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Organocatalytic synthesis of β-enaminyl radicals as the single-electron donors for phenyliodine(III) dicarboxylates: Direct one-pot alkylation-aminoxidation of styrenes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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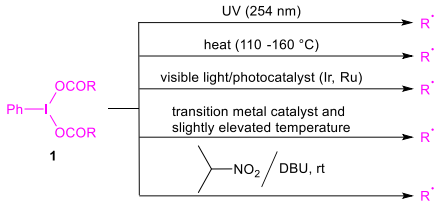
A direct one-pot alkylation-aminoxidation of styrene derivatives was achieved by using in-situ-generated alkyl and *N*-oxyl radicals. The corresponding *O*-alkylated hydroxylamine derivatives were obtained in moderate to good yields. The reaction features the generation of the alkyl radicals from phenyliodine(III) dicarboxylates via an organocatalytic process, the use of phenyliodine(III) dicarboxylates as the source of the alkyl radicals and the oxidant for the generation of the *N*-oxyl radicals, and the first generation of the β-enaminyl radicals via a HAT process and their use as the single-electron donors.

Introduction

Alkylation reactions are very useful in synthetic organic chemistry since they provide an easy way for structural elaborations via the formation of a new carbon-carbon. Additionally, introducing alkyl group, such as a methyl group, to biologically active molecules can dramatically change their biological activities. For example, the potency of an inhibitor of p38α MAP3 kinase can be improved by more than 208-fold after methylation.[1] Methylation also plays a very important role in biological systems. For example, methylation of norepinephrine's amino group produces epinephrine (adrenaline), which plays a significant role in the fight-or-flight response and can cause an increase in heart rate, muscle strength, blood pressure, and sugar metabolism.[2] As a result, alkylation reactions, especially methylation and trifluoromethylation, have played a very significant role in medicinal chemistry.[3-4]

Most recently, hypervalent iodine(III) reagents, such as phenyliodine(III) diacetate [PhI(OAc)$_2$, **1a**], are extensively used in alkylation reactions due to their environmentally benign character and easy availability.[5-8] While these reagents have been used in many alkylation reactions via polar mechanisms, many recent reports have investigated the radical alkylation reactions of these reagents. Indeed, radical decarboxylative alkylation reactions using phenyliodine(III) dicarboxylates (**1**) as alkyl radical precursors have attracted the attention of chemists because of their versatility and high selectivity.[8] As summarized in Scheme 1, alkyl radicals can be generated directly from **1** under the irradiation of UV light[9] or high temperatures.[10]



Scheme 1 Reported methods for the generation of alkyl radicals from phenyliodine(III) dicarboxylates (**1**).

Nonetheless, the reaction conditions of these methods are rather harsh. Later, milder methods involving the combination of photocatalysts with visible light[11-13] or transition metal catalysts at slightly elevated temperature have been developed.[14] In 2018, Xu and co-workers reported the first metal-free method for the generation of alkyl radicals from **1** using the carbanion of 2-nitropropane as the reducing reagent.[15] To our knowledge, there is no organocatalytic approach available for releasing the alkyl radicals from **1** for alkylation reactions.[16] Moreover, despite these advances, the generation of the high-energy methyl radical from PhI(OAc)$_2$ (**1a**) proved to be more challenging.[11-13,15]

MacMillan and others have demonstrated that the single-electron oxidation of the enamine intermediates, formed from aldehydes/ketones via organocatalysis, can be used to achieve a range of enantioselective catalytic transformations via the resulting enamine radical cations, which is known as the SOMO catalysis (Scheme 2, top equation),[17-20] Chemical oxidation, photoredox oxidation, or electrooxidation can be used for the oxidation of the enamine intermediates via the SET mechanism.[21] MacMillan and co-workers also demonstrated that under photoredox oxidation conditions and in the presence of a persistent radical species or a Michael acceptor, the enamine radical cations can lose a proton to form the

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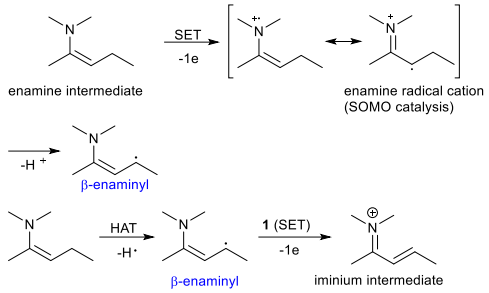
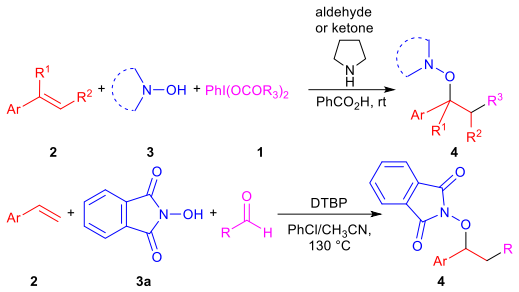


Scheme 2 Reported formation of the β-enaminyl radical (top equation), the proposed HAT synthesis, and its application as a SET donor for **1** (bottom equation).



