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Oxidation of Heteroaryl Isoprenes towards Functionalized Pyridinyl Methyl Ketones Facilitated by a Potent KMnO4 / H2INa3O6 System via a Contemporary Malaprade Reaction

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Chemoselective, Osmium-Free, Dihydroxylation / Oxidative Cleavage of Heteroaryl Isoprenes by a Contemporary Malaprade Reaction

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Supporting Information Placeholder

ABSTRACT: The methyl ketone is a central synthetic building block for the construction of advanced heteroaryl scaffolds and systems. Reactions, including oxidative cyclization strategies, are often predicated on efficient access to this ubiquitous moiety. In the context of arenes, standard approaches leveraging Markovnikov hydration/oxidation or oxidative cleavage of the C-C π bond often afford satisfactory performance. However, when the substrate contains an electron-deficient heteroaryl core, the traditional Malaprade reaction, and related oxidative-cleavage strategies, frequently result in diminished performance over carbon-based arenes. In this work we present the development and application of an oxidative cleavage reaction of various pyridinyl isoprenes toward accessing the downstream methyl ketone for utilization in advanced cyclizations for the preparation of soft-N-donor complexant scaffolds. This efficient protocol follows the principles of Green chemistry by exchanging $KMnO_4$ for the toxic OsO_4 and offers the end-user an efficient, more environmentally friendly option for accessing heteroaryl methyl ketones in one hour of reaction time using potassium permanganate and sodium paraperiodate as a synergistically potent oxidative cleavage system. The wide substrate scope defined access to simple, as well as advanced heteroaryl methyl ketones. Method development, optimization, substrate scope, preliminary mechanistic observations, and a scale up reaction are delineated herein.

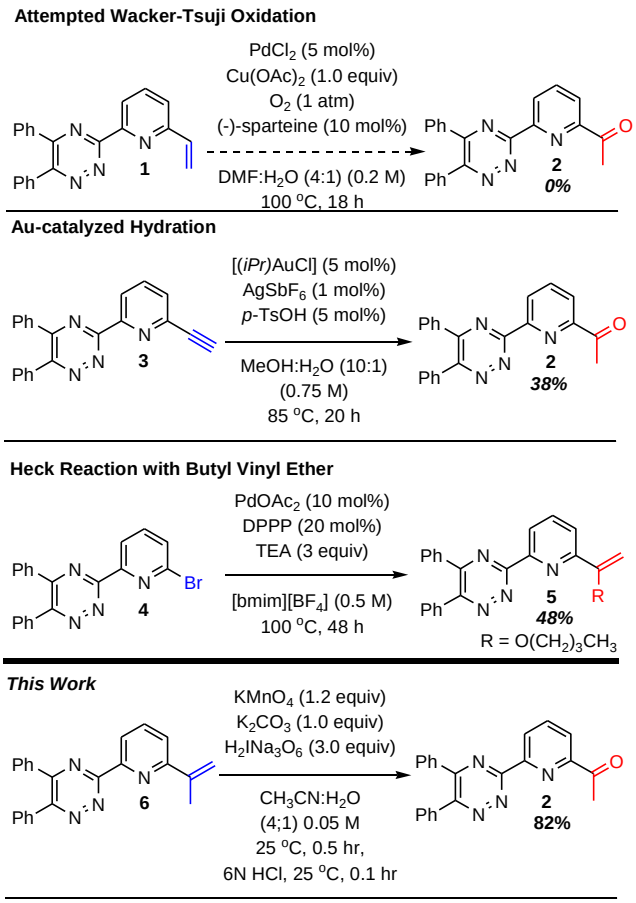
INTRODUCTION

As chemistry related to the construction of soft-N-donor complexants continues to evolve beyond commercially available substrates, the practitioner's synthetic toolbox must likewise parallel. Oxidative cyclization approaches to complexant scaffolds frequently necessitates the availability of carbonyl moieties for the generation of the requisite synthons.[1] In the case of functionalized carbon-based arenes, access to the corresponding methyl ketone is frequently possible through standard functional group interconversions including the Friedel-Crafts Acylation[2] for neutral, or electron-rich variants and oxidative cleavage strategies including ozonolysis, osmylation/cleavage, or metalation strategies.[3] However, when the aromatic substrate exchanges a carbon atom for one, or more heteroatoms, electronic deactivation results and often strongly inhibits the desired oxidation outcome.

