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Ruthenium-catalyzed *ortho*-selective C_{Ar}–H amination of heteroaryl arenes with *di-tert*-butyldiaziridinone

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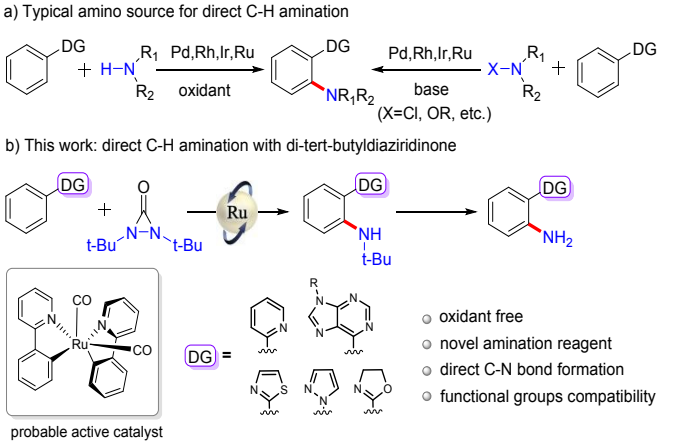
An oxidative amination reagent (*di-tert*-butyldiaziridinone) applied to the $Ru_3(CO)_{12}$-catalyzed *ortho*-selective C_{Ar}–H amination reaction is described. This strategy shows good functional group compatibility with various phenyl-substituted *N*-heterocycles, including biologically active substrates, thus providing a synthetic potential of this methodology. Mechanistic studies showed that the reaction process involves an octahedral ruthenium species, and the carbon monoxide ligand plays a crucial role in the C–H activation.

Anilines are ubiquitous building blocks that are widely employed in synthetic intermediates, natural products, pharmaceutical agents, and materials science,[1] according to the Retail's 2016 Top 200 medicines, they exist in the forms of 16 active moieties.[2] Devising improved methods for the high-efficiency construction of C–N bonds[3] has been recognized as a particularly important challenge. As one of the transition-metal-catalyzed cross coupling reactions between aryl- or alkenyl-(pseudo)halides and nucleophilic reagents, the Buchwald–Hartwig reaction[4] inevitably generates stoichiometric amounts of halide salt by-products. Direct C–H bond amination does not require prefunctionalized arenes, so it is a highly desirable pathway. Several types of amination reagents have been employed in this process, distinguished with the nucleophilic amine source,[5] electrophilic amino sources[6] without an additional oxidant predominated in terms of high efficiency (Scheme 1a). In addition, organic azides[7] is also an importantly benign amine source. These considerations led us to envision whether *di-tert*-butyldiaziridinone,[8] with a highly strained structure, could act as an amination reagent in the absence of an additional oxidant for direct sp^2 C–H amination.



Scheme 1 Transition-metal-catalyzed C-H bond amination

To date, palladium[9] has been the most studied metal in transition-metal-catalyzed amination. However, ruthenium is one-third the cost ($243/mol) of palladium ($879/mol),[10] showing an evident economic superiority. After Lewis group [11]pioneered Ru-catalyzed C–H activation, Ackermann,[12] Dixneuf,[13] Szostak,[14] and others have greatly furthered its progress, especially for the *ortho*-C–H activation of (hetero)arene. Despite some historical bias regarding the *para*-substitution within pharmaceutical chemistry, the *ortho*-C_{Ar}–H activation process can expand the chemical space via distorting planar structures,[15] which makes it superior to the *para* and *meta* ones. However, the ruthenium-catalyzed *ortho*-C–H bond activation has been almost confined to the introduction of aryl, alkenyl, or alkyl groups,[16] and direct C–H amination remains largely unexplored.