Scheme 3 Alkylation-aminoxidation of alkenes reported in this paper and by Yang, et. al. (bottom equation).

β-enaminyl radicals (Scheme 2, top equation), which can also be employed for developing novel synthetic methodologies.[22-25] We envisioned that β-enaminyl radicals can also be accessed from the enamine intermediate via a HAT reaction (Scheme 2, bottom equation). Moreover, since a single-electron oxidation of the β-enaminyl radical should lead to the formation of an α,β-unsaturated iminium intermediate, which is relatively more stable and can be hydrolyzed to a very stable α,β-unsaturated carbonyl compound, we believe that β-enaminyl radical intermediate can be used as a single-electron donor to phenyliodine(III) dicarboxylates (**1**) (Scheme 2, lower equation). Herein, we wish to report the first organocatalytic procedure for the generation of the β-enaminyl radicals via a HAT process and the application of these intermediates as the single-electron reductants for phenyliodine(III) dicarboxylates to release the alkyl radicals. The radical intermediates generated in this process can be employed in the alkylation-aminoxidation of alkenes (Scheme 3, top equation). It should be pointed out that similar alkylation-aminoxidation products were previously obtained by Yang and co-workers from the reaction of alkenes and alkyl and PINO radicals produced from the di-*tert*-butyl peroxide (DTBP) oxidation of *N*-hydroxyphthalimide (NHPI, **3a**) and aldehydes (Scheme 3, bottom equation).[26]

Results and Discussion

To test whether the β-enaminyl radical can be produced from an enamine via the HAT process, 3-phenylpropanal (**5a**) was chosen as the β-enaminyl radical precursor because the existence of a similar β-enaminyl radical has been documented.[22] Pyrrolidine (**6a**) was selected as the organocatalyst and benzoic acid (**7a**) as the co-catalyst for the formation of the enamine intermediate from **5a**. $PhI(OAc)_2$ (**1a**) was used as the single-electron oxidant and the source of the methyl radical, which is the more challenging to produce.[11-13,15] NHPI (**3a**) was adopted as the precursor of the PINO radical that is needed for the HAT process, since the PINO radical can be easily generated from NHPI via the oxidation by phenyliodine(III) dicarboxylates, such as **1a**.[27] While Wang's earlier result hints that $PhI(OAc)_2$ (**1a**) can't oxidize the enamine intermediate derived from **5a** directly,[28] little is actually known about its reactivity towards enamines. Therefore, initially we conducted some control oxidation reactions of **5a** by **1a** under the catalysis of **6a**/**7a**, in the absence or presence of NHPI (**3a**) (For details, please see Table S-1 in the SI). The results of these experiments showed that, in the absence of NHPI (**3a**), no conversion of **5a** to *trans*-cinnamaldehyde was observed. This negative result verifies that $PhI(OAc)_2$ (**1a**) alone can't oxidize the enamine intermediate to the iminium intermediate and, therefore, excludes the possible involvement of the MacMillan type enamine radical cation-deprotonation pathway (Scheme 2, top equation) in the current system. In contrast, in the presence of NPHI (**3a**), depending on the loadings of **3a** and **1a**, the conversion of **5a** to *trans*-cinnamaldehyde or *trans*-cinnamic acid was observed, suggesting that the PINO radical is crucial for the successful conversion of the enamine intermediate to the iminium intermediate, most likely through the proposed β-enaminyl radical intermediate formed via the HAT process.

Next, styrene (**2a**) was added to the reaction mixture to trap the methyl radical produced during the single-electron reduction of $PhI(OAc)_2$ (**1a**). As results in Table 1 show, the methylation-aminoxidation of styrene product **4a** was obtained 19% yield in chlorobenzene at rt (entry 1). Control experiments were carried out without either $PhI(OAc)_2$ (**1a**), NHPI (**3a**), aldehyde **5a**, catalyst **6a**, or co-catalyst **7a**, and no desired product was obtained (entries 2-6). It is interesting to note that when **5a**, **6a**, or **7a** is absent, the formation the bisaminoxidation product **8** was observed (entries 4-6), which is a direct result of the reaction between **2a** and the PINO radicals.[29] These results unequivocally demonstrate that the single-electron reduction of **1a** is not possible without the enamine formation. Similar results were also obtained when the reactions were carried out in toluene (For details, please see Table S-2, entries 1-7). The loadings of materials used in this reaction was then carefully optimized (please see Table S-2 in the SI), and we found that the highest yield of 39% could be obtained for the desired product **4a** when 3.0 equiv. of **2a** and **5a**, 2.0 equiv. of **1a**, and 0.30 equiv. of **6a** and **7a** were used in toluene (entry 7). Using toluene as the solvent, we further screened various acid co-catalysts **7** (Table 2), and found that benzoic acid (**7a**) was the best co-catalyst for this reaction, while the other acid co-catalysts screened all led to lower product yields (Table 2). When the same reaction was conducted in chlorobenzene with **7a** as the co-catalyst, the yield of **4a** could be further improved 50% (Table 1, entry 8). Since the amine catalyst determines the formation rate of the enamine intermediate and its stability, it was screened next (Table 3). Pyrrolidine (**5a**) turned out to be the best catalyst for this

