Direct C–H α-Arylation of Enones with $ArI(O_2CR)_2$ Reagents

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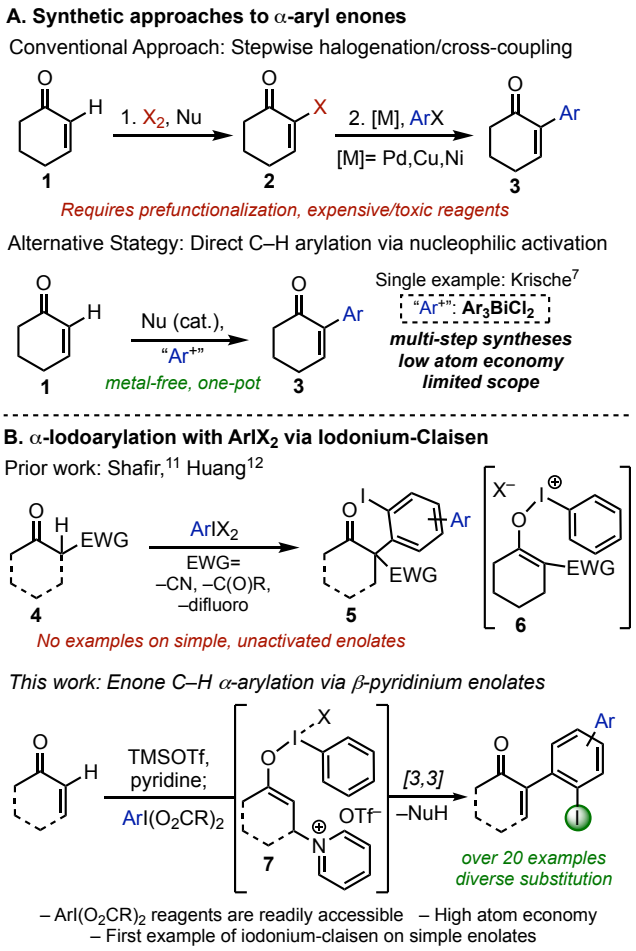
ABSTRACT: The alpha arylation of α,β-unsaturated ketones constitutes a powerful synthetic transformation. It is most commonly achieved via cross coupling of α-haloenones, however this stepwise strategy requires pre-functionalized substrates and expensive catalysts. Direct enone C–H α–arylation would offer an atom and step economical alternative, however such reports are scarce. Herein, we report the metal-free direct C–H arylation of enones mediated by hypervalent iodine reagents. The reaction proceeds via a reductive iodonium Claisen rearrangement of *in situ* β-pyridinium silyl enol ethers. The aryl groups are derived from $ArI(O_2CCF_3)_2$ reagents, which are readily accessed from the parent iodoarenes. It is tolerant of a wide range of substitution patterns and the incorporated arenes maintain the valuable iodine functional handle. Mechanistic investigations implicate arylation via an umpoled "enolonium" species and that the presence of a β-pyridinium moiety is critical for desired C–C bond formation.

The alpha arylation of carbonyl compounds represents a powerful class of C–C bond forming reaction. While transition metal and organocatalysis have resulted in numerous methods for α-arylation of ketones and aldehydes via enolate and enolate equivalents,[1,2] the corresponding C(sp^2)–H arylation of enones (**1**) has seen less development despite the resulting arylated products serving as valuable synthetic intermediates.[3] Currently, enone α-arylation is achieved via first conversion to the α-haloenone (**2**), followed by metal-catalyzed coupling with a suitable arene partner (Scheme 1A), or the roles of the two coupling partners can be reversed.[4] While enabling, such stepwise strategies are not without drawbacks; they require pre-functionalization, sometimes multi-step, of both the starting enone and arene coupling partner, and often use expensive and/or toxic metals in both the catalysts and cross coupling partners (e.g. Pd, Sn).

Direct enone C–H arylation offers a step- and atom-economical alternative, however the development of such methods has proven challenging and no metal-catalyzed approaches have been reported to date.[5,6] In 2000, the Krische laboratory disclosed an elegant solution through the use of nucleophilic phosphine catalysis, in combination with hypervalent bismuth(V) species as aryl transfer reagents (Scheme 1A).[7] Despite offering a metal-free, one-pot strategy for enone C–H arylation, this method has not seen broad adoption, likely due to the use of Ar_3BiCl_2 reagents, which are unfamiliar to most chemists, require multi-step syntheses,[8] and suffer from low atom economy as two of the aryl groups serve as sacrificial "dummy ligands". However, if a more practical and efficient aryl transfer reagent could be identified, then this nucleophilic activation strategy could provide an appealing general solution to metal-free enone C–H arylation.

