C-H Activation



tert-Butyl Nitrite Mediated Regiospecific Nitration of (*E*)-Azoarenes through Palladium-Catalyzed Directed C—H Activation

Biju Majhi, Debasish Kundu, Sabir Ahammed, and Brindaban C. Ranu^{*[a]}

Abstract: An efficient protocol for the Pd-catalyzed regiospecific *ortho*-nitration of (*E*)-azoarenes has been achieved for the first time using *t*BuONO as a nitrating agent under atmospheric oxygen. A series of both symmetrical and unsymmetrical azoarenes were nitrated efficiently by this procedure providing excellent chemo- and regioselectivity and compatibility with a broad array of functional groups.

The azoarenes are of much interest due to their applications as dyes, indicators, nonlinear optics, photochemical switches and pharmaceuticals.^[1] Thus, functionalization of azoarenes has attracted considerable attention.^[2] The C–H activation directed by the azo group has been an important tool in regiospecific aromatic ring functionalization. The Pd-catalyzed *ortho*-acylation, alkoxylation, amination and halogenation of azoarenes involving C–H activation are a few of the examples reported recently.^[3] Surprisingly, although the –NO₂ functionality possesses remarkable significance due to its transformation to the other important functional groups, the nitration of azoarenes has not yet been explored.

Nitration of aromatic compounds through electrophilic aromatic substitution is one of the most common processes.^[4] However, this protocol suffers from severe drawbacks such as harsh reaction conditions, poor regioselectivity, and functional group intolerance among others. Thus, regioselective nitration in aromatic systems remains a challenge. Several new strategies such as ipso-nitration,^[5] nitrodemetalation of C–B and C– Li bonds,^[6] indirect nitration of amines and azides through ipso-oxidation and nitrodecarboxylation^[7] have been developed. However, transition-metal-catalyzed directed C-H functionalization is considered one of the effective ways for the regioselective inclusion of a group in an aromatic ring.^[8] Liu and co-workers reported palladium-catalyzed N-donor directed ortho nitration in the aromatic ring using AqNO₂ as a nitrating agent and $K_2S_2O_8$ as an oxidizing agent.^[9] Cu^{II[10]} and Rh^{III[11]} catalyzed directed C-H nitration have also been developed. However, most of these protocols involve the use of expensive and toxic metal nitrites as nitrating agent in combination with oxi-

 [a] B. Majhi, D. Kundu, Dr. S. Ahammed, Prof. Dr. B. C. Ranu Department of Organic Chemistry Indian Association for the Cultivation of Science Jadavpur, Kolkata-700032 (India) E-mail: ocbcr@iacs.res.in
 Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201403325. dizing agents like $K_2S_2O_8$ or Phl(OAc)₂. Moreover, the coppermediated reaction uses the metal catalyst in stoichiometric amount.^[10a] Being driven by a need of an efficient method for an access to nitroazoarenes we report here a Pd-catalyzed chelation directed regiospecific C–H nitration of azoarenes at the *ortho* position using *tert*-butyl nitrite as a nitrating agent under atmospheric oxygen in the absence of any other oxidant (Scheme 1).



Scheme 1. Pd-catalyzed ortho-directed C-H nitration of azoarenes.

To standardize the reaction conditions a series of experiments were performed with variation of reaction parameters, such as catalyst, solvent, temperature and time for a representative reaction of (E)-1,2-di-p-tolyldiazene and tert-butyl nitrite. The results are summarized in Table 1. The use of Pd(OAc)₂, PdCl₂ or (PPh₃)₂PdCl₂ as catalyst furnished relatively low product yields (Table 1, entries 1-3). The best yield of product was obtained using Pd(CH₃CN)₂Cl₂ (15 mol%) as a catalyst and 4 equivalents of tBuONO as a nitrating agent in 1,4-dioxane at 90 °C (Table 1, entry 6). 1,4-Dioxane was found to be a more effective solvent compared to xylene, THF, DMF, NMP and DMSO (Table 1, entries 7–11) although CH₃CN and dichloroethane provided relatively improved yields (Table 1, entries 12 and 13). The use of 10 mol% of catalyst produced a lower yield of product (Table 1, entry 5). The increase of the amount of tBuONO beyond 4 equivalents or Pd catalyst more than 15 mol% did not affect the outcome of the reaction (Table 1, entries 14 and 16). Use of 3 equivalents of tBuONO led to a lower yield (Table 1, entry 15). The reaction at a lower temperature (80 °C) furnished lower yield of product (Table 1, entry 17). Only trace amount of product was obtained when the reaction was carried out under argon atmosphere (Table 1, entry 18). The reaction did not proceed at all in the presence of 2,2,6,6,-tetramethylpiperidine N-oxide (TEMPO; Table 1, entry 19). No product was formed in the absence of catalyst (Table 1, entry 20).

