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Authors: Jian Chen, Tianle Huang, Xinrui Gong, Zhu-jun Yu, Yuesen Shi, Yu-Hang Yan, Yang Zheng, Xuexin Liu, Guobo Li, and Yong Wu

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Ruthenium-Catalyzed *meta*-Selective C-H Nitration of Biologically Important Aryltetrazoles

Jian Chen, Tianle Huang, Xinrui Gong, Zhu-Jun Yu, Yuesen Shi, Yu-Hang Yan, Yang Zheng, Xuexin Liu, Guo-Bo Li* and Yong Wu*[a]

[a] Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, P. R. of China
E-mail: wyong@scu.edu.cn (Y. Wu), liguobo@scu.edu.cn (G.-B. Li)
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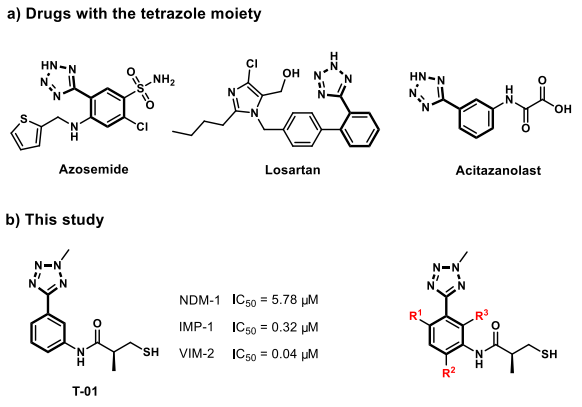
Abstract. The first example of tetrazole-directed *meta*-selective C-H nitration is described. This transformation provided a straightforward approach for the synthesis of biologically important *m*-nitroaryltetrazoles in moderate to excellent yields with good functional group compatibility. In addition, new metallo-β-lactamase inhibitors were obtained by further transformation of the synthesized *m*-nitroaryltetrazoles.

Keywords: tetrazole; *meta*-selective; C-H nitration; metallo-β-lactamase inhibitors.

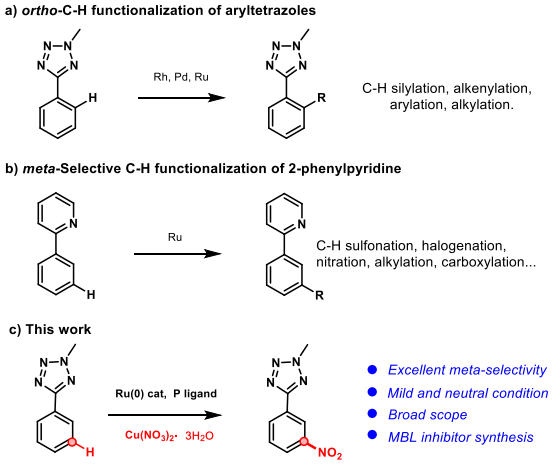
Aryltetrazoles make up a class of biologically active moieties, which have been used for the development of antimicrobial,[1] antihypertensive,[2] anticancer,[3] anti-inflammatory and analgesic agents[4]. Notably, the 5-phenyltetrazole moiety frequently occurs in clinically useful drugs, such as the loop diuretics Azosemide, the hypertension drug Losartan, and the anti-allergic drug Acitazanolast (Figure 1a). In recent years, this moiety has also been used in the development of inhibitors targeting β-lactamases,[5] which are an important class of enzymes that cause the β-lactam antibiotic resistance.[6] We are interested in developing new β-lactamase inhibitors,[7] particularly the metallo-β-lactamases (MBLs), which can hydrolyze almost all β-lactam antibiotics. Recently, we obtained a 5-phenyltetrazole containing compound, **T-01**, which showed potent inhibition against the clinically relevant B1 subclass of MBL enzymes NDM-1, IMP-1, and VIM-2 (Figure 1b). In the synthesis of such MBL inhibitors, the construction of *meta*-C-N bonds of aryltetrazoles is one of the key steps. Motivated by the pharmacophore feature of tetrazole rings and our continuous interests in C-H activation, we aimed to develop a new strategy for the synthesis of *meta*-nitroaryltetrazoles, with the aim to readily construct the C-N bond with high regioselectivity and excellent functional group tolerance.