Friedel-Crafts strategies are typically nonviable for electron poor heteroarenes. Additional collateral concerns regarding unwanted oxidation focus on the potential for the formation of the N-oxide in the case of pyridines, or oxidation of remote benzylic positions. Many of the aforementioned strategies also involve toxic heavy metals and associated reagents. Standard approaches described above, including catalytic osmylation,[4] while frequently competent in the case of electron-rich alkenes, often struggle to afford the desired product in the case of heteroarenes. Pursuant to the aforementioned, exploration of cyclization strategies towards the synthesis of 1,2,3-triazole derivatives of pyridine necessitated the construction of the methyl ketone of 1-[6-(5,6-diphenyl-[1,2,4]triazin-3-yl)-pyridin-2-yl]-ethanone (**2**) as a synthon. Contemporary approaches to ketone formation in the cases of carbon-based arenes including Wacker-Tsuji oxidation, Au(I)-catalyzed hydration, or a Heck reaction with butyl vinyl ether were unsuccessful in the conversion of **1**, **3**, or **4** to the corresponding ketone (Figure 1).

Conversion of 3-(6-bromopyridin-2-yl)-5,6-diphenyl-[1,2,4]triazine (Br-MTPPhen) (**4**) to the vinyl derivative **1** afforded the necessary substrate for evaluation of Wacker-Tsuji oxidation[5] which was unsuccessful in our hands. Previous success with Sonogashira cross-couplings of Br-MTPPhen derivatives[6] inspired our pursuit of alkyne hydration strategies with Markovnikov regiochemistry under metal-free, copper catalyzed,[7] or gold-catalyzed transformations[8] with salen[9] and N-heterocyclic carbene ligands.[10] Each of the aforementioned resulted in no conversion of the starting material (**3**). Addition of the weakly coordinating SbF_6^- counterion afforded marginal conversion of **3** to **2**.[11] The addition of *p*-TsOH as an additive increased conversion to a maximum of 50%, but the isolated yield in this case was a tepid 38%. Attempts at an α-selective Heck reaction with butyl vinyl ether[12] did not convert starting material to product. An ionic liquid variant evaluated in [bmim][BF_4][13] afforded 48% conversion of **5** by ^{1}H NMR to the desired 1-(butyloxyvinyl) derivative, but additional attempts at optimization and dealkylation proved unsatisfactory.

Figure 1. Common Strategies for the Formation of Heteroaryl Methyl Ketones



RESULTS AND DISCUSSION

Confronted with the reality that traditional, as well as contemporary, synthetic methods were unable to serve the needs of this seemingly straightforward functional group interconversion, we subsequently undertook a bottom up approach focusing on the development of a suitable oxidation strategy with a more Green Chemistry appropriate metal, Mn. Incorporating $KMnO_4$[14] into the dihydroxylation step, as opposed to Os or Cr oxidants, improves the safety profile of the functional group interconversion to humans and the environment. Manganese is the fifth most abundant metal in the Earth's crust in contrast to Os, which is the least abundant. Employment of acetonitrile as the reaction solvent incorporates a solvent which can be derived from a bio-renewable ethanol feedstock and is non-carcinogenic, in contrast to alternatives. The challenge with regard to solvation was maximizing reaction concentration while maintaining homogeneity for increased conversion rates. In the case presented, with the examples screened, solubility in water was not an option and solubility in the solvent system with acetonitrile concentrations higher than 0.05 M negatively impacted homogeneity of the reaction matrix.

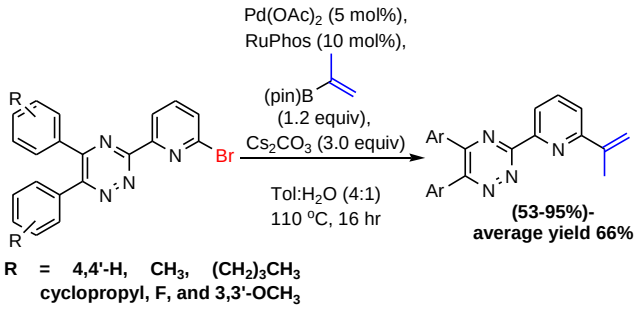
There are three critically important and relevant sustainability improvements over traditional methods for similar functional group interconversions highlighted in this work. The first, and most obvious is that osmium tetroxide is not used to form the vicinal diol precursor. The toxicity to humans and the environment of this reagent need not require any further discussion. The reaction, as developed, is not catalytic in regards to the dihydroxylation oxidant, $KMnO_4$, or the oxidative cleavage oxidant, $H_2Na_3IO_4$. Presumably, $H_2Na_3IO_4$ does not appreciably reoxidize MnO_2 to $KMnO_4$. The reaction sequence utilizes reagents which are stoichiometric/super-stoichiometric and homogeneous in the acetonitrile:water solvent system. Full on recycling via recovery of the unused portions of the reagents is not possible in the case of residual $KMnO_4$, or HIO_4 which is formed *in situ* from $Na^+ {}^-IO_4$ as these materials are retained on the solid filtration media during product recovery. The major byproducts of this transformation include MnO_2 which has a GHS toxicity to humans rating of 1-a marked improvement from the toxicity of OsO_4.