Scheme 1. A. Traditional approach to α-arylation and alternative nucleophilic activation strategy B. α-Arylation with I(III) reagents: Prior art and this work

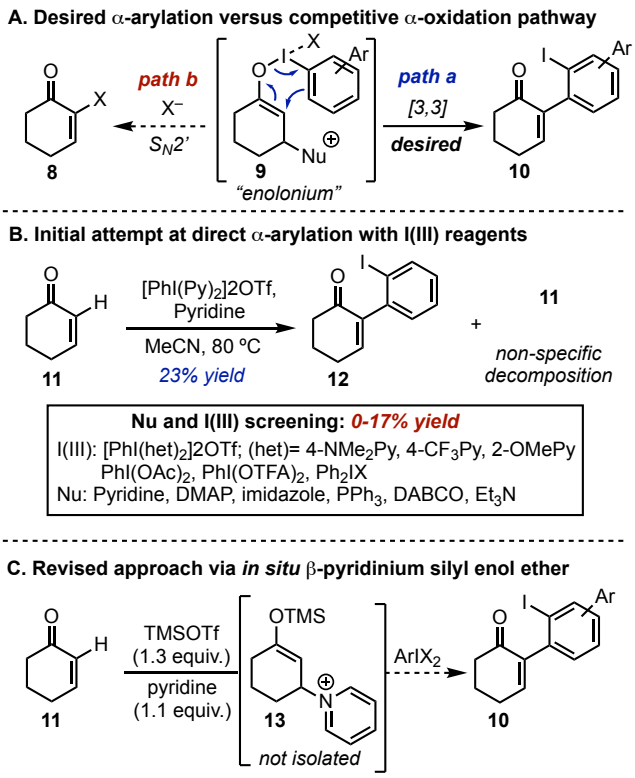


As a part of our laboratory's ongoing interest in novel applications of hypervalent iodine compounds, we were intrigued by the possibility of I(III)-reagents acting as aryl transfer agents with enolates derived via *in situ* nucleophilic activation. Hypervalent iodine compounds have garnered recent attention due to their low cost, ease of handling, ready accessibility, and versatile reactivity.[9] Within I(III)-species, diaryliodonium salts [Ar_2IX] have seen broad utility as aryl transfer reagents, however they suffer from low atom economy and issues of chemoselectivity can arise in non-symmetrical salts.[10] We were inspired by the recent pioneering work of Shafir[11] and others[12] who have demonstrated that $ArIX_2$ reagents can affect α-(2-iodo)arylation of activated enolates (**4**), including 1,3-dicarbonyls, α-cyanoketones, and α,α-difluorosilyl enol ethers via reductive iodonium Claisen rearrangements of O–I bound enolates (**6**) (Scheme 1B). The use of $ArIX_2$ species as aryl transfer reagents is particularly appealing as they are either commercially available or readily accessible from the parent iodoarenes and notably, the entire aryl iodide motif is transferred intact, making this highly atom economical, and retaining a valuable *ortho*-functional handle for downstream manipulations. However, to date, no successful examples of arylative [3,3] iodonium-Claisen rearrangements on simple enolates or enol ethers such as those required of the envisioned nucleophilic activation strategy have been described.

Herein, we report the direct C–H α-arylation of enones via reductive iodonium-Claisen rearrangement of *in situ* generated β-pyridinium silyl enol ethers (**7**) and $ArI(O_2CCF_3)_2$ reagents (Scheme 1B). The necessary $ArI(O_2CCF_3)_2$ reagents are readily synthesized from the parent iodoarenes, the reaction shows broad arene scope, and the products retain the *ortho*-iodo functional handle. Mechanistic studies indicate the reaction proceeds via the formation of an O–I enolonium species[13] followed by reductive [3,3]-rearrangement, and that this sequence is highly contingent on the presence of the β-pyridinium moiety. This represents the first example of an iodonium-Claisen rearrangement of simple silyl enol ethers. The synthetic utility of the resulting α-(2-iodo-Ar)enones is demonstrated via the rapid diversification to key synthetic building blocks and heterocyclic frameworks.