In 2013, Yu[17] and co-workers first reported an intermolecular C–H amination with an electrophilic amine source enabled by ruthenium(II) catalysis. The resulting amination products are tertiary amines and cannot be converted to secondary amines in one step via C–H functionalization, and it is also difficult to directly produce *ortho*-selective amination products. Therefore, developing a novel, Ru-catalyzed, chemo-selective amination method, the products of which contain a naked N–H bond, is extremely

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challenging. Herein, we have achieved a $Ru_3(CO)_{12}$-catalyzed *ortho*-selective C_{Ar}–H amination by employing *di-tert*-butyldiaziridinone and further conversion can provide functionalized aniline derivatives (Scheme 1b), which could effectively expand the application and synthetic potential of C–H bond amination.

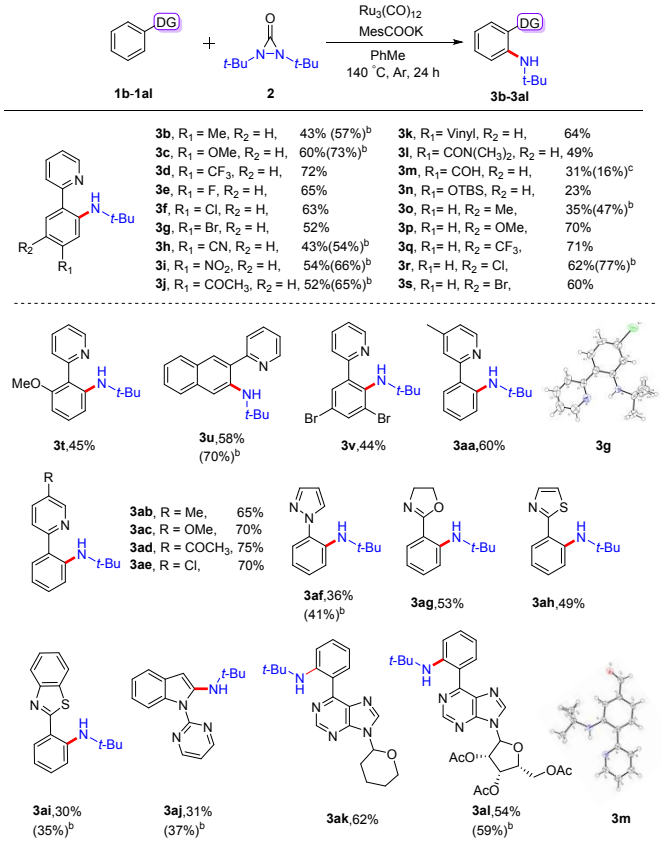
The initial study was carried out with 2-phenylpyridine **1a** and *di-tert*-butyldiaziridinone **2** catalyzed by the commonly used Ru(II) catalytic system ($[RuCl_2(p\text{-cymene})]_2$/DCE). Unfortunately, the desired product **3a** was not detected. A screening of alternative ruthenium catalysts indicated that **3a** was obtained in a 35% isolated yield when employing $Ru_3(CO)_{12}$. A further optimization of the solvents revealed that toluene was the most efficient one. Alternative bases were also tested, and MesCOOK (potassium 2,4,6-trimethylbenate) was found to promote the complete conversion of **1a**, the yield of **3a** was increased to 72% in toluene at 140 °C for 24 h. No better results were achieved by adding other additives. Control experiments demonstrated that $Ru_3(CO)_{12}$ was essential for this reaction, and **3a** was obtained in a 34% yield in the absence of base, indicated a ruthenium assisted deprotonation of the *ortho*-C–H bond, which is consistent with the DFT calculation (see the ESI†).