Second, the developed method combines two synthetic functional group interconversions, dihydroxylation and oxidative cleavage, into one reaction pot which decreases solvent, workup, and purification requirement towards a more sustainable alternative, in contrast to performing two discrete reactions, all while maintaining robust chemoselectivity described.

Finally, isolation of the reaction products via plug filtration with minimal solvent, as opposed to standard flash column chromatography, reduces the environmental impact of significant volumes of traditionally non-green solvents used in standard chromatographic purifications.[15] Method development and optimization, as well as applied substrate scope to derivatives of **6**, are reported in Tables 1 and 2.

Our lab has previously demonstrated the ability to leverage Suzuki-Miyaura cross-coupling strategies[16] with various sp^2 boron reagents to yield derivatives of **4** (Scheme 1). With the preparation of **6** secured, our focus shifted to the evaluation of oxidative cleavage strategies.

Scheme 1. Synthesis of Heteroaryl 2-Methyl Propenes



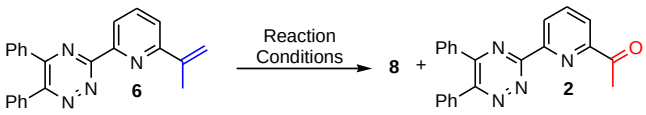
The versatility of the hypervalent iodine Dess-Martin oxidant[17] applied towards ketone synthesis piqued our interest, but ultimately resulted in no conversion of **6** to **2**. Metal-halogen exchange was a logical forward step given prior results in the cases of Negishi[18] and Ullman-type[19] cross-couplings with **4** described in earlier work from our lab. In both of the preceding cases, mechanistic theory substantiates the need for transmetalation as a requisite step for a successful cross-coupling outcome. Aided with the aforementioned, treatment of **4** with *i*PrMgCl[20] followed by quenching with acetyl chloride as the electrophile (entry 1), or transmetalation of the putative organomagnesium derivative to the corresponding zinc reagent, with (entry 2), or without LiCl as a Lewis acid additive with electrophile variance resulted in no conversion of **4**.

Execution of the NBS-mediated halohydrin synthesis under the Wohl-Ziegler conditions[21] via tautomerization of the E2-type elimination of the intermediate enol product did afford initial success, but was unable to be optimized further (entry 3). Screening of polar aprotic solvents, THF, and polar protic solvents, CH_3OH, afforded no improvement in this regard. NBS reagent integrity also led to inconsistent performance.[22] Metal-mediated reactions including copper trifluoromethanesulfonic acid, or $RuCl_3$ (entries 4–6) also did not afford **2**.

The utility of $KMnO_4$-mediated oxidation of alkenes, alkynes, and benzylic positions is well known. Frequently, carbon in the alkene oxidation state affords comparable products

to ozonolysis with a reductive workup, namely carbonyls. Preliminary success was observed in the conversion of **6** to **2** employing $KMnO_4$ (entry 7). Manipulation of reaction variables including a copper-coadditive, solid support, as well as molecular O_2 afforded varying levels of performance (entries 8−10). It is important to note in the cases of entries 7, and 8 which resulted in the formation of **2**, the increased loading of $KMnO_4$ facilitated both, the dihydroxylation and oxidative cleavage of **6** to **2**, but over two equivalents of oxidant were required. The increase in $KMnO_4$ loading presented challenges with product isolation and was optimized further to include sodium paraperiodiate for use in the oxidative cleavage to afford **2**. Additional $KMnO_4$ loading did not increase production of **2**.

