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Ruthenium porphyrin catalyzed diimination of indoles with aryl azides as the nitrene source†

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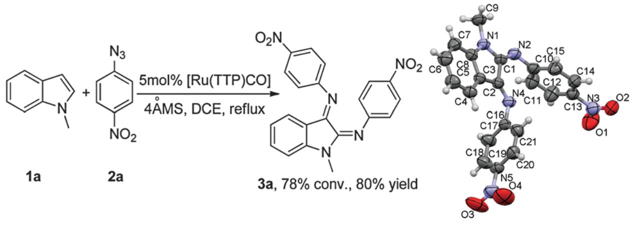
By using [Ru(TTP)CO] [H_2TTP = *meso*-tetrakis(4-tolyl)porphyrin] as catalyst and aryl azides as the nitrene source, the sp^2(C–H) bonds of a series of indoles undergo oxidative C–N bond formation to give unique 2,3-diimination products in good to high yields.

Indoles are ubiquitous structural motifs present in bioactive natural products and pharmaceuticals.[1] Direct C–H bond functionalization of indoles represents a straightforward and atom-economic strategy for the synthesis of indole derivatives. While many methodologies have been developed to functionalize indole's C–H bonds such as alkylation and arylation,[2] the routes to 2- and 3-amino substituted indoles *via* direct C–H bond amination are relatively sparse. The conventional method to introduce nitrogen atoms into indoles relies on nitration of indoles with nitric acid.[3] This method suffers from the harsh reaction conditions and low product yields. Recently, Li and coworkers reported a mild Cu(I)-catalyzed oxidative amidation of *N*-methylindole with amide *via* C–H functionalization.[4] By using sulfonyl azides as the nitrogen source, Zhou and coworkers described a Rh(III)-catalyzed amidation of indoles *via* chelation-assisted C–H bond activation.[5] Dauban and coworkers used [$Rh_2(esp)_2$] (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid) as catalyst, sulfamate as the nitrene source and $PhI(OCOR)_2$ or PhIO as an oxidant to achieve oxyamidation of *N*-phenylsulfonylindole.[6] Liu and coworkers reported a palladium-/copper-catalyzed intermolecular C–H amination reaction of indoles using chlorosulfonamides as the nitrogen source.[7] In spite of these advances, there are only a few examples of transition metal catalyzed C–H amination of indoles; thus a new methodology for this transformation is highly desired. Furthermore, all of these reported methods only afforded monoaminated indoles, no catalytic diamination or diimination of indole's C–H bonds has been reported. Recently, we demonstrated that ruthenium porphyrins are effective catalysts for C–H amidation of furan, pyrroles and thiophene with PhI═NTs.[8] Herein an efficient ruthenium porphyrin-catalyzed diimination of indoles with aryl azides as the nitrene source is described. 2,3-Diiminoindoles and their derivatives have been reported to display a broad spectrum of bioactivities.[9]

In our preliminary study, we found that the reaction of *N*-methylindole **1a** (1 equiv.) and 4-nitrophenyl azide **2a** (3 equiv.) in the presence of [Ru(TTP)CO] (H_2TTP = *meso*-tetrakis(4-tolyl)-porphyrin) (5 mol%) in 1,2-dichloroethane under reflux for 3 h gave diiminated product **3a** in 80% yield based on 78% substrate (**1a**) conversion (Scheme 1). No monoiminated indole or aminated indole was detected. The structure of **3a** was determined by ^{1}H NMR, ^{13}C NMR, mass spectrometry (see ESI†) and single crystal X-ray crystallography. The X-ray crystal structure of **3a** reveals the C(1)–N(2) and C(2)–N(4) distances to be 1.279 Å and 1.275 Å, respectively, in agreement with the C═N formulation. [Ru(F_{20}TPP)CO] (H_2F_{20}TPP = *meso*-tetrakis(pentafluorophenyl)-porphyrin) and [Ru(TDCPP)CO] (H_2TDCPP = *meso*-tetrakis(2,6-dichlorophenyl)porphyrin) were less efficient than [Ru(TTP)CO] giving **3a** in 21% and 47% yields and with 46% and 81% substrate conversion, respectively (see ESI†). [$Rh_2(OAc)_4$], [$Rh_2(esp)_2$], [$Cu(OTf)_2$], [Fe(TTP)Cl], and [Co(TTP)] failed to catalyze the diimination with the recovery of the starting materials or gave low product yield under similar reaction conditions (see ESI†). With [Ru(TTP)CO] as catalyst, 1,2-dichloroethane was the best solvent (see ESI†). Lowering the reaction temperature to room temperature resulted



