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A directing group assisted ruthenium catalyzed approach to access *meta*-nitrated phenol

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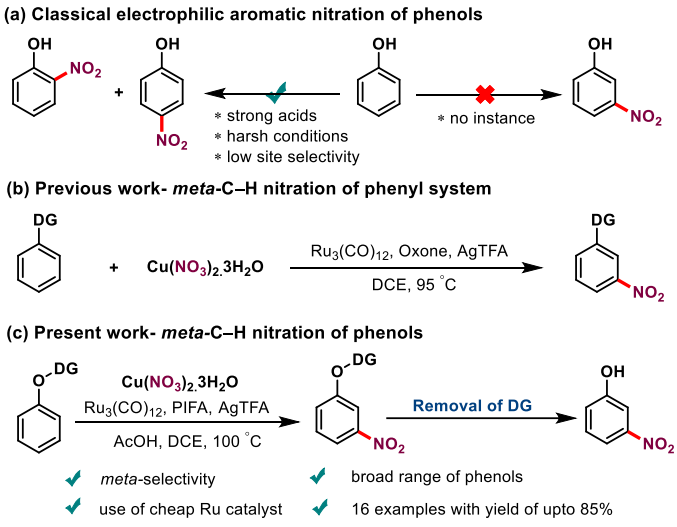
A *meta*-selective C–H nitration of phenol derivatives have been developed using a Ru-catalyzed σ-activation strategy. $Cu(NO_3)_2.3H_2O$ has been employed as the nitrating source while $Ru_3(CO)_{12}$ was found to be the most suitable metal catalyst for the protocol. Mechanistic studies suggest the involvement of an *ortho*-C_{Ar}–H metal intermediate, which promotes the *meta*- electrophilic aromatic substitution and silver assisted radical pathway.

Phenols are prevalent in a wide variety of pesticides and household commodities. In low concentrations, phenols are used as disinfectants in household cleaners while in industries, it is widely used as a precursor for various explosives.[1] These class of compounds are also known for their reactivity towards electrophilic aromatic substitution reactions. The non-bonding electrons on oxygen make the intermediate cation highly stable and this stabilization is most effective at *ortho* or *para* positions.[2] A simple limitation that awaited resolving was how to initiate an electrophilic substitution at the electron poor *meta* position of phenols where only the *ortho* and *para* positions were suitably activated for functionalization ?

Transition metal catalysed C–H activation has inspired chemists to evolve in an unprecedented manner.[3,4] Proximal[5] and distal[6,7] C–H functionalization has advanced immensely in the past few decades. Very recently, *meta*-C_{Ar}–H functionalization has been achieved by utilizing the *ortho*-metalation strategy, in which Ru-catalyst and an easily removable DG were employed. Instead of standard oxidative addition/reductive elimination chemistry, a Ru–C_{Ar} σ-bond in ruthenium (II) complexes activates its *ortho*/*para* position, which is the *meta* position with respect to the substituent.[8] The use of Ru-based metal catalyst was first deployed by Frost[9] and Ackermann[10] when they reported the *meta* functionalization of 2-phenylpyridine based templates. Huang and Greaney simultaneously reported *meta*-bromination.[11, 12] Inspite of significant development in this field, the formation of C–N bonds remained unknown until Zhang came up with the nitration of 2-phenylpyridine (Scheme 1)[13].

Scheme 1. Evolution of nitration of phenols



Recently, transition-metal-catalyzed C–H bond activation has successfully been used to functionalize phenol derivatives.[14-19] The employment of 2-phenoxypyridine which can be converted to *meta*-substituted phenol post-modification was observed by Li group and Cui group.[15, 16] Significant progress has been made with regards to the *meta*- nitration of oxime and other arenes.[20] However, *meta*-nitration of phenols has remained an enigma to the field of synthetic organic chemists.