Table 1. Method Optimization of Oxidative Cleavage



entry	reagents	substrate	additive	solvent	temp (°C)	time (h)	ratio[a] (6:8:2)
1	*i*PrMgCl (1.10 equiv) $ZnCl_2$ (3.0 equiv)	**4**	AcCl	THF	−78− 25	8	99:0:1
2	$ZnCl_2$ (3.0 equiv) LiCl (20 mol%)	**4**	AcCl	THF	−78− 66	8	98:0:2
3	NBS (1.2 equiv)	**6**	-----	EtOAc:H_2O (10:1)	75	18	44:0:56
4	$Cu(OTf)_2$ (20 mol%)	**6**	H_2O (2.0 equiv)	EtOAc	78	16	99:0:1
5	TfOH (20 mol%)	**6**	H_2O (2.0 equiv)	CF_3CH_2OH	25−40	24	99:0:1
6	$RuCl_3$ (3.5 mol%)	**6**	2,6-Lut. (2.0 equiv); $H_2INa_3O_6$ (4.0 equiv)	CH_3CN:DCM:H_2O (1:1:1.5)	25	48	85:0:15
7	$KMnO_4$ (2.4 equiv)	**6**	-----	CH_3CN	25	0.5	**10:0:90**
8	$KMnO_4$ (2.4 equiv)	**6**	$CuSO_4$·H_2O	CH_3CN	25	0.25	**30:0:70**
9	$KMnO_4$ (2.4 equiv)	**6**	Celite	CH_3CN	25	0.5	**10:90:0 (48%)**
10	$KMnO_4$ (1.2 equiv)	**6**	O_2 (1 atm)	CH_3CN	25	0.5	**38:0:62**
11	*$KMnO_4$ (1.2 equiv)*	**6**	*$H_2INa_3O_6$ (3.0 equiv) K_2CO_3 (1.0 equiv)*	*CH_3CN: H_2O (4:1)*	*25*	*0.5*	***1:0:99 (82%)[b]***

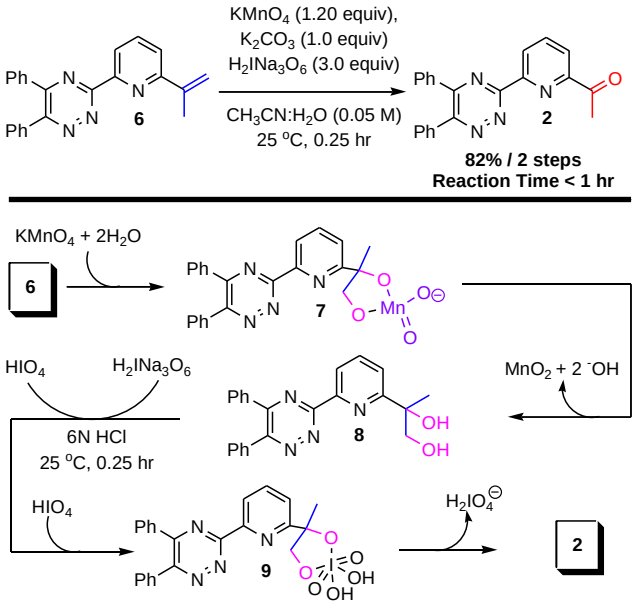
Reaction conditions: In an 8 mL reaction vial with magnetic stirring bar at ambient temperature was charged: **6** (0.500 mmol), in solvent indicated (0.05 M), at the temperature and time indicated. [a]Molar ratio of **6:7:2** via integration of selected resonances from ^{1}H NMR spectrum of crude reaction mixture. [b]Reaction mixture acidified with 6N $HCl_{(aq)}$ to pH of 2.

Incorporation of sodium paraperiodate ($H_2INa_3O_6$) followed by adjustment of the reaction mixture to a pH of 2 completely consumed **6** and afforded the desired methyl ketone **2** in 82% isolated yield with lower $KMnO_4$ loading (entry 11). Without an increase in acidity, the reaction moderates to **8**. It is postulated that upon incorporation of 6M $HCl_{(aq)}$ sodium paraperiodate is converted to periodic acid and oxidative cleavage subsequently proceeding through the Malaprade reaction[23] is observed (Scheme 2).