Scheme 1

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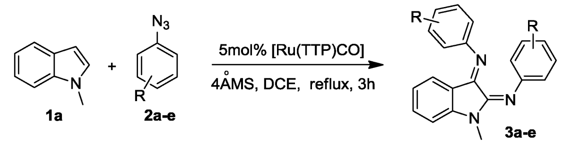
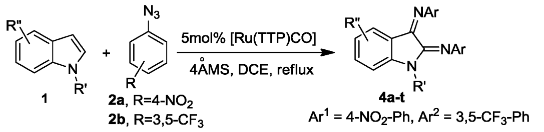
Table 1 Substitution effect of aryl azides[a]

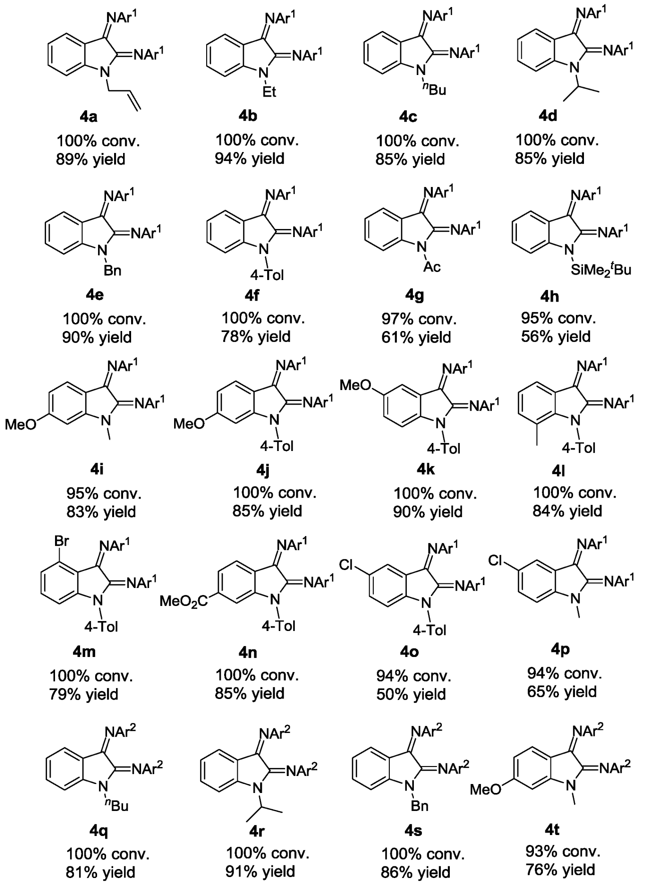


Entry	R	Product	Conv.[b] (%)	Yield[c] (%)
1	3,5-CF_3 (**2b**)	**3b**	84	80
2	4-Cl (**2c**)	**3c**	71	25
3	H (**2d**)	**3d**	0	0
4	2-NO_2 (**2e**)	**3e**	97	31
5[d]	4-NO_2 (**2a**)	**3a**	94	90

[a] Conditions: *N*-methyl indole (0.2 mmol), aryl azide (0.6 mmol), [Ru(TTP)CO] (5 mol%), 200 mg of 4 Å MS, 2 mL of DCE, argon, reflux. [b] Based on indole. [c] Based on substrate conversion. [d] Addition of aryl azides in two batches was adopted.

Table 2 [Ru(TTP)CO]-catalyzed diimination of indoles with 4-nitrophenyl azide **2a** and 3,5-bis(trifluoromethyl)phenyl azide **2b**[a]





4a
100% conv.
89% yield

4b
100% conv.
94% yield

4c
100% conv.
85% yield

4d
100% conv.
85% yield

4e
100% conv.
90% yield

4f
100% conv.
78% yield

4g
97% conv.
61% yield

4h
95% conv.
56% yield

4i
95% conv.
83% yield

4j
100% conv.
85% yield

4k
100% conv.
90% yield

4l
100% conv.
84% yield

4m
100% conv.
79% yield

4n
100% conv.
85% yield

4o
94% conv.
50% yield

4p
94% conv.
65% yield

4q
100% conv.
81% yield

4r
100% conv.
91% yield

4s
100% conv.
86% yield

4t
93% conv.
76% yield

[a] Conditions: indole (0.2 mmol), aryl azide (0.4 + 0.25 mmol), [Ru(TTP)CO] (5 mol%), 200 mg of 4 Å MS, 2 mL of DCE, argon, reflux until aryl azide was completely consumed; conversion is based on indole and yield is based on substrate conversion.

in low substrate conversion and product yield. Tosyl azides and phosphoryl azides failed to react with the indoles under the [Ru(TTP)CO] catalyzed conditions.