Under the optimized reaction conditions established, the scope and functional group compatibilities of the 2-arylheterocycles were investigated (Table 1). It was found that electron-donating and electron-drawing groups at the *para*-position could produce the mono-aminated products **3b**–**3o** in good yields (16%–73%). Various synthetically useful functional groups, such as halogen, nitro, cyano, vinyl, formyl, and trifluoromethyl groups, on the phenyl ring were well tolerated. One notable case involved [1,1'-biphenyl]-4-ylmethanol as the substrate, which was oxidized to *formyl*-substituted phenylpyridine by **2**, and then participated in this reaction. For *meta*-substituted arylpyridines, amination produced on the less sterically hindered side, furnishing the corresponding products **3o**–**3s** in good yields. When one of the *ortho*-positions on the phenyl was occupied, amination on the other *ortho*-position occurred, and **3t** was afforded in 45% yields. It is worth mentioning that the disubstituted arylpyridine derivate was also tolerant and provided a 44% yield of **3v**. Substrates bearing different substituents on the pyridine moiety performed well, and all gave good results (**3aa**–**3ae**). Furthermore, pyrazole, oxazole, and thiazole were well-tolerant in the reaction and afforded the products with moderate yields (**3af–3ai**). Importantly, the reaction was suitable for the C2-selectivity amination of indolic heterocycle **3aj**. The derivatives of 6-arylpurine were also compatible, and gave corresponding amination products in 62% and 59% yields, respectively. In addition, some of the substrates were not completely converted, increasing the amount of MesCOOK could effectively improve the conversion and yield of the reaction, such as **3b**, **3c**, **3h**, and others.

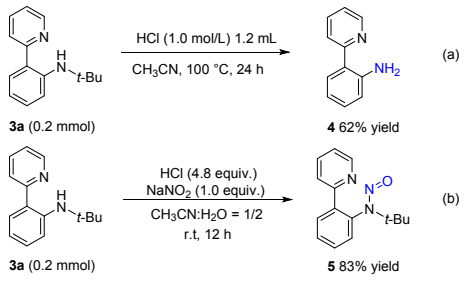
After that, a potential application of the amination product in this reaction was made. The *tert*-butyl group of **3a** could be removed by treatment with hydrochloric acid (Scheme 2a), providing efficient access to a variety of pyridine-substituted aniline derivatives. *N*-nitrosoaniline was prepared in a 83% yield from **3a** in one step (Scheme 2b).

To gain a mechanistic insight of this reaction, a series of control experiments were performed (Scheme 3). Firstly, intermolecular competition reactions between differently substituted aryl pyridines indicated that the electron-rich substrate reacted preferentially (Scheme 3a). Secondly, the standard reaction was uninhibited in the presence of radical scavengers such as **TEMPO**, and this result implied that a radical process may not be involved in this reaction (Scheme 3b). Thirdly, the use of a deuterated co-solvent **D_2O** led to H/D scrambling solely in the *ortho*-position, illustrating the feasibility and reversibility of the C–H metalation elementary step and the tolerance of water in this transformation (Scheme 3c). Finally, the intermolecular competition experiment with

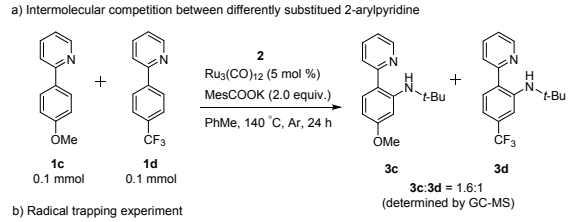
Table 1 Substrate scope of pyridine and *N*-Heterocycle as the DG[a]



[a] Reaction conditions: 1 (0.2 mmol), 2 (2.0 equiv.), $Ru_3(CO)_{12}$ (5 mol %), MesCOOK (2.0 equiv.), PhMe (2.0 mL), under Ar, 140 °C, 24 h. Isolated yields. [b] Using 3.0 equiv. of MesCOOK. [c] [1,1'-biphenyl]-4-ylmethanol as the substrate.



