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Pd(dba)$_2$/*t*BuONO-Catalyzed Cyclization of *o*-Alkynylanilines with *t*BuONO: Synthesis and Applications of Indazole 2-oxides

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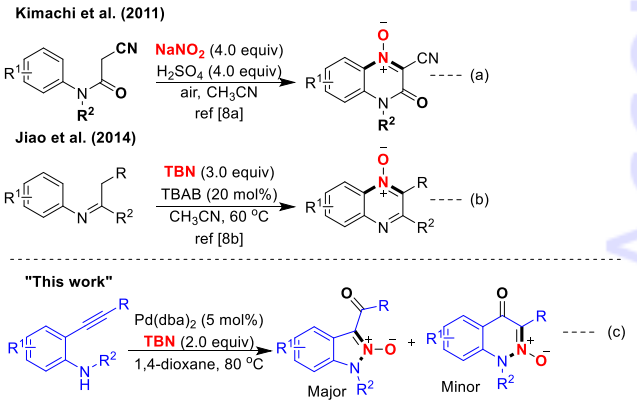
Abstract. An efficient method for the synthesis of 1-benzy/aryl-indazole *2*-oxides via a bis(dibenzylidene acetone)palladium(0) (Pd(dba)$_2$)/*tert*-butyl nitrite (TBN)-catalyzed reaction of *o*-alkynylaniline derivatives with TBN is reported. The overall transformation involved the formation of three new bonds via *N*-nitrosation (N-NO), 5-*exo*-dig cyclization (C-N) and oxidation (C=O). The notable features were the mild reaction conditions, broad substrate scope and dual role of TBN as a NO source and redox co-catalyst. This strategy was implemented for the synthesis of indazole-3-carbaldehyde derivatives and the formal syntheses of pharmaceutically active YC-1, an anticancer agent (lonidamine), and the male contraceptive experimental drugs AF2785 and adjudin (AF-2364).

Keywords: Indazole *2*-oxides; palladium; *tert*-butyl nitrite; catalysis; formal syntheses

Aza-heterocyclic compounds have widespread applications in biology,[1] chemistry[2] and materials science[3a]. In particular, *N*-oxides of these molecules are ubiquitous structural motifs found in alkaloids[3b] and bioactive compounds[3c] and have several chemical applications.[3d] The classical approach to synthesize *N*-oxides is from the corresponding aza-heterocyclic molecules with oxidants, such as peroxyacids.[4] However, this method has certain limitations, such as the unselective over-oxidation of other *N*-atoms present in the molecules, the excessive amount of strong oxidant needed and the requirement of previously prepared parent heterocycles. A brief literature survey revealed that the modern/non-classical methods for the synthesis of heterocyclic-*N*-oxides are the electrophilic cyclization[5a-e]/[2,3]-rearrangement to *N*-allenyl nitrones followed by 6π-3-azatriene electrocyclization[5f] of oximes tethered with alkynes,[5] the oxidative cyclization of oximes[6] and the transition-metal-catalyzed C-H functionalization of oximes with diazo compounds[7a-b]/1,4,2-dioxazol-5-ones.[7c]

Furthermore, the direct synthesis of *N*-oxides from *in situ* generated NO sources has been scarcely reported in the literature.[8] Therefore, the identification of new reaction conditions/strategies for the synthesis of a variety of heterocyclic *N*-oxides is still an unexplored area of research. In this context, Kimachi et al. (2011) reported the synthesis of quinoxalinone-*N*-oxides from cyanoacetanilides through the *in situ* generation of NO using a combination of $NaNO_2/H_2SO_4/O_2$ (Scheme 1a).[8a] In 2014, Jiao et al. reported the efficient synthesis of quinoxaline *N*-oxides using *tert*-butyl nitrite TBN as a NO source via imidoyl C(sp^3)-H and arene C(sp^2)-H bond functionalizations (Scheme 1b).[8b] Herein, we discovered a new *in situ* NO source by synthesizing 3-acyl-indazole *2*-oxides from *o*-alkynylaniline derivatives with TBN in the presence of Pd(dba)$_2$/TBN as a catalytic system.[8c] The reaction proceeded through a sequence of (i) *N*-nitroso formation (N-NO); (ii) regioselective 5-*exo*-dig-cyclization (C-N); and (iii) oxidation (C=O) (Scheme 1c).



