).[14]

On the basis of the evidence of our mechanistic studies described above, a plausible reaction mechanism was proposed for the copper-mediated chelation-assisted *ortho* nitration of (hetero)arenes (Scheme 3). 2-Phenylpyridine-coordinated and nitrate ion-containing copper(II) complex (B) was first formed by an anion exchange either from the complex (A) (path a) or between $Cu(OAc)_2$ and a nitrate salt (path b).[15] Subsequently, *ortho* nitration took place through a concerted mechanism, in which cleavage of C−H and N−O bonds, formation of O−H and C−N bonds, and transfer of hydrogen from carbon to oxygen occurred simultaneously on a four-centered transition state. This mechanistic speculation is consistent with previous reports in that a four-centered transition state was generally proposed to account for the observed large KIEs in C−H bond activation/functionalization.[10a,16] Also, a linear four-centered transition state is possible by a stepwise mechanism, involving first homolytic cleavage of N−O bond of nitrate anion to give $^{\bullet}NO_2$ and $^{\bullet}OCuOAc$, followed by hydrogen transfer and nitration.[17,18]

Scheme 3. Plausible Mechanism



In conclusion, we have developed a novel copper-mediated chelation-assisted *ortho* C−H bond nitration of (hetero)arenes using dioxygen as a terminal oxidant and 1,2,3-TCP as solvent, leading to the synthesis of nitroaromatics with excellent regioselectivity and in good yields. 1,2,3-TCP as solvent was found to be crucial for achieving high conversion in the reaction. Mechanistic investigations suggested a four-centered transition state mechanism involving simultaneous cleavage of an *ortho* C−H bond and a N−O bond of nitrate anion on the 2-arylpyridine-coordinated copper(II) complex.

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Supporting Information Available. Experimental procedures, spectra, and analytical data for **2a/2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Lee, J. M.; Park, E. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 7824.

(15) Note that the nitration of **1a1** under the optimal reaction conditions (Table 1, entry 3) was slightly retarded in the presence of KOAc (50 mol %). The added acetate ion is assumed to prevent the anion exchange with nitrate ion.

(16) A four-centered transition state was proposed to account for observed large KIEs; see: Wayland, B. B.; Ba, S.; Sherry, A. E. *J. Am. Chem. Soc.* **1991**, *113*, 5305.

(17) For a related mechanistic speculation that phenol was nitrated by $^{\bullet}NO_2$ produced from the decomposition of an iron peroxynitrite complex, see: (a) Tran, N. G.; Kalyvas, H.; Skodje, K. M.; Hayashi, T.; Moënne-Loccoz, P.; Callan, P. E.; Shearer, J.; Kirschenbaum, L. J.; Kim, E. *J. Am. Chem. Soc.* **2011**, *133*, 1184. For a report that nitration of phenols with gaseous nitrogen dioxide, see: (b) Astolfi, P.; Panagiotaki, M.; Greci, L. *Eur. J. Org. Chem.* **2005**, 3052.

(18) For examples of C−H bond activation with possible linear four-centered transition state, see: Cui, W.; Wayland, B. B. *J. Am. Chem. Soc.* **2004**, *126*, 8266.