With the rapid development of direct C-H functionalization in recent years,[8] several tetrazole templates have been reported as the directing groups (DG) to assist the Ru-, Rh- or Pd-catalyzed *ortho*-C-H activation (Scheme 1a). For instance, the Murai group developed a method for *ortho*-silylation of aryltetrazoles with triethylsilane,[9] and then the C–H arylation/olefination reactions of aryltetrazoles were reported.[10] The Weck group reported an iridium-catalyzed *ortho*-H/D and H/T exchange of

Figure 1. The 5-phenyltetrazole containing drugs and MBL inhibitors



Scheme 1. C-H activation examples of aryltetrazoles or 2-phenylpridine



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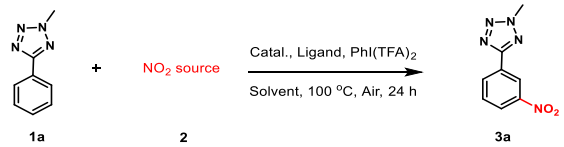
aryltetrazoles.[11] However, tetrazole-directed *meta*-C-H activation had not been reported, to the best of our knowledge.

Fortunately, *meta*-C-H functionalizations have been achieved by using the *ortho*-metalation strategy, in which less expensive ruthenium catalysts and common DGs can be used.[12] Representative reactions included sulfonation,[13] halogenation,[14] nitration,[15] carboxylation,[16] alkylation[17] and so on (Scheme 1b). Compared with the widely used pyridyl DG, the tetrazole as a DG is relatively challenging, as it has multiple potential chelating sites that may deactivate the metal catalysts. We herein report a method for tetrazole-directed metal-catalyzed *meta*-selective C-H nitration.

Table 1. Optimization of reaction conditions [a)]

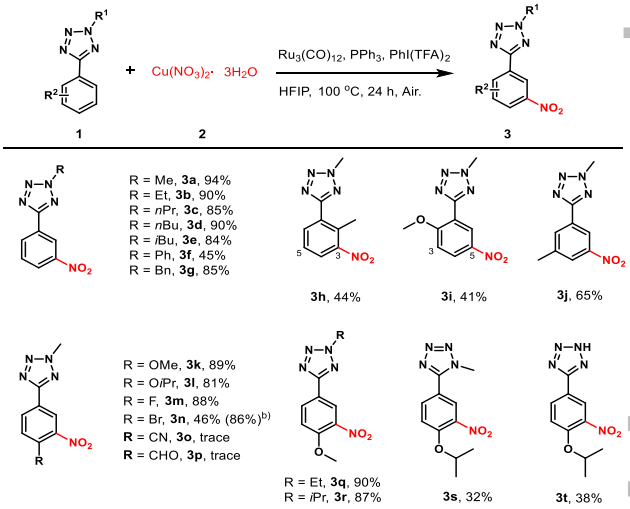


Entry	Catal.	NO_2 source	Solv.	Yield [b)]
1	$Ru_3(CO)_{12}$	$AgNO_3$	DCE	33%
2	$[RuCl_2(p\text{-cymene})]_2$	$AgNO_3$	DCE	N.R.
3	$Ru(bpy)_3Cl_2$	$AgNO_3$	DCE	<5%
4 [c)]	$Ru_3(CO)_{12}$	$AgNO_3$	DCE	N.R.
5 [d)]	$Ru_3(CO)_{12}$	$AgNO_3$	DCE	<5%
6	$Ru_3(CO)_{12}$	$AgNO_3$	HFIP	55%
7	$Ru_3(CO)_{12}$	$AgNO_3$	Tol	N.R.
8 [e)]	$Ru_3(CO)_{12}$	$AgNO_3$	HFIP	61%
9 [e)]	$Ru_3(CO)_{12}$	KNO_3	HFIP	7%
10 [e)]	$Ru_3(CO)_{12}$	$Cu(NO_3)_2{\cdot}3H_2O$	HFIP	94%
11[e), f)]	$Ru_3(CO)_{12}$	$Cu(NO_3)_2{\cdot}3H_2O$	HFIP	59%
12 [g)]	$Ru_3(CO)_{12}$	$Cu(NO_3)_2{\cdot}3H_2O$	HFIP	N.R.
13	-	$Cu(NO_3)_2{\cdot}3H_2O$	HFIP	N.R.
14	$RuCl_3$	$Cu(NO_3)_2{\cdot}3H_2O$	HFIP	N.R.

[a)] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), Catal. (7.5 mol %), ligand (30 mol %), $PhI(TFA)_2$ (0.22 mmol), solvent (2.0 mL) in a sealed tube; [b)] Isolated yields; [c)] $K_2S_2O_8$ as the oxidant; [d)] Oxone as the oxidant; [e)] PPh_3 as the ligand; [f)] 80 °C; [g)] no oxidant.

