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Actinide (Th^{4+} and UO$_2^{2+}$) assisted oxidative coupling of *ortho*-phenylenediamine in the presence of oxygen

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ABSTRACT

While the actinide salts because of their Lewis acidity and flexible coordination geometry demonstrate unique possibilities as catalysts, research with actinide catalysts typically involves complexed organoactinide frameworks. Many actinide salts have yet to be explored in catalysis or as reagents in metal mediated synthesis. Here, the synthesis of the heterocycle 2,3-diaminophenazine has been reported in good yields in the presence of oxygen via the first use of thorium nitrate or uranyl nitrate as the catalyst.

Introduction

Recently, the early 5f elements have been of interest for their potential use in catalysis, metal mediation, and stoichiometric reactivity.[1–6] Actinides have 5f valence orbitals and large ionic radii, both of which offer distinguishing chemical characteristics that can be exploited in catalysis.[7] Reports detailing some of these synthetic methods[3,4,8,9] or catalytic reactions[2,5,10,11] incorporating actinide metals have become more common as new starting materials have been developed.[12–14] For example, thorium catalysts have been used for the cyclization and hydroalkoxylation of alkynyl alcohols[2] and thorium and uranium Cp* complexes have been used in the ring-opening metathesis polymerization of cyclic esters.[11] The focus of this work is typically based on an actinide center saddled with sterically hindering ligands (such as cyclopentadiene,[13] pentamethylcyclopentadienyl, or *N*-ethylmethylamine[11,15]), although UI_3 has been reported to catalyze Diels–Alder and Mukaiyama aldol reactions.[16,17] Ultimately, the ligand and the metal are bound covalently to some degree, and the reactivity of these ligand–actinide complexes and their mechanisms of action have not been fully explained.[11,15] For example, Arnold and coworkers have used an organothorium metallacycle precatalyst, $[(Me_3Si)_2N]Th[k_2\text{-}(N,C)\text{-}CH_2Si(CH_3)N(SiMe_3)]$, to regioselectively oligomerize terminal alkynes producing organic enynes and this demonstrates the first example of using a Th catalyst such as this in C–C bond formation.[18] Although all of these methods have aided in the understanding of the chemistry of the actinides, they require laborious preparation and, being either air or moisture sensitive, have short shelf-lives. In contrast to these organoactinide catalysts, actinide salts offer longer shelf-lives and increased ease of use. They are commercially available, and still remain to be characterized.

The heterocycle 2,3-diaminophenazine (DAP), is of interest in the self-assembly of nanobelts,[19] and it is typically prepared via H_2O_2 catalysis with horseradish peroxidase and fungal laccase enzymes.[20] Li took advantage of the electroactivity of DAP when using the rapid oxidation of OPD to DAP via cupric ion-catalysis to synthesize electroactive nanoparticles that were to dope a graphene nanolabel. This graphene nanolabel was then coupled with a peptide-based probe to target SMO, a protein connected to metastatic tumor cells that is used as a biomarker, to determine the metastatic activity of tumor cells.[21,22] Non-biological synthetic pathways are known, including catalysis by Fe(III), Co(II), and Cu(II) metal salts.[19,23–25] We noted that the unencumbered 5f orbitals of actinide salts may offer another non-biological pathway to catalyze this synthesis. Here, we describe the thorium nitrate, uranyl nitrate, and oxygen mediated synthesis of 2,3-diaminophenazine from *ortho*-phenylenediamine (OPD) (see Scheme 1). Of note, simple, sterically unencumbered actinide centers have rarely been reported in the literature.[17,18] Few reactions have been reported with simple actinide salts,[17,18,26] and no catalytic reactions have been reported using simple thorium salts.

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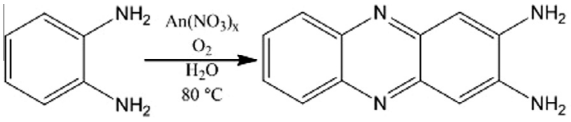


Scheme 1. Oxidation of *ortho*-phenylenediamine to 2,3-diaminophenazine.

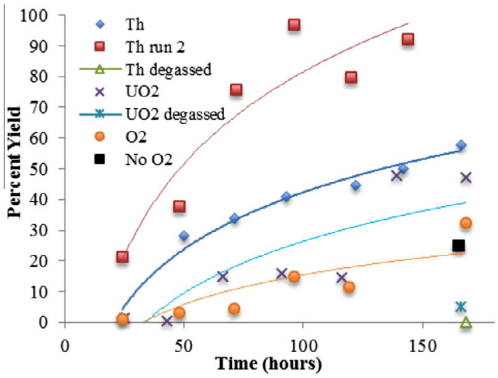


Figure 1. Percent yield of oxidative coupling of *ortho*-phenylenediamine versus time.