Thus, in a general experimental procedure a mixture of azoarene and *tert*-butyl nitrite was heated with stirring in 1,4-dioxane at 90 °C in the presence of $Pd(CH_3CN)_2Cl_2$ (15 mol%) for 20–24 h as required for completion. A wide range of di-

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Table 1. Standardization of reaction conditions. ^[a]					
Me M					Me
Entry	Catalyst	Catalyst [mol %]	Solvent	<i>Т</i> [°С]	Yield [%] ^[b]
1	Pd(OAc) ₂	10	1,4-dioxane	110	45
2	PdCl ₂	10	1,4-dioxane	110	39
3	(PPh ₃) ₂ PdCl ₂	10	1,4-dioxane	110	46
4	Pd(CH ₃ CN) ₂ Cl ₂	10	1,4-dioxane	110	65
5	Pd(CH ₃ CN) ₂ Cl ₂	10	1,4-dioxane	90	70
6	$Pd(CH_3CN)_2Cl_2$	15	1,4-dioxane	90	82
7	$Pd(CH_3CN)_2Cl_2$	15	xylene	90	12
8	$Pd(CH_3CN)_2Cl_2$	15	THF	90	15
9	$Pd(CH_3CN)_2Cl_2$	15	DMF	90	trace
10	$Pd(CH_3CN)_2Cl_2$	15	NMP	90	trace
11	$Pd(CH_3CN)_2Cl_2$	15	DMSO	90	trace
12	$Pd(CH_3CN)_2Cl_2$	15	CH₃CN	90	72
13	$Pd(CH_3CN)_2Cl_2$	15	DCE	90	60
14 ^[c]	Pd(CH ₃ CN) ₂ Cl ₂	15	1,4-dioxane	90	82
15 ^[d]	$Pd(CH_3CN)_2Cl_2$	15	1,4-dioxane	90	68
16	Pd(CH ₃ CN) ₂ Cl ₂	20	1,4-dioxane	90	81
17	Pd(CH ₃ CN) ₂ Cl ₂	15	1,4-dioxane	80	71
18 ^[e]	Pd(CH ₃ CN) ₂ Cl ₂	15	1,4-dioxane	90	trace
19 ^[f]	Pd(CH ₃ CN) ₂ Cl ₂	15	1,4-dioxane	90	0
20 ^[g]		-	1,4-dioxane	90	0

[a] Reaction conditions: azoarene (0.5 mmol), tBuONO (2 mmol), solvent, catalyst, 20 h, air; [b] yield of isolated product; [c] 8 equiv of tBuONO used; [d] 3 equiv of tBuONO used; [e] under argon atmosphere; [f] in the presence of TEMPO (3 equiv); [g] in the absence of catalyst.

versely substituted azoarenes were subjected to nitration with this procedure. The results are summarized in Table 2. Both electron donating (–OMe, –Me, –Et) and electron withdrawing groups (–CF₃, –F, –Cl, –COAr) on the aromatic ring are compatible with the reaction conditions. In every reaction only *ortho*-mononitrated product was obtained. When compound **2a** was subjected to further C–H nitration under the same reaction conditions, no reaction occurred leaving the starting material (Scheme 2).



Scheme 2. C–H nitration of mononitroazoarene.

The nitration of halo-substituted azoarenes provided interesting results. The reaction of azoarenes bearing halogen moieties on the *para* position of aromatic ring, furnished decreasing yields of C–H nitrated products with increasing electronegativity of the halogen moieties (I > Br > CI > F; Table 2, 21, 2m, 2n and 2o). However, a reverse order was noticed in the nitration of azoarenes with halogen substituents in the *ortho* positions (F > CI > Br > I; Table 2, 2p, 2q, 2r and 2s). This observation may be related to the electronic effect of d orbitals of halogens (Cl, Br, I). The reaction did not proceed at all with *ortho*-



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Scheme 3. C-H nitration of meta-substituted azoarenes.

iodo azoarene as the iodo moiety has the most diffused d orbital compared to the others. Significantly, in all these Pd-catalyzed reactions only the C–H nitrations are observed and the halo groups remained unaffected under the reaction conditions although Pd-catalyzed nitration of aryl halides is very common.^[5d]

Interestingly, azoarenes bearing *meta* substituents showed excellent regioselectivity towards C–H nitration under the reaction conditions (Scheme 3). In both the substrates (**3a** and **3b**) the nitration occurred at the position *para* to Me (**4a**) and Cl (**4b**) groups.