Scheme 1 Syntheses of heterocyclic *N*-oxides from *in situ* NO sources.

The *in situ* generation of NO was initially studied with *N*-benzyl-2-(phenylethynyl)aniline **4aa** and

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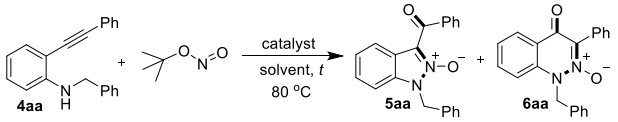
TBN.[9] The desired product **5aa**[10] was isolated in 25% yield along with 35% of the 6-*endo*-dig product 1-benzyl-4-oxo-3-phenyl-1,4-dihydrocinnoline 2-oxide **6aa** in 1,4-dioxane at 80 °C over 24 h (entry 1, Table 1). The structures of compound **5aa** and **6aa** were confirmed by X-ray analyses.[11] The 5-*exo* selectivity was increased when 5 mol % of tetrabutylammonium bromide (TBAB) was used, affording 45% **5aa** and 24% **6aa** (entry 2, Table 1). However, the best regioselectivity was obtained using 5 mol % I_2, albeit in low yields without any *endo* product (entry 3, Table 1). Increasing the ratio of I_2 to 10 mol% also failed to increase the yield of **5aa** (Supporting Information, Table S1). When transition-metal catalysts, such as Fe, Cu, Zn, Ag and Pd were tested (Table S1), the desired 5-*exo*-dig product was obtained in 88% yield along with a trace amount of the *endo*-dig product using 5 mol % $Pd(dba)_2$ as a catalyst (entry 4, Table 1). Subsequent tests of the solvents were studied using **4aa** and TBN with 5 mol % $Pd(dba)_2$ in DMSO, DMF, CH_3CN, THF or MeOH (Table S1). We found that DMSO and CH_3CN gave similar yields to that of 1,4-dioxane; however, the *endo*-dig selectivity was slightly increased (entries 5-6, Table 1). A lower catalyst loading increased the reaction time, and no notable changes were observed upon increasing the loading of the catalyst (entry 7-8, Table 1). Decreasing the reaction temperature to 60 °C resulted in a longer reaction time, whereas at refluxing temperature, the selectivity was reduced (Table S1). Reducing the quantity of TBN to 1.2 equiv resulted in some remaining unreacted *N*-nitroso intermediates and a low yield (entry 9, Table 1). Thus, the reaction conditions listed in entry 4, Table 1 were chosen as the optimal conditions.

With the optimized reaction conditions in hand, the scope of this *in situ* NO source reaction was investigated. The scope of the R group attached to the

Table 1 Screening of the reaction conditions.[a]