Under the classical methods, nitration of phenol generate a mixture of *ortho* and *para*-products which suffers from the use of strong acids and low site selectivity. Inspired by the need to develop a methodology converting phenol to *meta*-nitrophenol, we demonstrate the first transition metal catalyzed *meta*-nitration of phenol utilizing pyridine as the template.

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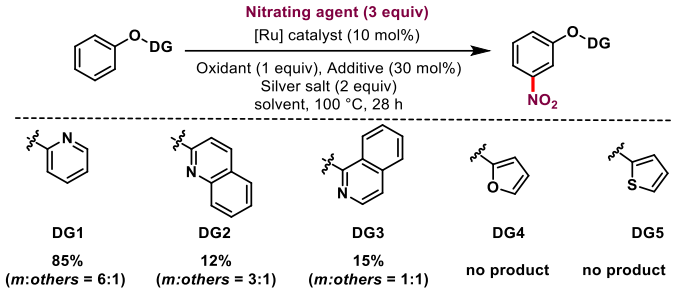
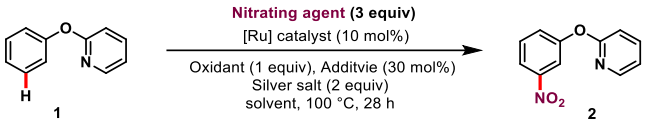
At the outset, various templates were studied ranging from pyridine, quinolone, isoquinoline, thiophene and furan (Scheme 2). With the pyridine template, moderately selective *meta*-nitro product was acquired over the more favoured *ortho*-product. The requirement of nitrogen as a coordinating group can be deduced from the absence of any product in case of thiophene and furan based templates.



Scheme 2. Directing groups for *meta*-C–H nitration of phenols

Table 1. Optimization of the reaction conditions



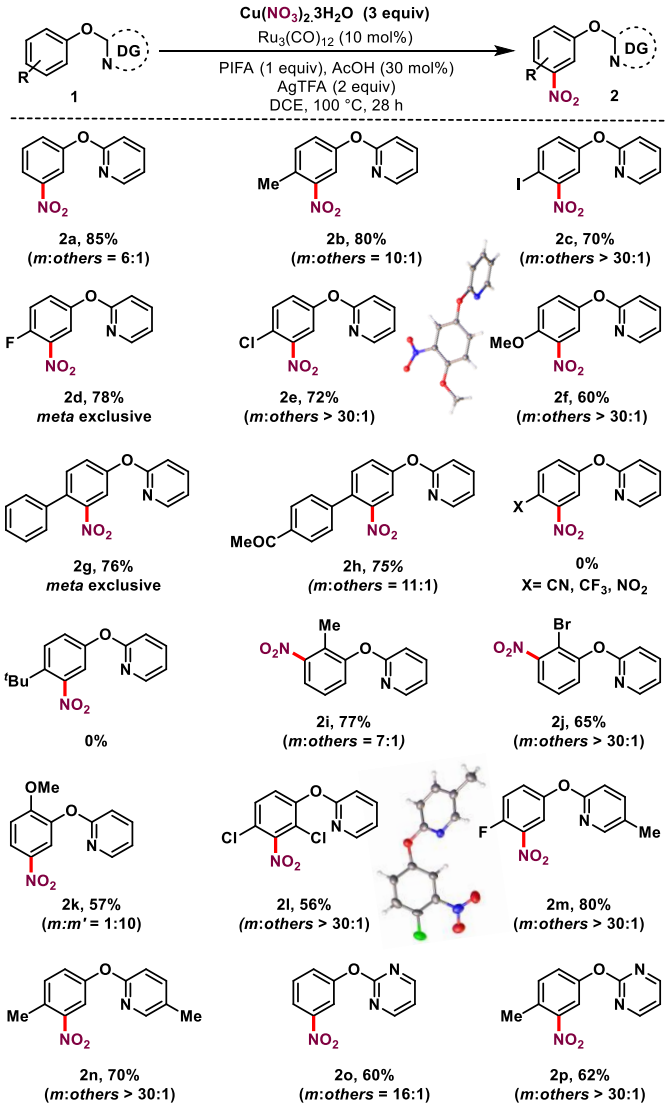
Entry	[Ru]-catalyst	Oxidant	Nitrating reagent	Yield[a] (*m*:*others*)
1	$Ru_3(CO)_{12}$	PIFA	$AgNO_3$	12 (2:1)[b]
2	$Ru_3(CO)_{12}$	PIFA	$AgNO_2$	10 *ortho*[b]
3	$Ru_3(CO)_{12}$	PIFA	$Cu(NO_3)_2.3H_2O$	27 (3:1)[b]
4	$RuCl_3$	PIFA & AcOH	$Cu(NO_3)_2.3H_2O$	18 (2:1)[c]
5	$[Ru(p\text{-cymene})Cl_2]_2$	PIFA & AcOH	$Cu(NO_3)_2.3H_2O$	20 (1:2)[c]
6	$Ru_3(CO)_{12}$	$K_2S_2O_8$	$Cu(NO_3)_2.3H_2O$	54 (1:2)[c]
7	$Ru_3(CO)_{12}$	PIFA & AcOH	$Cu(NO_3)_2.3H_2O$	85 (6:1)[d]
8	-	PIFA & AcOH	$Cu(NO_3)_2.3H_2O$	-