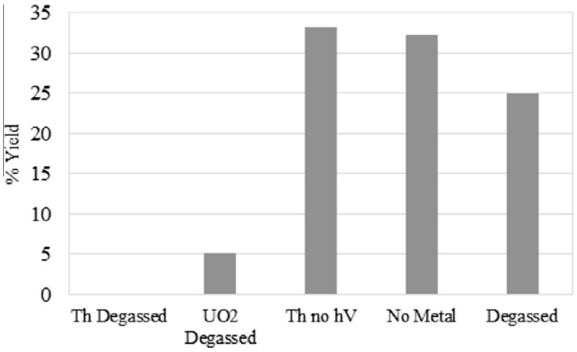


Figure 2. Percent yield of oxidative *ortho*-phenylenediamine coupling with varying conditions.

Results and discussion

As shown in Figure 1, dioxygen alone can oxidize *ortho*-phenylenediamine to 2,3-diaminophenazine. Incorporating the simple actinide nitrate salts [$Th(NO_3)_4$ or $UO_2(NO_3)_2$] as a catalyst with just 1% catalyst loading, enhances the oxidation of *ortho*-phenylenediamine to 2,3-diaminophenazine, by factors of 2 and 1.5, respectively, in the presence of dioxygen. While this oxidation occurs much slower than results found using simple $FeCl_3$ salt—in that case 80% catalyst loading was required (0.48 mmol $FeCl_3$ to 0.60 mmol of *ortho*-phenylenediamine).[19] Here, only a 1% catalyst loading with $Th(NO_3)_4$ or $UO_2(NO_3)_2$ is required. It is evident that the addition of actinide ions (Th^{4+} and UO_2^{2+}) to the aqueous solution provides metal mediation for the oxidative generation of 2,3-diaminophenazine. Increasing the Th^{4+} concentration by a factor of 2 increases the formation of the 2,3-diaminophenazine product as seen in Figure 1 (Th and Th run 2). This indicates that the inclusion the actinide (Th^{4+} or UO_2^{2+}) ions in the presence of dioxygen exhibits a synergistic behavior, as the sum of the 'O_2' and degassed actinide salt reactions is less than the isolated product in the ($Th^{4+} + O_2$) reaction alone.

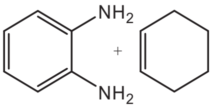
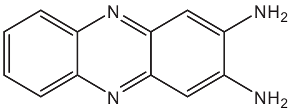
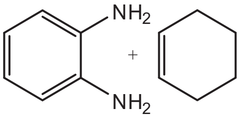
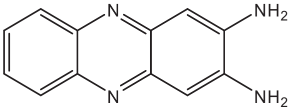
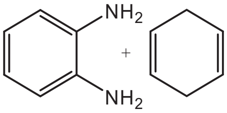
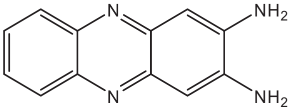
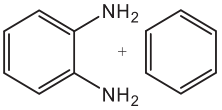
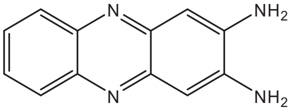
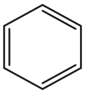
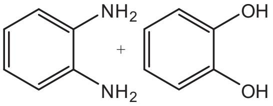
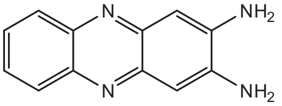
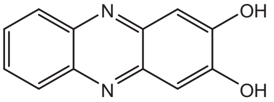
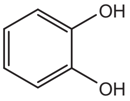
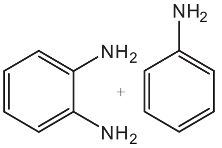
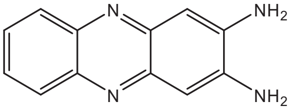
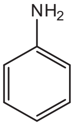
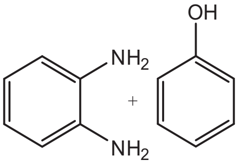
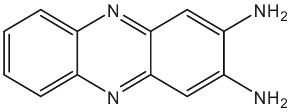
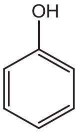
To better understand the influence of dioxygen in the mechanism of the oxidation reaction, two reactions were prepared and allowed to react for seven days. In the first, a Schlenk flask containing water and *ortho*-phenylenediamine with $Th(NO_3)_4$ as the actinide source was degassed by bubbling Argon using a freeze–pump–thaw method to remove as much dioxygen as possible. In the second reaction, a Schlenk flask containing water and *ortho*-phenylenediamine with $UO_2(NO_3)_2$ as the actinide source was also degassed using freeze–pump–thaw. After 7 days, no observable precipitate was present in the reaction flask containing $Th(NO_3)_4$, and no color change was observed. No phenazine was detected upon workup and analysis. The reaction flask with $UO_2(NO_3)_2$ was found to contain 5.2% yield of isolable 2,3-diaminophenazine. This result indicates that the presence of dioxygen, is needed for the oxidation to occur effectively.[16]

A third reaction scheme was initiated to further determine how vital oxygen was to the reaction scheme. A Schlenk flask was set up with only a stir bar in an aqueous solution of *ortho*-phenylenediamine. Argon was bubbled through the solution for two hours, and then put through three cycles of freeze–pump–thaw in an effort to remove all possible traces of O_2. This resulted in a 25% yield of 2,3-diaminophenazine. Thus, it is evident that an oxygen donor present in the reaction mixture participates in the reaction pathway. This result would require the oxygen from H_2O to serve as the oxidant. Interestingly, as this reaction contained only H_2O and *ortho*-phenylenediamine, a literature search was unable to find any previous Letters on the temperature induced oxidation of *ortho*-phenylenediamine in an inert atmosphere.