With [Ru(TTP)CO] as catalyst, we examined the substitution effect of aryl azides on the diimination. As depicted in Table 1, when 3,5-bis(trifluoromethyl)phenyl azide **2b** was used, the corresponding diiminated product **3b** was obtained in 80% yield and 84% substrate conversion (entry 1) comparable to those obtained when 4-nitrophenyl azide **2a** was used as the nitrene source. In contrast, the use of 4-chlorophenyl azide **2c** and phenyl azide **2d** led to the diimination product in 25% yield and in a trace amount, respectively (entries 2 and 3). These results showed that a strong electron-withdrawing group on aryl azides facilitates the nitrene transfer to indoles. Compared with **2a**, 2-nitrophenyl azide **2e** gave lower product yield (31%, entry 4) attributed to the steric effect of *ortho*-substitution. Considering the importance of nitro group in organic synthesis, azide **2a** was employed as the nitrene source for subsequent studies.

In the diimination reaction, a considerable amount of aniline was produced as the byproduct from the decomposition of aryl azides. This could be the main cause for the incomplete consumption of indoles. To circumvent this problem, addition of aryl azides in two batches was adopted. At first, 2 equivalents of aryl azides were added to the reaction mixture prior to heating. Upon the complete consumption of azides monitored by TLC, another batch of aryl azides (one equivalent) was added. The reaction conversion and the product yield were improved to 94% and 90%, respectively (Table 1, entry 5). Therefore, this optimized addition of aryl azides was adopted in the subsequent studies.

With the optimized reaction conditions, the scope of indoles for the [Ru(TTP)CO]-catalyzed diimination was examined. As depicted in Table 2, a variety of indoles reacted with 4-nitrophenyl azide **2a** in the presence of [Ru(TTP)CO] to give corresponding diimination products **4a–4p** in good to high yields (50–94%) and with quantitative substrate conversions. This reaction shows good functional group tolerance as various functionalities including alkene, acyl, silane, methoxy, halide and ester groups are compatible with the protocol.

The N-substitution effect on the Ru(II)-catalyzed diimination was first examined. *N*-Alkyl and -phenyl indoles displayed high reactivity towards the diimination giving **4a–4f** in high yields (78%–94%). The reaction of *N*-acetyl indole gave **4g** in 61% yield. When the N–H group of indoles was substituted with a strong electron-withdrawing tosyl group, the reaction was completely inhibited. It is noteworthy that the reaction of *N*-allyl indole exhibited an excellent chemoselectivity giving only diimination product **4a** in 89% yield without the detection of nitrene insertion into the α C–H bond or aziridination of the allyl group.

We next examined the effect of substitution on indoles toward the diimination. The indoles bearing electron-donating groups (methyl or methoxy groups) exhibited high reactivity giving **4i–4l** in 83–90% yields and with the reaction completed within 5 h. Electron-withdrawing groups (ester, bromo, chloro) render indoles less reactive than their electron-donating counterparts leading to **4m–4p** in 50–85% yields and a long reaction time of 15 h was required. These findings revealed that the reaction intermediate is electrophilic and prefers to react with electron-rich indoles. 3,5-Bis(trifluoromethyl)phenyl azide **2b** is also an effective nitrene source for the diimination giving the corresponding products **4q–4t** in good to excellent yields. No reaction was observed when 2- or 3-methyl indole was used under the same reaction conditions.

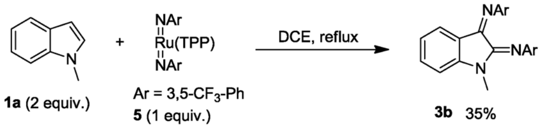
It should be noted that only 2,3-diimination products of indoles were isolated as depicted in Tables 1 and 2. No mono-iminated or aminated indole was obtained or detected by ESI-MS analysis of the reaction mixture. The underlying reason for this observation is not clear. Attempts to synthesize monoiminoindole or aminoindole were unsuccessful. For example, performing the reactions of **1a** and **2a** in a ratio of 1 : 1 or 1 : 2 under the optimized reaction conditions only led to **3a** in 26% and 53% product yields, respectively, without the mono-iminated or the mono-aminated product being detected.