At the outset of these studies, it was envisioned that the most significant challenge would be controlling for desired C–C vs. C–X bond formation (Scheme 2A), as the latter is very well-precedented for $ArIX_2$ species and enolates.[9,14] Either product would arise from the same O–I bound "enolonium" intermediate **9**,[13b] which is rendered electrophilic at the α-carbon and is subject to umpolung attack by nucleophiles. Desired α-arylation would proceed via a reductive [3,3] rearrangement (path a),[11,12] which would need to occur selectively over competitive intermolecular attack by a displaced X-ligand (path b)[9,13a, 13b] leading to undesired α-oxidation products (**8**). Based on these two possible mechanisms, we hypothesized that the use of $ArIX_2$ reagents with weakly coordinating and relatively non-nucleophilic X-ligands would be optimal for favoring α-arylation. Therefore *N*-HVIs or $[ArI(het)_2]X_2$, which possess datively bound heterocyclic nitrogen ligands and are the subject of ongoing study in our laboratory,[15] seemed an ideal platform for reaction development due to the relatively non-nucleophilic and highly tunable ligands.

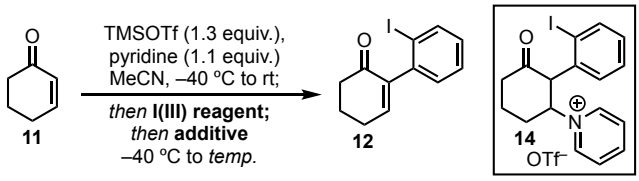
Scheme 2 A. Initial attempts at one-pot arylation B. Modified strategy via β-pyridinium silyl enol ethers



As an initial test with cyclohexenone as a model substrate, pyridine-ligated *N*-HVI $[PhI(Py)_2]2OTf^-$ was combined with stoichiometric pyridine as an exogenous nucleophile, which provided a promising 23% yield of the desired α-iodoarylated enone (**10**). Subsequent tuning of the electronics and sterics of the heterocyclic ligand did not offer any improvements and despite extensive screening, including other I(III) reagents, β-nucleophiles, and reaction conditions, the yield of desired arylation never exceeded 23%. We hypothesized that the consistently low yields could be the result of competitive background reactions between the I(III) reagents and the nucleophiles (i.e. ligand exchange, oxidative degradation, ligand coupling) or inefficient enolate generation. To address both of these potential issues, a sequential, one-pot arylation process was envisioned wherein stoichiometric generation and trapping of the necessary *in situ* enolate would be followed by addition of the I(III)-reagent. To this end, it was found that use of 1.3 equiv. of TMSOTf and 1.1 equiv. of pyridine, slight modification of conditions reported by Kim,[16] gave clean conversion to β-pyridinium silyl enol ether **13** as determined by ^{1}H-NMR (Scheme

2C). With efficient conditions for silyl enol ether generation in hand, α-arylation of *in situ* generated **13** was then examined (Table 1), beginning with $[PhI(Py)_2]2OTf$ which gave **12** in a similar 30% yield when the reagent was added at low temperature and then warmed to 80 °C for 18h (entry 1). Turning to other X-ligands, $PhI(O_2CCF_3)_2$ gave an improved yield of 46% after 12h (entry 2); interestingly, no α-oxidation products were observed and the only other species present by NMR was assigned as intermediate arylated pyridinium salt **14**, which was not stable to isolation. An NMR study then revealed that α-arylation occurred rapidly (<10 min) at low temperature and that final conversion of **14** to **12** was in fact the slow step. Based on this finding, various additives were then examined to facilitate elimination of the β-pyridinium moiety. The addition of NEt_3 gave a significant boost in yield to 83% at just 40 °C (entry 3) and the use of acidic silica/MeOH gave further improvement to 90% (entry 4). The use of $PhI(OAc)_2$ was less efficient under both basic and acidic conditions (entries 5 and 6). For comparison, arylation was then attempted with diaryliodonium salts (entries 7 and 8), which have been shown to efficiently arylate silyl enol ethers,[3a, 10, 17] however no reaction was observed, highlighting the unique reactivity of these β-pyridinium species.