Initially, 2-methyl-5-phenyl-2*H*-tetrazole (**1a**) was selected as a model substrate to react with $AgNO_3$ in DCE at 100 °C for 24 hours in a sealed tube, using $Ru_3(CO)_{12}$ as the catalyst and $PhI(TFA)_2$ as the oxidant (Table 1). The desired product **3a** was obtained in a yield of 33% (entry 1). We then tried other Ru catalysts (entry 2 and 3); however, the results showed that $Ru_3(CO)_{12}$ remained the best catalyst for this transformation. Subsequently, we screened different oxidants, which did not improve the conversion (entry 4 and 5). Further screening of reaction solvents revealed that only hexafluoroisopropanol (HFIP) improved the yield (entry 6 and 7). Next, extensive ligands were screened (see Supporting Information). PPh_3 led to a better yield of 61% in this model reaction (entry 8). To our surprise, a substantial increase in conversion was observed by using $Cu(NO_3)_2{\cdot}3H_2O$ as the nitro source (entry 9 and 10). When the reaction was carried out at 80 °C, the yield of **3a** notably dropped (entry 11). Control experiments in the absence of $PhI(TFA)_2$ or $Ru_3(CO)_{12}$ revealed that these components were crucial for this transformation (entry 12 and 13). Further attempts by using simple $RuCl_3$ as the catalyst failed to realize the nitration (entry 14). Taken together, the reaction conditions in entry 10 were selected as the optimal conditions.

Scheme 2. Substrate scope of tetrazole as the DG [a)]



[a)] Reaction conditions: **1** (0.2 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (0.3 mmol), $Ru_3(CO)_{12}$ (7.5 mol %), PPh_3 (30 mmol %), $PhI(TFA)_2$ (0.22 mmol) in HFIP (2.0 mL) for 24 h at 100 °C in a sealed tube; isolated yields. [b)] Yield based on the recovered starting material is listed in parentheses.

With the optimized conditions in hand, we moved on to extend the scope of 5-aryltetrazole substrates (Scheme 2). A series of R^1 substituted tetrazoles were first tested. Introduction of various groups on the tetrazole moiety could proceed smoothly, affording the corresponding products in moderate to good yields, although electron-donating groups were likely more favorable to this transformation (**3a**-**3g**). Interestingly, in the case of the *ortho*-methyl substituted 5-aryltetrazole as the substrate, the corresponding product **3h** was produced in 44% yield. A different preference was observed for the *ortho*-methoxy substituted 5-aryltetrazole; *meta*-C-H nitration occurred at the less hindered site (C5), affording the corresponding product **3i**, which may attribute to the different electronic effects.[14b, 15b, 15d] When a methyl group was introduced to the *meta*-position, the desired product **3j** was produced in 65% yield. The *para*-substituted 5-aryltetrazoles appear to be more suitable substrates for this reaction (**3k**-**3n**, **3q**-**3r**). The substrates bearing a *para*-CN or CHO

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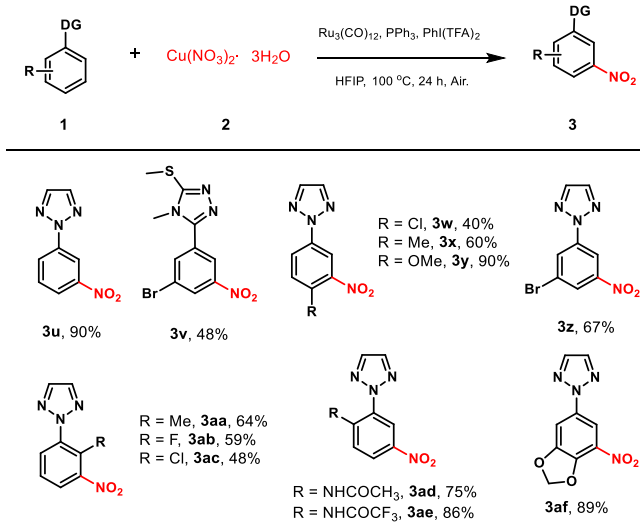
substituent retarded the reaction, further indicating the reaction seems sensitive to the electronic effects (**3o** and **3p**). The 1-substituted or non-substituted tetrazoles were also compatible with the catalytic system, albeit in low yields (**3s** and **3t**).