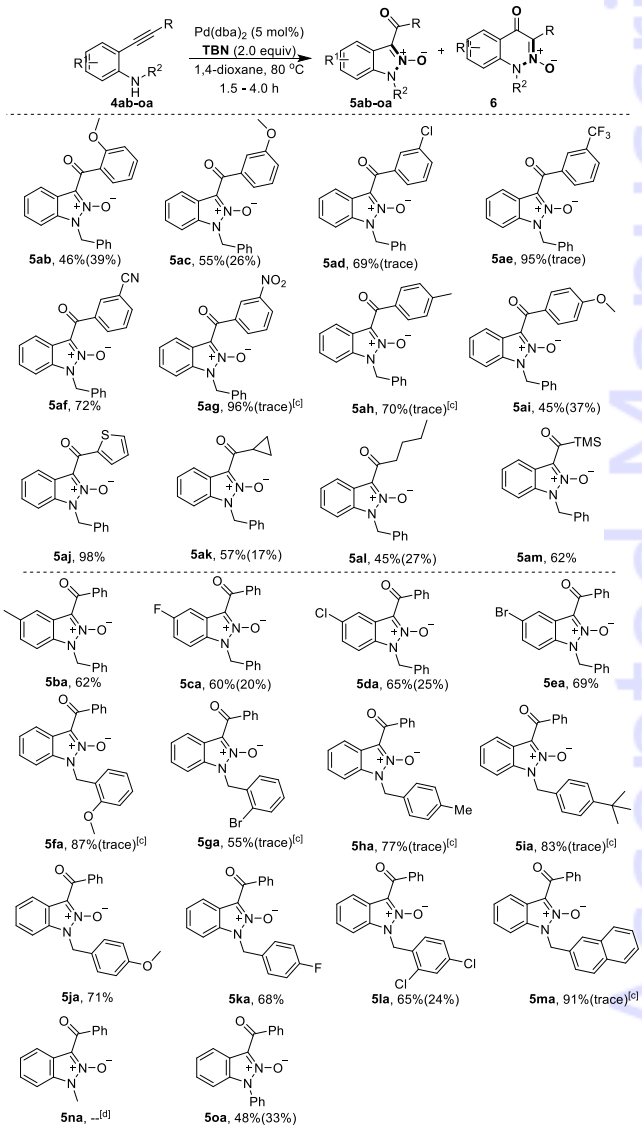


Entry	Catalyst (mol %)	Solvent	t, *h*	Yield (%)[b]	
				5aa	**6aa**
1	---	1,4-dioxane	24	25	35
2	TBAB (5)	1,4-dioxane	24	45	24
3	I_2 (5)	1,4-dioxane	16	30	0
4	$Pd(dba)_2$ (5)	1,4-dioxane	1.5	88	<5
5	$Pd(dba)_2$ (5)	DMSO	1.5	80	14
6	$Pd(dba)_2$ (5)	CH_3CN	1.5	78	12
7	$Pd(dba)_2$ (2)	1,4-dioxane	4	82	<5
8	$Pd(dba)_2$ (10)	1,4-dioxane	1.5	73	10
9[c]	$Pd(dba)_2$ (5)	1,4-dioxane	1.5	60	<5

[a] Reaction conditions: **4aa** (0.5 mmol), TBN (1.0 mmol), catalyst and solvent (0.2 M) unless otherwise noted. [b] Yields of the isolated product. [c] The amount of TBN was changed to 1.2 equiv.

alkyne was tested with aryl (**4ab-ai**), heteroaryl (**4aj**), alkyl (**4ak-al**) and silyl (**4am**) functionalities, as shown in Table 2. The reaction worked well with *o*-/*m*-/*p*-functional groups on the R group of the aryl ring, affording products with various functionalities, such as *o*-MeO (**5ab**), *m*-MeO (**5ac**), *m*-Cl (5ad), *m*-CF_3 (**5ae**), *m*-CN (**5af**), *m*-NO_2 (**5ag**), *p*-Me (**5ah**) and *p*-MeO (**5ai**), in 45-96% yields irrespective of the electronic properties. However, strong electron-donating functionalities on the aryl group gave 6-*endo*-dig products, such as *o*-Me (**6ab**), *m*-MeO (**6ac**) and *p*-MeO (**6ai**) products, in 26-39% yields. The likely reason could be the strong donating ability of the methoxy group, which stabilized the *endo*-vinyl

Table 2 Scope of the $R/R^1/R^2$ functionalities to afford indazole 2-oxides.[a,b]