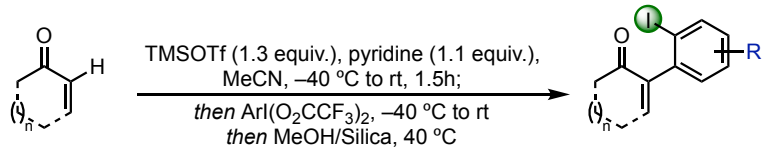
Table 1. Optimization of α-arylation of *in situ* β-pyridinium silyl enol ether



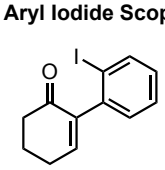
Entry	I(III) reagent	Temp.	Additive	Yield (%)
1	$[PhI(Py)_2]2OTf$	80 °C	none	30%
2	$PhI(OTFA)_2$	80 °C	none	46%
3	$PhI(OTFA)_2$	40 °C	Et_3N	83%
4	$PhI(OTFA)_2$	40 °C	Silica/ MeOH	90%
5	$PhI(OAc)_2$	40 °C	Et_3N	43%
6	$PhI(OAc)_2$	40 °C	Silica/ MeOH	76%
7	Ph_2IBF_4	80 °C	——	0%
8	NPIF	80°C	——	0%

Using this sequential activation strategy, the scope of the arylation was examined and found to be quite general (Table 2). It is worth noting that all of the necessary $ArI(O_2CCF_3)_2$ reagents shown can be either purchased or synthesized via oxidation of the corresponding commercially available aryl iodides using literature procedures.[18] With regards to the aryl moiety, alkyl groups at the *ortho*-, *meta*-, and *para*-position relative to the iodide were well tolerated giving α-(2-iodoaryl)enones **15-19** in good to excellent yields. Both an electron-donating methoxy (**20**) and electron-withdrawing ester (**21**) could be incorporated, however more strongly electron-withdrawing groups such as $–NO_2$ (**22**) or –CN (**23**) led to significant drops in yield. Iterative halogen substitution at the *o*-, *m*-, and *p*-positions was then examined using chlorine, bromine, and fluorine as these products would provide several orthogonal functional handles and be challenging to synthesize using traditional metal catalyzed cross couplings. While all successfully yielded arylated products (**24-32**), a clear trend of *para*>*meta*>>*ortho* emerged between yield and substitution pattern. Given that the trend was least pronounced with fluorine, this is likely a steric effect, impacting the efficiency of the initial ligand exchange between the enolate oxygen and the iodine center. Multiple substituents including a polyhalogenated species (**34**) and 3-Me-4-Cl-iodoarene (**33**) were also produced in good yields. In all cases where multiple regioisomeric products were possible, i.e. those with substitution *meta*- to iodine, rearrangement occurred with complete regioselectivity for the less hindered site, in contrast to previous reports.[19] The arylation was also capable of incorporating electron-rich heteroaromatics. 3-Iodothiophene was installed to give **35** in 77% yield and α-pyrazole enone **36** was obtained as the desiodo compound from the parent 3-iodopyrazole via rearrangement and subsequence C–C bond migration assisted by the adjacent nitrogen atom. Lastly, the scope of the enone was examined and found to work well with cyclopentenone to give **37** in 78% as well as an acyclic crotanaldehyde, giving **39** in 42% yield as a mixture of E/Z isomers. Arylation on cycloheptenone (**38**) proceeded in only 12%, likely due to increased conformational flexibility inhibiting the rate of rearrangement.

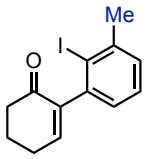
Table 2. Scope of enone C–H α-arylation with ArI(O_2CCF_3)$_2$ via sequential activation strategy



Aryl Iodide Scope



12, 90%, (76%)[a]



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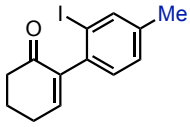

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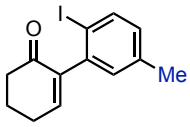

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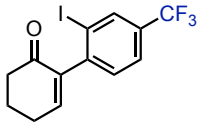

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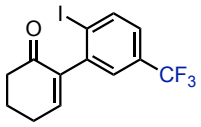

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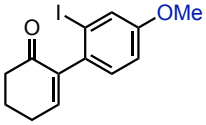

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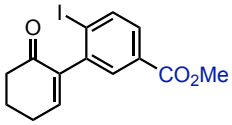

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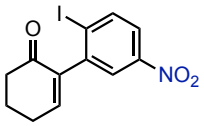

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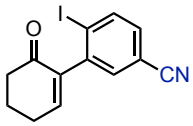
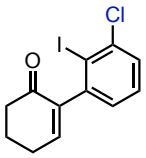


23, 13%



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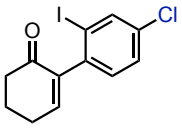