Scheme 3. Scope of triazole as the DG [a)]



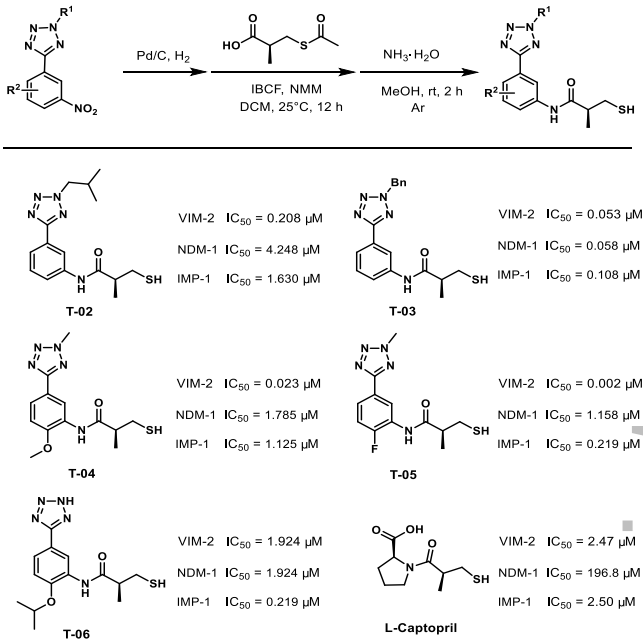
[a)] Reaction conditions: 1 (0.2 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (0.3 mmol), $Ru_3(CO)_{12}$ (7.5 mol %), PPh_3 (30 mol %), $PhI(TFA)_2$ (0.22 mmol) in HFIP (2.0 mL) for 24 h at 100 °C in a sealed tube. Isolated yields.

We then examined 2-aryl-1,2,3-triazole and 2-aryl-1,2,4-triazole,[18] which are structurally similar to aryltetrazoles, as the substrates to react with $Cu(NO_3)_2{\cdot}3H_2O$ under the standard conditions (Scheme 3). To our delight, the corresponding *meta*-nitration products **3u** and **3v** were obtained with considerable yields. Various triazoles bearing diverse aryl substituents were also investigated. The 2-phenytriazoles substituted with electron-donating and electron-withdrawing groups at *ortho*-, *meta*- or *para*-positions of the 2-phenyl moiety were compatible with this transformation, generating the desired products (**3w-3af**) in moderate to high yields.

We used the generated nitrated products to synthesize new compounds **T-02** to **T-06**, containing a metal-binding moiety of (*S*)-3-mercapto-2-methylpropanamide. These compounds displayed potent inhibition against MBL enzymes VIM-2, NDM-1, and IMP-1 (Scheme 4). In particular, **T-03** manifested IC_{50} values of 0.053, 0.058 and 0.108 μM to VIM-2, NDM-1, and IMP-1, respectively, which is more potent than the control compound L-captopril (Scheme 4). This application may also suggest a possible strategy to obtain new MBL inhibitor by incorporating aryltetrazoles and other appropriate metal binding pharmacophores.[19]

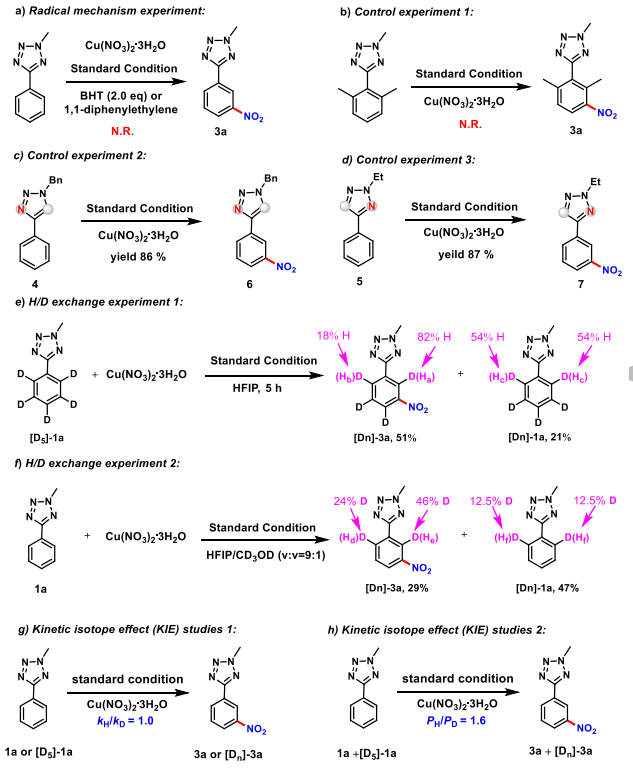
To understand the mechanism of Ru-catalyzed *meta*-selective C-H nitration of aryltetrazoles, a preliminary mechanism study for the reaction was conducted. With the addition of the radical inhibitor

Scheme 4. MBL inhibitors and their activities.