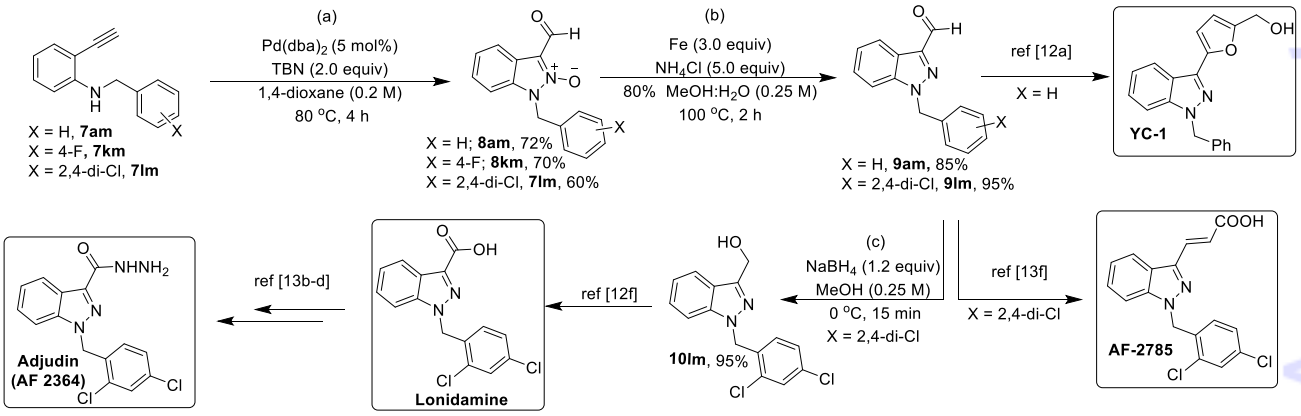


[a] Reaction conditions: **4ab-ma** (0.5 mmol), TBN (1.0 mmol), 5 mol % $Pd(dba)_2$ and 1,4-dioxane (0.2 M) with stirring under air for 1-4 h at 80 °C. [b] Yields in the parentheses refer to the 6-*endo*-dig product. [c] Trace refers to 2-5% of the 6-*endo*-dig product, which was not isolated. [d] Reaction was stopped at *N*-nitrosoyl intermediate.

palladium complex. The reaction underwent smooth derivatives, under the standard conversion with a thiophenyl derivative to get compound **5aj** in 98% yield. The structure of compound **5aj** was confirmed by X-ray analysis.[11] However, with alkyl derivatives, such as cyclopropyl and butyl conditions gave considerable amounts of the *endo* products along with desired products **5ak**-**al**, albeit in low yields. These results suggest that an electron-donating R group increases the ratio of the *endo* product. Interestingly, the reaction proceeded smoothly with a trimethylsilyl derivative to produce compound **5am** in 62% yield.

Next, the scope and limitations of this reaction were tested on the R^1 and R^2 groups of the *o*-alkynylanilines **4ba**-**oa**, as shown in Table 2. The reaction underwent smoothly when the R^1 group was substituted with *p*-Me, *p*-F, *p*-Cl and *p*-Br to afford the corresponding derivatives **5ba**-**ea** in 60-69% yields. However, electron-withdrawing groups at the R^1 position gave moderate regioselectivities due to the formation the 6-*endo*-dig products **6ca**-**da** in 20-25% yields. Then, the scope of the R^2 group was investigated with benzyl derivatives with different electronic and steric properties, such as *o*-MeO-Bn, *o*-Br-Bn, *p*-Me-Bn, *p*-*tert*-butyl-Bn, *p*-MeO-Bn, *p*-F-Bn, 2,4-di-Cl-Bn and 2-(bromomethyl)naphthalene. The reaction worked well irrespective of the *o*/*m*/*p* positions or the electron-donating/withdrawing properties to get the desired compounds **5fa**-**ma** in 55-91% yields. The structure of compound **5ga** was confirmed by X-ray analysis.[11] However, a 2,4-dichloro benzyl derivative exhibited an average regioselectivity, producing 24% of the *endo*-dig product **6la**. Changing the R^2 functionality from benzyl derivative to methyl substitutent under standard conditions gave the corresponding nitroso intermediate **4na'** rather than the desired *N*-methyl indazole 2-oxide **5na**. Interestingly, the reaction proceeded smoothly with *N*-phenyl substituent **4oa** to afford the desired 5-*exo*-product in 48% yield albiet in moderate selectivity along with the formation of 33% of 6-*endo*-product.