[a]Yields based on recovered starting material. [b]No AgTFA and AcOH. [c]No AgTFA. [d]1 (0.05 mmol), $Cu(NO_3)_2.3H_2O$ (0.15 mmol), PIFA (0.05 mmol), AcOH (0.01 mmol), AgTFA (0.1 mmol) in DCE (1 mL).

Our initial investigation involved the utilization of $AgNO_3$ as the nitrating source and $Ru_3(CO)_{12}$ as the metal catalyst. Although, we got *meta*-nitrated product but with a 12% yield and 2:1 selectivity (Table 1, entry 1). In absence of AgTFA, $AgNO_2$ gives *ortho*-nitration (Table 1, entry 2) while in the presence of AgTFA and AcOH, $AgNO_2$ gives 2:1 *meta*:*ortho* products. It appears that regioselectivity is quite dependent on the use of oxidant and additive rather than the choice of nitrating agent. Among other nitrating agents, $Cu(NO_3)_2.3H_2O$ was found to be the best. Ruthenium complex $Ru_3(CO)_{12}$ was found to be the optimum metal catalyst. Thorough optimizations of the oxidants were inquired into whereby a combination of PIFA [PIFA=Iodosobenzene bis(trifluoroacetate)] and AcOH was established to give the best yield (Table 1). Transition metal catalyzed nitration is generally known to proceed through a radical process.[21] Consequently, we decided to study various silver salts and alkyl iodides as radical initiators.[22] The use of 2 *equiv.* AgTFA improved both the yield and selectivity of *meta* nitrated product significantly (See Supporting Information). No significant improvement in yield and selectivity was observed after use of bases while the presence of ligands was found to be detrimental for the reaction protocol (See Supplementary Information).

Once we had the optimized conditions in hand, we tried to find the scope and limitations of our protocol. *Para*-substituted phenols proceeded well under the reaction conditions (Table 2, **2b-2h**). X-ray analysis confirmed the structure of 2f. Both electron donating and neutral *para*- substituted phenols gave synthetically useful yields and selectively *meta*-nitrated products. Halogenated phenols were nitrated with excellent *meta*-selectivity (**2c**-**2e**). However, the presence of strong electron withdrawing *para*-substitution on benzene ring such as cyano, nitro, trifluoromethyl and aldehyde group were detrimental towards the reaction condition. This was supposedly because of deactivation of the

Table 2. Scope with respect to different phenols[a]