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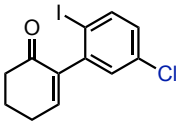

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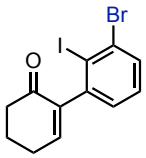

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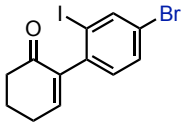

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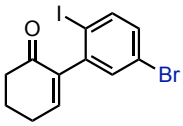

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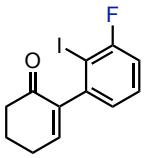

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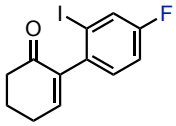
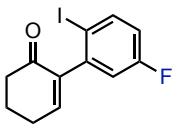
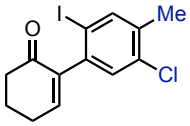


31, 60%



32, 85%



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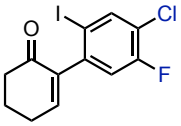
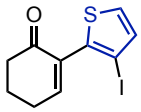
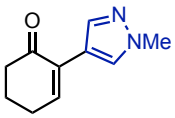


34, 40%

Heterocyclic Aryl Iodides

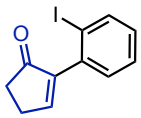


35, 77%[a]

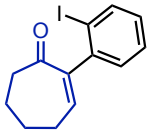


36, 61%[a]

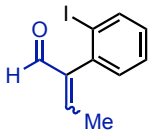
Enone Scope



37, 78%



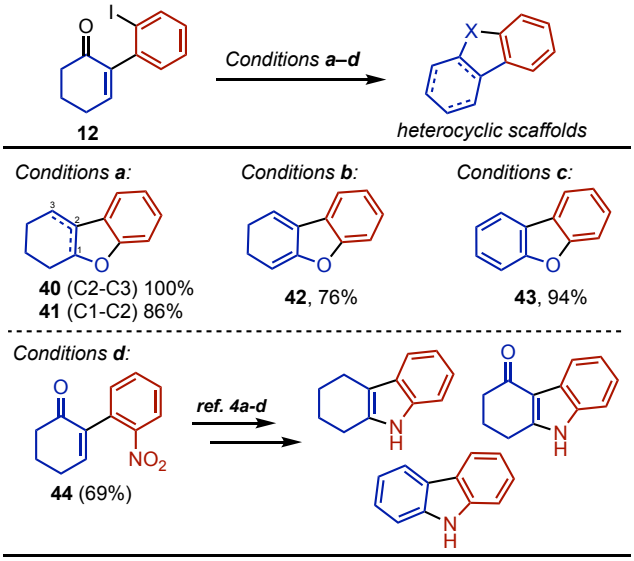
38, 12%



39, 42%

[a]Arylation performed with ArI(OAc)$_2$ derivative. In cases of **35** and **36**, analogous ArI(O_2CCF_3)$_2$ reagents were not stable.

Scheme 3. Derivatization of α-(2-iodoaryl)enones



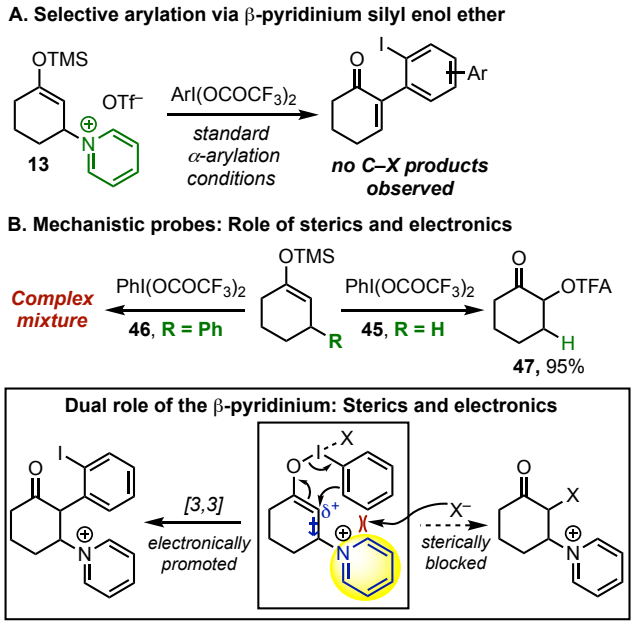
a. to **40:** $NaBH_4$, MeOH; CuI, 1,10-phenanthroline, MePh, 100 °C; then TsOH, 50 °C gives **41**. ***b.*** CuI, 1,10-phenanthroline, μω, 100 °C ***c.*** CuI, 1,10-phenanthroline, μω, 100 °C, then toluene 95 °C ***d.*** *m*-CPBA, anisole, TfOH, CH_2Cl_2; KNO_2, EtOAc, 60 °C