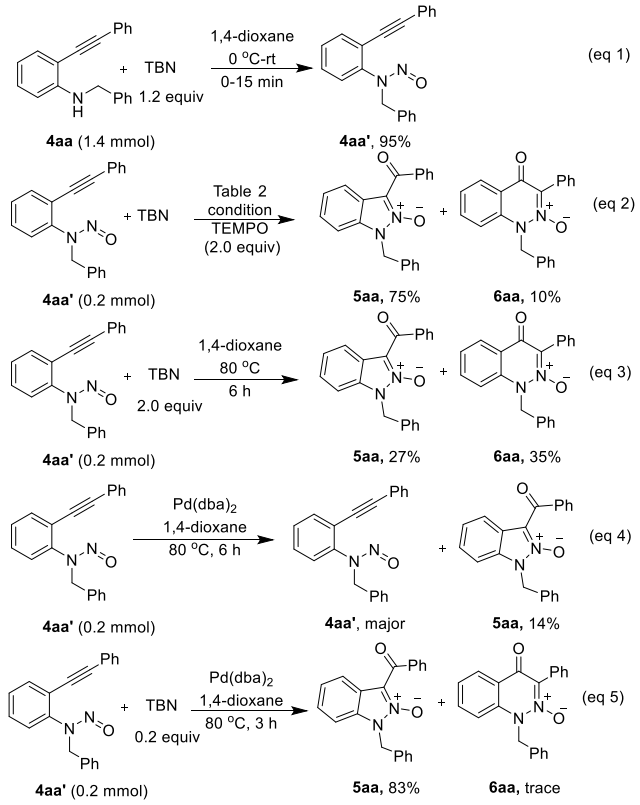
This methodology was applied to the synthesis of indazole-3-carbaldehyde derivatives (Scheme 2). Indole-3-carbaldehyde, an alkaloid isolated from a species of *Vibrio marine bacteria* in the red sea, possesses antibacterial activity against Gram-positive bacteria and is also cytotoxic to mice lymphocytic leukemia and Jurkat-T-cell leukemia cells.[1a] The representative indazole-3-carbaldehye derivatives **8am** and **8km** were produced from terminal alkynes under the standard conditions of Table 2, as shown in Scheme 2a. Furthermore, the formal synthetic precursor of YC-1 was achieved through the reduction of compound **8am** in the presence of Fe/NH_4Cl to get compound **9am** in 85% yield (Scheme 2b).[12a] YC-1 is an important pharmaceutical active compound that inhibits platelet aggregation, smooth muscle proliferation[12b] and hepatocellular carcinoma cell proliferation.[12c] With this successful outcome, we next explored the formal synthesis of lonidamine, an anticancer and antifertility drug.[12d] The key steps involved were the reductions of the *N*-oxide (**8lm**) and the aldehyde functional groups (**9lm**) (Scheme 2c). Then, compound **10lm** was converted to lonidamine by the reported Jones oxidation.[12f] Similarly, the male contraceptive experimental drug adjudin[12e, 13a] was prepared in two steps from lonidamine via esterification[13b] and a nucleophilic displacement reaction with hydrazine hydrate.[13c-d] Additionally, AF2785[13e] was prepared from a basic condensation reaction with malonic acid and aldehyde **9lm**.[13f]



Scheme 2 Synthesis of indazole-3-carbaldehyde derivatives; formal syntheses of YC-1, lonidamine, AF-2785 and Adjudin (AF 2364).

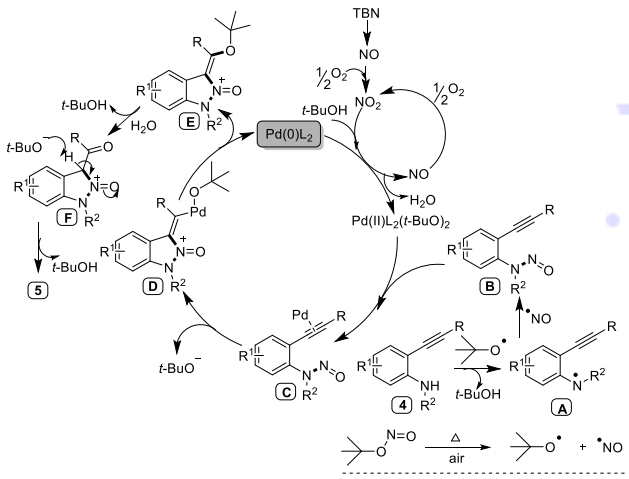
To understand the preliminary reaction mechanism, a few control experiments were carried out, as shown in Scheme 3. The key *N*-nitroso intermediate **4aa'** was prepared by reacting compound **4aa** with TBN (1.2 equiv) in 1,4-dioxane at room temperature for 10 min (Scheme 3, eq 1). Then, the *N*-nitroso intermediate was reacted under the standard conditions in the presence of TEMPO. The desired compound **5aa** was obtained in 75% yield along with 10% of the *endo* product (Scheme 3, eq 2). This ruled