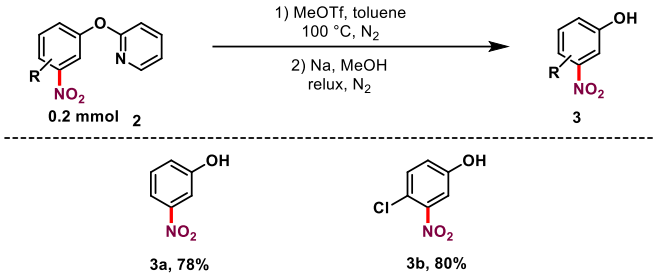


[a]1 (0.2 mmol), $Cu(NO_3)_2.3H_2O$ (0.6 mmol), PIFA (0.2 mmol), AcOH (0.04 mmol), AgTFA (0.4 mmol) in DCE (3 mL). Yields of the isolated products.

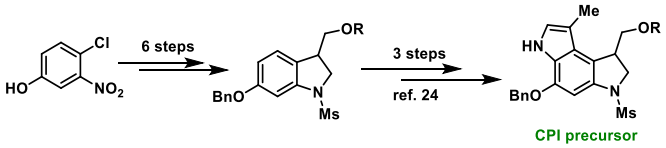
aromatic ring in presence of such substituent, thus rendering phenol ineffective towards *meta*-functionalization. In addition, substrate having bulky *tert*-butyl group at *para* position of benzene ring gave only trace amount of the desired product

(Table 2). *Ortho*- substituted phenols were also compatible under the reaction protocol with the *ortho*-metallic intermediate forming on the unsubstituted side to direct the *meta*-nitration on the more sterically congested side (**2i** and **2j**). An exception was found in case of *ortho*-methoxy phenol that shows greater selectivity towards the less sterically crowded side (**2k**).[20a] Further, disubstituted phenols did not create any obstacle towards *meta*-functionalization (**2l**). Substitutions on the pyridine directing group did not hinder nitration at the *meta* position of phenols (Table 2, **2m** and **2n**). Product **2m** was characterized by X-ray, which further confirms *meta*-nitration overriding the more favoured *ortho* position. Pyrimidine is structurally comparable to pyridine. The presence of an extra nitrogen atom in case of pyrimidine reduces the π-electron density, making the metal co-ordination more favourable. Consequently, changing template from pyridine to pyrimidine improved the selectivity of the *meta*-nitration product albeit in slightly lower yields (Table 2, **2o** *vs* **2a** and **2p** *vs* **2b**).

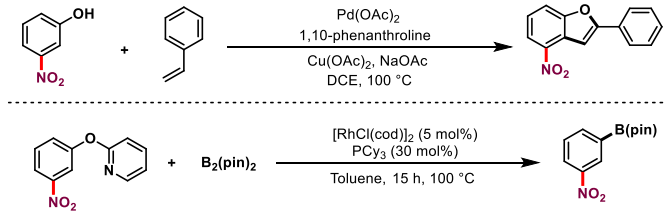
Removal of the 2-pyridine template was a necessary pre-requisite for our methodology. The 2-pyridyl directing group can be removed methodically in good yields to generate *meta*-nitrophenols (Scheme 3).[15] Consequently, ruthenium catalyst provided an expedited and viable process for the synthesis of *meta*-nitrophenols. The importance of these *meta*-nitrophenols lies in it being an important precursor of high energy materials such as potent antitumor agent CC-1065 (Scheme 4).[23]



Scheme 3. Directing group removal to generate *meta*-nitrophenol



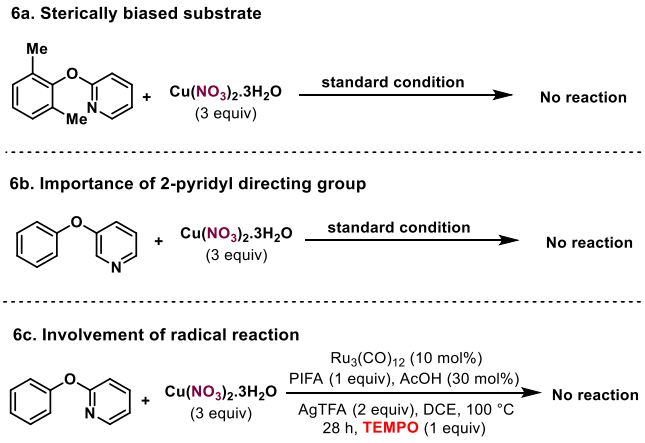
Scheme 4. Utility of nitrophenols as important precursor