The utility of the resulting α-(2-iodoaryl)enones was then demonstrated through efficient conversion to synthetic building blocks and polycyclic aromatic heterocycles. By leveraging the carbonyl oxygen, benzofurans in a range of oxidation states could be accessed in excellent yield (**40**-**43**). In particular, the synthesis of dibenzofurans (**43**) via this protocol could be a powerful strategy for accessing non-symmetrical substitution patterns as the two phenyl rings derive from either the enone ring or iodoarene. Turning to nitrogen-containing scaffolds, conversion to the nitro derivative **43** was of particular interest as this functionality has been utilized in the synthesis of indole natural products and related scaffolds.[3a-3j] Initial screening found that typical nitration procedures led to degradation of the enone moiety,[20] however conversion of **12** to the diaryliodonium salt (not shown, see Supporting Information) followed by treatment with KNO_2 gave **43** in good yields.[22]

Mechanistically, the results are consistent with our initial proposal of an "umpoled" enolonium species which undergoes nucleophilic arylation in the C–C bond forming step (see Scheme 3A), analogous to other recent

reports of reductive [3,3] iodonium-Claisen reactions.[11,12,23] Perhaps the more intriguing mechanistic question surrounded the role of the β-pyridinium moiety in modulating C–C vs C–X bond formation. Remarkably, during the course of our α-arylation studies, none of the anticipated side products arising from α-oxidation were ever observed (Scheme 4A). This would indicate that the installation of a β-pyridinium group was facilitating a complete divergence from the prototypical reaction pathway. To begin to probe this selectivity, β-unsubstituted silyl enol ether **45** was subjected to our optimized conditions and, as expected, this gave exclusively α-oxidized product **47** in near quantitative yield (Scheme 4B). Next, in order to mimic the sterics of the pyridinium while removing any potential electronic effects, β-phenyl silyl enol ether **46** was treated with $PhI(O_2CCF_3)_2$. Interestingly, this gave a complex mixture of non-specific degradation products, none of which could be identified as either α-oxidation or α-arylation. These results indicate that the β-pyridinium moiety is likely modulating reactivity via the interplay of both steric and electronic effects (Scheme 4, inset). Steric hinderance is required to effectively block intermolecular reactions which lead to α-oxidation products while inductive deactivation of the α-carbon is essential to facilitating a reverse polarity nucleophilic arylation event.

Scheme 4. Mechanistic role of β-pyridinium moiety



In conclusion, an efficient method for the direct C–H α-arylation of enones with $ArI(O_2CCF_3)_2$ reagents has been developed. The reaction proceeds via *in situ* generation of a β-pyridinium silyl enol ether followed by C–C bond formation via a reductive iodonium-Claisen rearrangement of an "umpoled" enolonium species. This report provides the first example of an iodonium-Claisen arylation of simple enol ethers. The required $ArI(O_2CCF_3)_2$ species are readily accessible from the parent iodoarenes and the entire iodoarene motif is transferred intact, making the process highly atom economical. The synthetic utility of the resulting α-(2-iodoaryl)enones was demonstrated through conversion various synthetic intermediates and heterocyclic scaffolds. Mechanistically, the β-pyridinium moiety is critical for obtaining the desired C–C bond formation over competitive α-oxidation pathways through both steric and electronic modulation. Further mechanistic investigations as well as probing the reactivity and applications of β-pyridinium silyl enol ethers are the subject of ongoing investigations in our laboratory.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The authors are grateful to the National Institutes of Health (NIH R01 GM123098) and the National Science Foundation (NSF CAREER 1752244) for financial support of this work. We thank Dr. Charles DeBrosse (Temple University) for NMR spectroscopic assistance and Dr. Charles W. Ross III, Director: Automated Synthesis and Characterization at University of Pennsylvania Chemistry for providing high-resolution mass spectral data. The Sun group and Sasitha C. Abeyweera are acknowledged for use of and assistance with the microwave reactor. We thank Dr. Anthony Tierno, Dr. Xiao Xiao and Bilal Hoblos for helpful discussions.

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