Thus, $KMnO_4$ oxidation of **6** affords the metallacycle **7** which hydrolyzes to provide the vicinal diol **8** and the reduced MnO_2. Retaining a basic pH for this step precludes the oxidative cleavage from occurring with $KMnO_4$. Adjustment of the reaction pH with 6N $HCl_{(aq)}$ converts $H_2INa_3O_6$ to the putative HIO_4 which forms hypervalent iodine intermediate **9**. Oxidative cleavage then yields methyl ketone **2**. Sodium paraperiodate was necessary as a precursor to the *in-situ* generated periodic acid to affect the 1,2-vicinal diol cleavage to afford the desired oxidation product. The intermediary 1,2-vicinal diol afforded from $KMnO_4$ oxidation of the isoprene precursor at basic pH was isolated during method development and structurally validated from ^{1}H NMR measurement. Adjustment of the pH to 2 converted sodium paraperiodate to periodic acid which subsequently completed the cleavage to afford the methyl ketone.

Table 2. Preliminary MTP derivative reaction scope

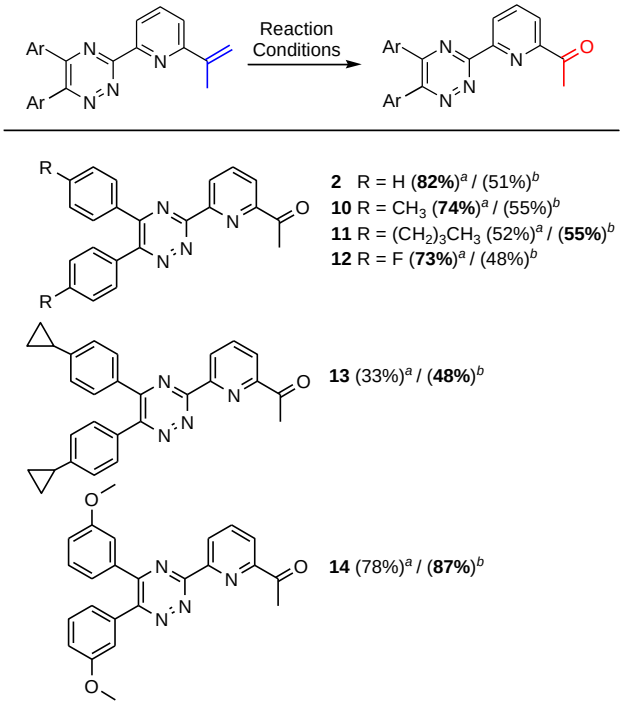
Scheme 2. Proposed Overall Reaction Sequence



Subsequent control experiments which negated the incorporation of $KMnO_4$ or the paraperiodate underscored the requisite synergistic inclusion of both reagents to affect the desired transformation as **8** was exclusively afforded with $KMnO_4$ only and no conversion of **2** was observed with $H_2INa_3O_6$. With a reproducibly viable strategy preliminarily defined, we turned our attention towards evaluation of 2-propenylMTP derivatives possessing various electronic environments and potentially collateral oxidation sites (Table 2).

The MTP derivatives evaluated under the optimized conditions in Table 1 addressed inductively donating and withdrawing substituents, as well as strong resonance donors. Gratifyingly, the reaction conditions afforded the various desired products in good, to excellent isolated yield (Table 2). Upon reaction completion, the mixture was diluted and filtered through a plug of silica gel to afford the desired products without further purification in most cases. Substrates leading to the formation of **2**, **12**, and **14** performed similarly even though the electronic environment varied widely.

Substrates with positions which are known to be competitively oxidized (benzylic or alkyl groups) in the case of carbon-based arenes (**10** and **11**), proved spectators to the current conditions. Product **13** highlighted the operational capacity of the reaction conditions to maintain the integrity of the Baeyer-



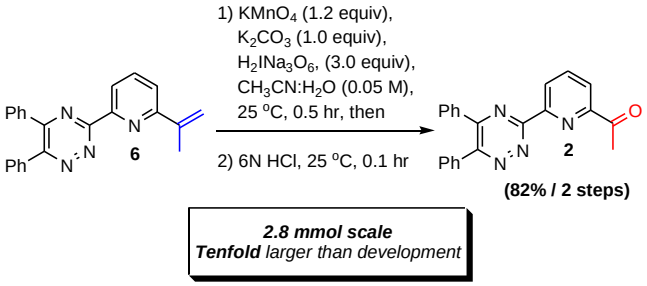
Reaction Conditions: [a]$KMnO_4$ (1.2 equiv), K_2CO_3 (1.0 equiv), $H_2INa_3O_6$ (3.0 equiv), CH_3CN:H_2O (4:1, 0.05 M), 25 °C, 0.5 hr, then 6N HCl, 25 °C, 0.1 hr. ***-or-*** [b]$KMnO_4$ (1.05 equiv), $H_2INa_3O_6$ (1.2 equiv), NaOH (1 equiv), CH_3CN:H_2O (4:1, 0.05 M), 25 °C, 0.25 hr, then 6N HCl, 25 °C, 0.25 hr.