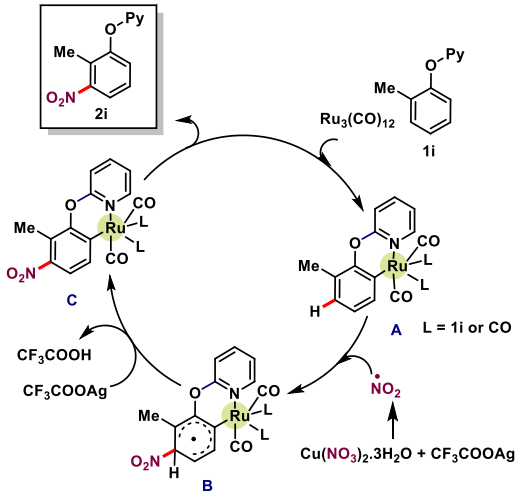
Scheme 5. Synthetic diversifications

Further, Synthesis of furan derivatives with free nitrophenols and olefin following our previous report[24] and borylative removal of pyridine directing group to acquire nitro-borylated compound[17a] have been outlined in Scheme 5.

To have a better understanding about the mechanism of the reaction, a series of control experiments were conducted (Scheme 6). The presence of two methyl substituents on the two *ortho* positions resulted in a complete shutdown of the reaction, suggestive of the fact that the formation of the ruthenium *ortho*-complex is a pre-requisite for the *meta*-nitration methodology (Scheme 6a). The importance of a 2-pyridyl template in making the heteroatom coordinate the metal catalyst to the *ortho*-C–H bond which in turn directs the functionalization to the *meta* position was also considered. Replacing 2-pyridyl directing group with a 3-pyridyl template terminates the formation of the *meta*-nitrated product completely (Scheme 6b), hence further emphasizing on the importance of the directing group. Involvement of radical inhibitors such as TEMPO and BHT prevented production of *meta*-nitrated product, as a result radical reaction might be prevalent in this *meta*-nitration methodology (Scheme 6c).



Scheme 6. Control experiments



Scheme 7. Plausible mechanistic cycle for *meta*-C–H nitration

In accordance with our experimental observations and related literature reports on ruthenium catalysed *meta*-functionalization, [9-13, 15] a mechanistic cycle is proposed as in Scheme 7. The coordination of $Ru_3(CO)_{12}$ with substrate **1i** forms an active *ortho* metallacomplex intermediate **A**. The Ru–C σ bond acts as a Friedel-Crafts type *ortho*/*para*-directing group to incorporate the incoming nitrating group, generated by homolytic cleavage of $Cu(NO_3)_2.3H_2O$ by AgTFA, at its *ortho*/*para* position which is *meta* with respect to the substrate **1i**. Deprotonation followed by ligand exchange with 2-

phenoxypyridine results in the formation of *meta*-nitrated product **2i** along with the regeneration of the active catalyst.

We have developed a highly regioselective ruthenium catalyzed *meta*-C–H nitration of 2-phenoxypyridine which after removal of directing group results in the *meta*-nitration of phenols. Mechanistic studies indicate the involvement of a radical intermediate and the protocol supposedly follows the formation of a six-membered metallacycle intermediate. This methodology in part overcomes an existing limitation of classical organic chemistry by executing *meta*-nitration of phenols selectively over the more favourable *ortho* and *para* positon of phenols.

Conflicts of interest

There are no conflicts to declare.

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