Scheme 2 Potential application of amination products



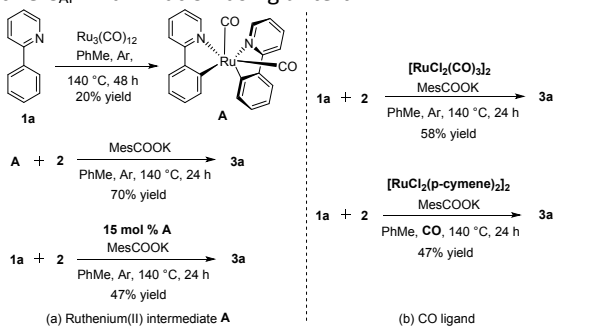
Scheme3 Mechanistic studies

1a and **[D$_5$]-1a** showed a kinetic isotopic effect (KIE) of k_H/k_D = **1.5**, suggesting that the *ortho*-C–H cleavage might be kinetically relevant (Scheme 3d).

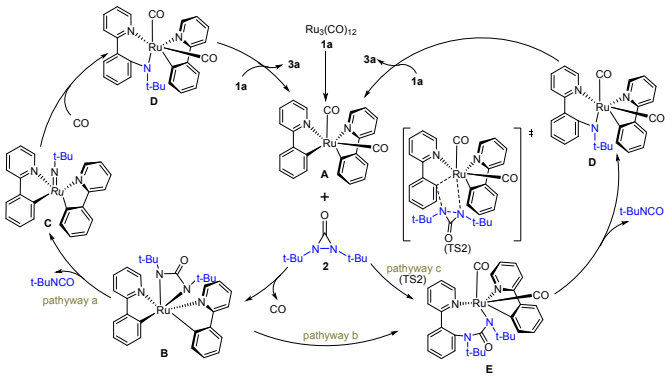
To further clarify the mechanism, the ruthenium (II) intermediate **A**[18] was isolated by mixing **1a** with 1.0 equiv. of $Ru_3(CO)_{12}$ in PhMe at 140 °C for 48 h under argon. The stoichiometric and catalytic reactions utilizing the intermediate **A** worked well and produced **3a** in 70% and 47% yields (Scheme 4), respectively. This result demonstrated the intermediate nature of the ruthenium (II) complex in this catalytic cycle. On the other hand, using $[RuCl_2(CO)_3]_2$ as the catalyst or $[RuCl_2(p\text{-cymene})]_2$ as the catalyst under CO atmospheres could provide good results for the production of **3a**. This result indicated the importance of carbon monoxide and allowed us to understand valence variation of ruthenium in the whole catalytic cycle. We speculate that the strong π-acidic nature of CO as the ligand makes the ruthenium complexes more electrophilic,[14b, 19] which might promote the formation of the ruthenium (II) complex.

Based on mechanistic research detailed above and the previous related literature, a plausible mechanism is proposed. The ruthenium (II) intermediate **A** is formed through $Ru_3(CO)_{12}$ and **1a** by C–H activation step. After the coordination of **A** with **2**, intermediate **B** is generated. Then, **B** releases a molecule of tert-butyl isocyanate[8b, 8e] to form Ru-nitrene species **C** (pathway a). The migratory insertion[20] of **C** leads to the generation of Intermediate **D**. It should be mentioned that the formation of an eight-membered ring intermediate[21] **E** is through the reduction elimination of **B** (pathway b), or an S_N2 nucleophilic ring-opening reaction pathway[22] (pathway c) is still elucidated. Finally, the ligand exchange of **D** with **1a** releases the desired product **3a** and regenerates intermediate **A** for recycling (Scheme 5).

In summary, we have presented a $Ru_3(CO)_{12}$-catalyzed *ortho*-selective C_{Ar}–H amination using *di-tert*-



Scheme 4 Ruthenium (II) intermediate **A** and CO ligand studies



Scheme 5 Proposed mechanism

butyldiaziridinone as an oxidative amination reagent. This strategy gives an expedient approach to generate synthetically useful, highly functionalized aniline derivatives. This method exhibits an excellent functional group compatibility for various phenyl-substituted *N*-heterocycles, including biologically active substrates. Mechanistic studies revealed that an octahedral ruthenium complex, as the probable active catalyst, is involved in this reaction, and the carbon monoxide ligand plays an important role in the C–H activation.

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Conflicts of interest

There are no conflicts to declare.

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