strained cyclopropyl ring at the 4,4'- positions, which frequently results in oxidative degradation. In certain cases, described in Table 2, as well as Table 3, potassium carbonate was exchanged for sodium hydroxide at the same loading resulting in the need for decreased loading of $KMnO_4$ and $H_2INa_3O_6$. These conditions were retroactively applied to the examples in Table 2 for comparison with three examples performing best under each discrete protocol. With satisfactory performance for the required MTP derivatives realized, we were interested in evaluating the generality of the method towards heteroarenes.

Focused on ascertaining the full substrate scope applicability of the transformation, a series of oxidative cleavage experiments with functionalized pyridines were evaluated as listed in Table 3. Isoprenyl pyridines with substituents in the 6-position afforded the desired products in consistent yield (**15**–**18**), with the exception of **16**, over two steps in one pot. Surprisingly, no collateral oxidation of the 2-isoprenyl-6-methylpyridine (**15**) was observed under the reaction conditions. Products **19**–**21** evaluated the positional impact of various methyl congeners of pyridine. Some of the aforementioned products demonstrated isolation challenges due to low boiling points, and not necessarily issues related to reaction performance. The 3,5-arrangment of isoprene and substituent, respectively in the case of the electron-withdrawing F-substitutent (**22**) as compared to the resonance donating methoxy substitutent (**23**) resulted in an improved yield of the latter compared to the former. Ketone substituted pyridines were competent substrates for the transformation (**24** and **27** procedure *a*). Attempts to extend carbonyl functionality to esters and carboxylic acids resulted in hydrolysis of the ester substrates and difficulty in isolating the acid substituted derivatives. Evaluation of pyridinyl carbonitriles resulted in inconsistent production of the amide cleavage product. Products **25** and **26** truly tested the performance of the described transformation by chemoselectively affording the desired isoprenyl oxidative cleavage product without oxidation of the alkyne in the case of **25**, or oxidation of the alkyne, or benzylic methyl group in the case of **26**.

The next series of substrates screened focused on complexant scaffolds relevant to separations which included double oxidative cleavage of the *bis*-isoprenes affording **27** procedure *b*, **29**, and **30** in serviceable yields over four synthetic steps in one reaction pot. Extension of the reaction conditions to 2-isoprenylquinoline afforded **31** in good yield. Other heteroaryl substrates including 5-isoprenylbenzofuran towards **32** and 2-isoprenylbenzothiophene for production of **33** were also successful. Product **34**, whose starting material was afforded from a Barluenga-type coupling, evaluated the utility of the transformation in regards to phenyl-substituted isoprenes and resulted in the desired phenyl-pyridin-2-yl-methanone (**34**) in 82% yield. With the expansion of the substrate scope to various substituted, and functionalized pyridines, complexant scaffold synthon precursors, as well related substrates, we subsequently evaluated the scalability of the transformation beyond development scale (Scheme 3).