To gain insight into the reaction mechanism, [Ru(TPP)(NAr)$_2$] (Ar = 3,5-bis(trifluoromethyl)phenyl) **5** was synthesized by the reaction of [Ru(TPP)CO] and 3,5-bis(trifluoromethyl)phenyl azide according to the literature[10] and employed in the stoichiometric reaction with indoles. Treatment of **5** (1 equiv.) with **1a** (2 equiv.) in 1,2-dichloroethane under reflux for 1.5 h gave **3b** in 35% yield (Scheme 2). No mono-iminated or aminated product was obtained. This finding suggests that the bis(imido)ruthenium complex [Ru(TPP)(NAr)$_2$] might be involved in the Ru(II)-catalyzed diimination.

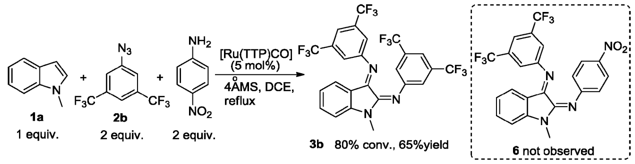
Dauban and coworkers recently reported an Rh(II)-catalyzed oxyamidation of *N*-phenylsulfonylindole in which initial aziridination of indoles with subsequent ring opening by methanol or carboxylic acid was proposed.[6] However, when acetic acid or methanol was added in our reaction, only a diimination product was obtained though in very low yield without oxyamidation of indoles being detected.

To examine whether the aniline, which was generated as the byproduct in the reaction course, was responsible for the diimination, a control experiment was performed. Treatment of **1a** (1 equiv.), **2b** (2 equiv.) and 4-nitroaniline (2 equiv.) in the presence of [Ru(TTP)CO] (5 mol%) in 1,2-dichloroethane under reflux gave **3b** in 65% yield based on 80% conversion of indoles (Scheme 3). *The dissymmetric imination product* **6** *was not observed*. This result does not support the involvement of aniline in the diimination.

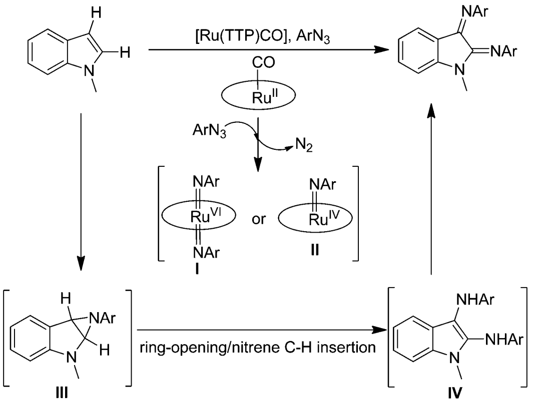
A tentative reaction mechanism is proposed. As depicted in Scheme 4, [Ru(TTP)CO] decomposes aryl azides to give metal–nitrene intermediate **I** or **II**, both of which can undergo aziridination with indoles to give **III**. A similar reaction mechanism was reported by Kumar in which 1-(phenylsulfonyl)indole or 2-substituted indoles reacted with phthalimidonitrene generated *in situ* by the oxidation of *N*-aminophthalimide with lead tetraacetate to give aziridination products in good yields.[11] Intermediate **III** may undergo rapid ring-opening followed by subsequent nitrene C–H insertion to give diamination product **IV**. Hydrogen atom abstraction of **IV** by **I** or **II** gives the diimination product. The dehydrogenation of amines to imines was reported previously.[12–14] The exclusive formation of the diimination product could be attributed to the high reactivity/instability of intermediate **III**.



Scheme 2



Scheme 3



Scheme 4

In summary, an efficient ruthenium porphyrin-catalyzed diimination of sp^2 C–H bonds of indoles has been developed. With [Ru(TTP)CO] as catalyst and aryl azides as the nitrene source, a variety of indoles were diiminated to give unique 2,3-diimination products in good to high yields. The reaction displays high functional group tolerance and excellent chemoselectivity. Furthermore, the stoichiometric reaction of bis(imido)ruthenium complex [Ru(por)(NAr)$_2$] with indoles gave a product identical to that observed in the catalytic reaction.

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