out the possibility of a radical intermediate after the *N*-nitroso formation reaction. Then, the *N*-nitroso intermediate was treated with TBN (2.0 equiv) without $Pd(dba)_2$, and the reaction showed poor *exo* vs *endo* regioselectivity (Scheme 4, eq 3). Furthermore, the reaction did not proceed to completion using $Pd(dba)_2$ as a catalyst in the absence of TBN (Scheme 3, eq 4). Finally, when **4aa'** was treated with 5 mol % $Pd(dba)_2$ and 20 mol% TBN in 1,4-dioxane at 80 °C for 3 h, the desired compound was obtained in 83% yield along with trace **6aa** (Scheme 3, eq 5). These results suggest that TBN plays a key catalytic role along with $Pd(dba)_2$ in the reaction.



Scheme 3 Control studies.

A plausible mechanism is proposed based on the preliminary control studies and previous literature reports, as shown in Scheme 4.[8,14,15] Initially, TBN could decompose into a *tert*-butoxy radical and an NO radical.[8b] *o*-Alkynylaniline radical **A** could be generated by the abstraction of a hydrogen atom by the *tert*-butoxy radical.[8b] Then, intermediate **A** could react with the NO radical to form intermediate **B**. From the control studies (eq 4 & 5), TBN is necessary for the catalytic conversion. Based on these above results, we presume that $Pd(dba)_2$ will oxidize to $Pd(dba)_2(t\text{-BuO})_2$ with *tert*-butanol (*t*-BuOH) in the presence of the nitrite generated *in situ* from TBN,[14] which eventually serves as the active catalyst responsible for the product formation. The coordination of the Pd(II) catalyst to intermediate **B** could increase the regioselectivity and electrophilicity of the alkyne intermediate **C**. The cyclic intermediate **D** could be generated by the regioselective 5-*exo*-dig cyclization of *N*-nitroso intermediate **C**. Reductive elimination of **D** could result in the vinyl ether intermediate **E** with the expulsion of the Pd(0) catalyst. Then, Pd(0) could oxidize to Pd(II) in the presence of NO_2 and $1/2O_2$ for the next catalytic cycle.[14] Finally, intermediate **E** could undergo hydrolysis to afford the carbonyl intermediate **F**,[15] and the base-mediated elimination of the proton from **F** could afford compound **5**.[16]



Scheme 4 Plausible mechanism for the synthesis of indazole 2-oxides.

In summary, we developed a novel $Pd(dba)_2$/TBN-catalyzed approach for the synthesis of 1-benzyl-indazole 2-oxides that involved the formation of three new N-NO, C-N and C-O bonds. The key features were the dual role of TBN as a NO source/redox co-catalyst, which was shown for the first time, the broad functional group tolerance and the mild reaction conditions. The synthetic application was demonstrated for the synthesis of indazole-3-carbaldehyde alkaloid derivatives and the formal syntheses of pharmaceutically active YC-1, an anticancer agent (lonidamine), and the male contraceptive experimental drugs AF2785 and adjudin (AF-2364).

Experimental Section

General procedure for the synthesis of compound 5. To a stirred solution of compound 4 (0.5 mmol) in 1,4-dioxane (0.2 M), *tert*-butyl nitrite (1.0 mmol) was added, followed by the addition of $Pd(dba)_2$ (5 mol %). The resulting solution was stirred under air at 80 °C. Upon completion of the reaction (~1.5-4 h), the reaction mixture was diluted with ice water and extracted with ethyl acetate (3x20 mL). The combined organics were washed with brine (1x20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography using 6-10% EA/hexane for compound **5** and 10-15% EA/hexane for compound **6**.

Acknowledgements

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