The effect of light on this reaction was explored by running the highest yielding actinide salt reaction, with $Th(NO_3)_4$, in the absence of light. The reaction was set up in a 250 mL round bottom flask and heated at 80 °C for 6 days while wrapped in aluminum foil to block out light. As shown in Figure 2, the absence of light did not completely quench the reaction and a 33% yield was obtained as compared to the reaction in the presence of light in which a yield 92% product was obtained. Thus, as with the actinide and the O_2 previously discussed, light is critical to optimizing the reaction, indicating that there are likely multiple concurrent reaction pathways and one of these is likely through a radical pathway.

To determine whether or not the reaction proceeds through interactions with the pi orbitals of the *ortho*-phenylenediamine or through interactions with lone pairs of the amines present on the *ortho*-phenylenediamine, various substrates were subjected to the same parameters as the highest yielding actinide catalyzed reaction. Table 1 outlines the substrates that were explored to determine if the $Th(NO_3)_4$ would also oxidatively couple them under these same conditions. To test the effect of the pi orbitals, reactions with cyclohexene, benzene, and 1,4-cyclohexadiene were examined. To determine the effect of the lone pairs, aniline, and catechol were used. Substrates were also reacted in the presence of *ortho*-phenylenediamine to determine if the oxidative coupling of *ortho*-phenylenediamine was favored. In the presence of *ortho*-phenylenediamine, the only product found during analysis was 2,3-diaminophenazine, in yields up to 64%. Thorium(IV) nitrate was proven futile as a catalyst to oxidatively couple the substrates with themselves. Mass spec analysis supported that the reaction between *ortho*-phenylenediamine with aniline and *ortho*-phenylenediamine with catechol were catalyzed. In both cases, however, 2,3-diaminophenazine was also synthesized and NMR analysis did not support the presence of the aniline/*ortho*-phenylenediamine product. Thus, for thorium(IV) nitrate reactions, what was observed is better suited to electron rich environments.

Table 1
Metal catalyzed oxidative coupling of varying benzene derivatives with *ortho*-phenylenediamine

Entry	Reagent(s)	Catalyst	Product	Yield (%)
1		$Th(NO_3)_4$		39.5
2		$Fe(NO3)_3$		16.0
3		$Th(NO_3)_4$		64.3
4		$Th(NO_3)_4$		57.4
5		$Th(NO_3)_4$	No reaction	N/A
6		$Th(NO_3)_4$	 	30.0*
7		$Th(NO_3)_4$	No reaction	N/A
8		$Th(NO_3)_4$		21.0
9		$Th(NO_3)_4$	No Reaction	N/A
10		$Th(NO_3)_4$		45.1
11		$Th(NO_3)_4$	No reaction	N/A

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* Unable to separate mixture of products.

Conclusions

While it is tough to argue that incorporating actinide ions into reaction pathways might result in green or 'greener' chemical methodologies following the principles as outlined by Anastas and Warner,[27] these reaction conditions allow for mild reaction conditions, safer solvents, and catalysis with good turnover. Fundamentally, these observations engage the idea of using the depleted actinide reserve, especially depleted ^{238}U, as a source for new routes of metal mediation. Previous Letters in the literature of phenazine prepared in this fashion feature metals that are able to go through one electron oxidations [Cu(II) and Co(II)], and the proposed mechanisms involved μ-dioxygen with hydrogen peroxide evolution, the Cu(II) does not clearly report the catalyst loading and the Co(II) catalyst loading was much higher, 50%.[20] In our reaction 40% loading is required for that same yield with the Cu(II) salts. The mechanism observed in that reaction would be highly unlikely here for either the Th^{4+} or the UO_2^{2+} ions, as both metal centers contain complete electronic shells (K, L, M, and N); also neither ion possess paired or unpaired electrons in the O shell. Future work will pursue computation analyses to determine what might be a more reasonable mechanism.

General procedure

Caution! The U and Th are radioactive, heavy metals and require special precautions and waste handling.

In a typical procedure, 4 mmol of substrate(s) was heated at 80 °C in a round bottom flask with a stir bar and 100 mL of deionized H_2O as solvent. Once dissolved, 1% of $UO_2(NO_3)_2$ or $Th(NO_3)_3$ was added to the mixture. The reaction was allowed to stir and heat at 80 °C. When the experiment time had lapsed; the solution was filtered, the solid was washed with hexanes, and dried in a vacuum oven.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.058.

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