Nitrations of unsymmetrically substituted azoarenes proceeded successfully with excellent regioselectivity (Scheme 4). Azoarene bearing an aryl substituent at the *ortho* position of one aromatic ring (**5 a**) underwent C–H nitration selectively at



However, compound **5b** bearing -CO-p-tolyl substituent at the *ortho* position of the aromatic ring was nitrated at the *ortho* position of the unsubstituted ring preferentially to produce **6b**' as major product along with nitration on the substituted ring (**6b**). When reaction of azoarene **5c** was performed,



Figure 1. ORTEP diagram of compound 6d in the form of two rotamers.





nitration occurred preferentially at the methyl substituted ring to give **6c** as a major product. On the other hand, compound **5d** having –OMe group on one of the aromatic rings underwent nitration preferentially on the unsubstituted ring giving **6d** as the major product. The structure of compound **6d** was confirmed by X-ray analysis (Figure 1).^[12]

Densely substituted azoarenes were also nitrated successfully (7 a, 7 b and 7 c) to produce the corresponding nitro-substituted products (Scheme 5).

In general, the reactions are clean and high yielding. A series of *o*-nitroazoarenes including densely substituted ones were

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Scheme 5. C-H nitration of densely substituted azoarenes.

obtained by this procedure and many of them are reported for the first time. The compounds are obtained in high purity. The nitration is compatible with several functional groups.

To understand the mechanism we performed a few competitive reactions with a pair of substituted azoarenes (Scheme 6).



Scheme 6. Intermolecular competition experiment.

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Scheme 7. Possible mechanism for Pd-catalyzed C-H nitration of azoarenes.

This observation of increased reactivity for electron-donating groups substituted azoarenes relative to those having electron-withdrawing moieties, suggests an electrophilic-type activation manifold. We propose that initially an intermediate A is formed by the chelation of azoarene and Pd^{II} (Scheme 7).^[3b] The reaction may involve either Pd⁰/Pd^{II} or Pd^{II}/Pd^{IV} catalytic process.^[13] As no external reducing agent or strong base was used in the reaction medium, the formation of Pd⁰ in the initial stage of the reaction is unlikely. It was also observed that a control experiment with 2 equivalents of Pd(CH₃CN)₂Cl₂ in the absence of air failed to initiate the reaction. Thus, the reaction may not follow the Pd⁰/Pd^{II} process. We suggest a C-H activation involving a Pd^{II}/Pd^{IV} pathway towards ortho nitration of azoarenes. In a first step in situ formed NO₂ radical undergoes chelation with Pd^{II} of intermediate **A** to form a Pd^{III} intermediate **B**. Intermediate **B** then suffers one electron oxidation by another NO_2 radical to form Pd^{V} intermediate **C**, which on reductive elimination leads to the product with regeneration of Pd^{\parallel} to start the next cycle.

We have performed UV experiments for the nitration of 4-Me azobenzene under the standardized reaction conditions, which shows an absorbance at 445 nm corresponding to Pd^{III} intermediate^[14] (see the Supporting Information) supporting our proposed reaction pathway.

In conclusion, we have developed an efficient procedure for the highly regioselective *ortho*-nitration of azoarenes by *tert*butyl nitrite with a Pd-catalyzed directed C–H activation. The azo-nitroarenes have much potential as useful materials and pharmaceuticals. The significant features of this protocol are: 1) mild reaction conditions avoiding use of any metal nitrite, acid and ligand; 2) applicability to a wide range of diversely substituted azoarenes; 3) excellent regioselectivity; and 4) high yield of products. In fact, we are not aware of any report for nitration of aromatic systems including azoarenes by C–H activation using an organonitrite, and thus this nitration of azoarenes by *tert*-butyl nitrite is significant and constitutes the first report of its kind. We believe, this method will find useful applications in organic synthesis.



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