Scheme 3. Scale-Up Experiment

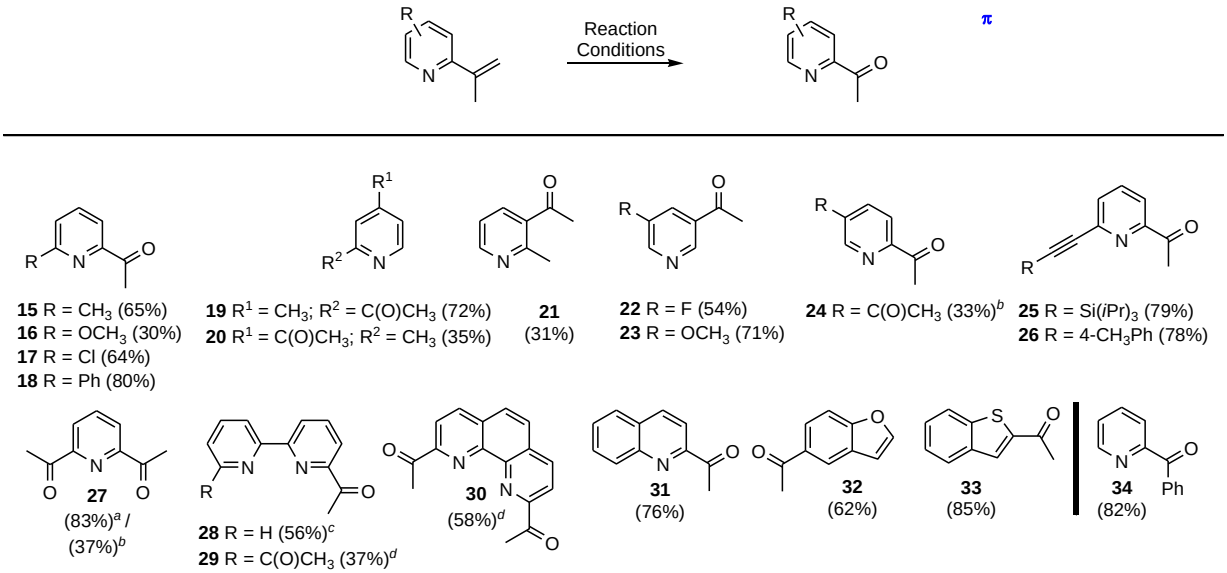


In order to ascertain the performance of the method a 2.8 mmol scale-up reaction, which was an order of magnitude larger than the development scale, was performed leading to the formation of **2** in comparable yield to the 0.28 mmol development scale transformation.

CONCLUSION

In summary, we have described an efficient method to access functionalized pyridinyl methyl ketones from the corresponding isoprene by leveraging the synergy between potassium permanganate and sodium paraperiodate in a modified Malaprade reaction with oxidant loadings as low as 1.05 equiv for $KMnO_4$ and 1.20 for $H_2INa_3O_6$. The conditions described offer a greener alternative to osmium-mediated dihydroxylation transformations by providing a solution to the oxidative cleavage of electron-poor heteroaryl isoprenes in good, to excellent yield over two, or four steps in one reaction pot. The broad reaction scope tolerates diversely functionalized pyridinyl heteroarenes and addresses a challenge for heteroaryl oxidative strategies in the context of electron-deficient alkenyl substrates. The utility of the advanced synthons prepared will be incorporated into oxidative cyclization approaches for the construction of unsymmetric soft-N-donor scaffolds and reported in due course.

Table 3. Functionalized heteroarene substrate scope



Reaction Conditions: $KMnO_4$ (1.05 equiv), $H_2INa_3O_6$ (1.2 equiv), NaOH (1.0 equiv), $CH_3CN:H_2O$ (0.05 M), 25 °C, 0.5 hr, then 6N HCl, 25 °C, 0.1 hr, reported yields over two steps in one pot (dihydroxylation / oxidative cleavage). [a]Reaction of 1-(6-isopropenyl-pyridin-2-yl)-ethanone ; [b]Reaction of 2,6-diisopropenyl-pyridine, yield over four steps; [c]Average yield of three experiments. Reaction of 6,6'-diisopropenyl-[2,2'] bipyridine, yield over four steps. [d]Reaction of 2,9-diisoprenyl-[1,10]phenanthroline, yield over four steps.

ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds, as well as purification chromatograms for select compounds. (PDF)

AUTHOR INFORMATION

Author Contributions:

Zachary Z. Gulledge-Reaction development, optimization, and MTP substrate scope definition

Connor C. Pinson-Heteroaryl substrate scope expansion, compound characterization

Alexander M. Stovall-Heteroaryl substrate scope expansion, compound characterization

Fortune O. Dzeagu-Heteroaryl substrate scope expansion, scale-up reaction, compound characterization, manuscript revisions

Jesse D. Carrick-Project conceptualization, formal analysis, funding acquisition, supervision, organizing, writing, and editing original manuscript draft

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Notes

The authors declare no competing interest.

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DEDICATION

The corresponding author dedicates this work to his Ph.D. mentor, Prof. Michael P. Jennings (1975–2022)-beloved father, husband, mentor, and friend.

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