1,1-diphenylethylene or 2,6-di-tert-butyl-4-methylphenol (BHT), the reactions were almost completely quenched, suggesting that a radical pathway might be involved (Scheme 5a). More importantly, we found that the aryltetrazole substrate bearing two methyl groups to block the two *ortho* positions of the phenyl ring failed to get the target molecule under the standard conditions, supporting the necessity of the *ortho*-C-H metalation in the reaction process (Scheme 5b). We then conducted the reaction with two substrates **4** and **5**, in which the N1 or N4

Scheme 5. Mechanistic studies



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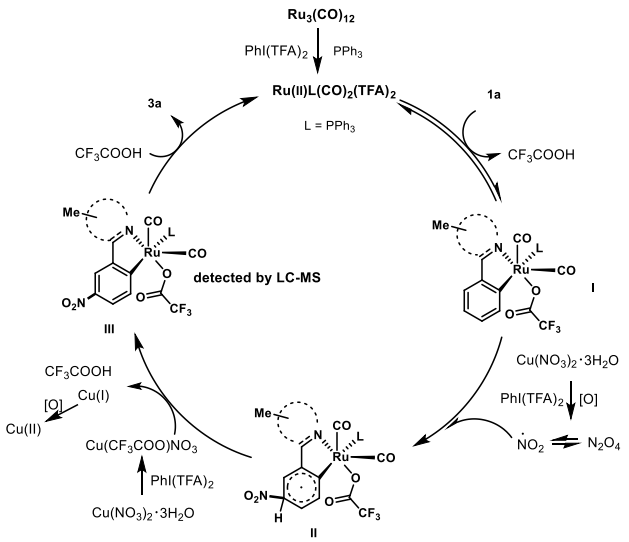
nitrogen atom is removed. Both *meta*-nitro products **6** and **7** were generated in good yield under the standard conditions, indicating that both N1 and N4 might be able to coordinate with Ru (Scheme 5c and 5d). Next, *ortho*-H/D exchange was observed in the NMR spectrum when treating [D_5]-**1a** or **1a** with $Cu(NO_3)_2{\cdot}3H_2O$ under the standard conditions, confirming that the initial *ortho*-C-H ruthenation was reversible (Scheme 5e and 5f). Finally, the competitive and parallel kinetic isotope effects were measured. The k_H/k_D and P_H/P_D values were 1.0 and 1.6, respectively, suggesting that the C-H cleavage of aryltetrazole was probably not involved in the rate-limiting step (Scheme 5g and 5h).

Scheme 6. Proposed mechanism



On the basis of the mechanistic experiments described above and the pertinent literatures,[15a-c] a plausible mechanism for this reaction is illustrated in Scheme 6. Firstly, the active Ru(II) catalysts are obtained by the oxidation of Ru(0) by $PhI(TFA)_2$. Then the active state species **I** is formed from substrate **1a** with the active Ru(II) catalyst *via* C-H activation process.[15c, 20] Next, electrophilic attack of the *para*-carbon relative to the C-Ru bond generates the active complex **II**.[15c] In this step, nitrogen dioxide radical ($\cdot NO_2$) is originated from $Cu(NO_3)_2{\cdot}3H_2O$ through N_2O_4 process.[21] An anion exchange between $Cu(NO_3)_2{\cdot}3H_2O$ and $PhI(TFA)_2$ gives a new active copper salt.[15a] Then, the active copper(II) assist the deprotonation of the complex **II** to generate the more stable complex **III**,[15a] which was detected by LC-MS(see SI). Finally, a ligand exchange of **III** with CF_3COOH releases the *meta*-nitrated product **3a** and regenerates the active Ru(II) catalysts for next catalytic cycles.

In summary, we established a strategy for tetrazole-directed, ruthenium-catalyzed *meta*-selective C-H nitration. The reactions proceeded smoothly, affording the desired products in moderate to excellent yields, and also had a good functional group compatibility. Further transformation of the synthesized *m*-nitroaryltetrazoles led to new potent MBL inhibitors. This work will be useful to derive new *m*-nitroaryltetrazoles and related derivatives, as well as the new types of MBL inhibitors.

Experimental Section

Synthesis of Compound 3a; Typical Procedure

Compound **1a** (0.2 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (0.3 mmol), $Ru_3(CO)_{12}$ (0.15 mmol), PPh_3 (0.06 mmol) and $PhI(TFA)_2$ (0.22 mmol) were charged into a sealed tube, to which was added HFIP (2.0 mL). The reaction mixture was stirred at 100 °C for 24 h. After cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using PE/EA as the eluent to afford the corresponding compound **3a**.

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Ruthenium-catalyzed *meta*-selective C-H nitration of biologically important aryltetrazoles

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