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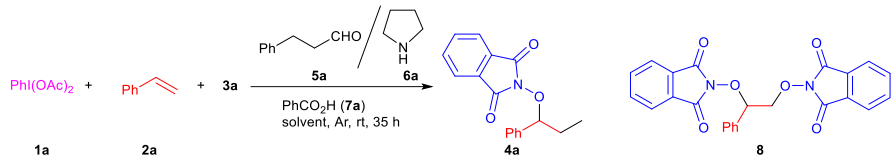
Table 1 Optimization of the reaction conditions[a]



Entry	**1a** (equiv.)	**2a** (equiv.)	**5a** (equiv.)	**6a** (equiv.)	**7a** (equiv.)	Solvent	Yield of **4a** (%)[b]
1	4.0	2.0	2.0	0.2	0.2	chlorobenzene	19
2	---	2.0	2.0	0.2	0.2	chlorobenzene	0
3[c]	4.0	2.0	2.0	0.2	0.2	chlorobenzene	0
4	4.0	2.0	---	0.2	0.2	chlorobenzene	0[d]
5	4.0	2.0	2.0	---	0.2	chlorobenzene	0[e]
6	4.0	2.0	2.0	0.2	---	chlorobenzene	0[f]
7	2.0	3.0	3.0	0.3	0.3	toluene	39
8	2.0	3.0	3.0	0.3	0.3	chlorobenzene	50
9	2.0	3.0	3.0	0.3	0.3	bromobenzene	24
10	2.0	3.0	3.0	0.3	0.3	$PhCF_3$	20
11	2.0	3.0	3.0	0.3	0.3	THF	46
12	2.0	3.0	3.0	0.3	0.3	1,4-dioxane	49
13	2.0	3.0	3.0	0.3	0.3	ether	21
14	2.0	3.0	3.0	0.3	0.3	EtOAc	14
15	2.0	3.0	3.0	0.3	0.3	$CHCl_3$	0
16	2.0	3.0	3.0	0.3	0.3	DMSO	15
17	2.0	3.0	3.0	0.3	0.3	DMF	30
18[g]	2.0	3.0	3.0	0.3	0.3	chlorobenzene	5
19[h]	2.0	3.0	3.0	0.3	0.3	chlorobenzene	30
20[i]	2.0	3.0	3.0	0.3	0.3	chlorobenzene	22
21[j]	2.0	3.0	3.0	0.3	0.3	chlorobenzene	10
22[k]	2.0	3.0	3.0	0.3	0.3	chlorobenzene	20

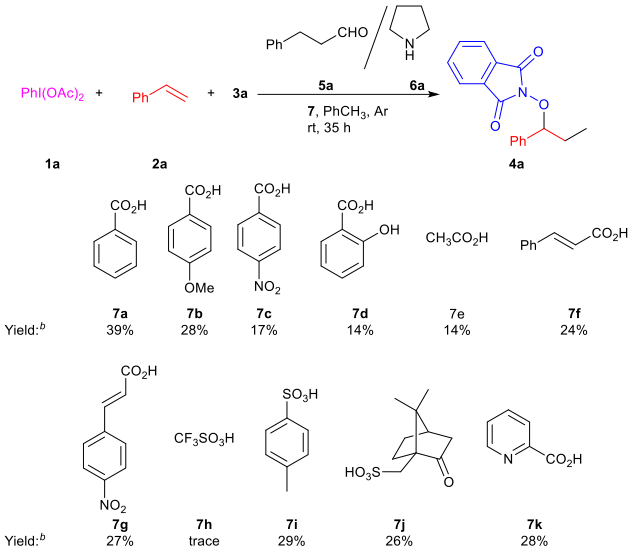
[a] Unless otherwise indicated, all reactions were carried out using NHPI (**3a**, 1.0 mmol), styrene (**2a**), $PhI(OAC)_2$ (**1a**), aldehyde **5a**, pyrrolidine (**6a**, 10 mol % of **5a**), and benzoic acid (**7a**, 10 mol % of **5a**) in chlorobenzene (4.0 mL) under argon at the room temperature for 35 h. [b] Yield of the isolated product after column chromatography. [c] Carried out without the addition of NHPI (**3a**). [d] Product **8** was isolated in 12% yield. [e] Product **8** was isolated in 19% yield. [f] Product **8** was isolated in 21% yield. [g] 4Å MS (150.0 mg) was added. [h] Water (4.0 equiv.) was added. [i] Carried out at 40 °C. [j] Carried out at 0 °C. [k] Carried out under air.

reaction, whereas piperidine was slightly less effective. All the other common secondary and primary amine catalysts we screened all led to poorer product yields (Table 3).

Another important parameter for this reaction is the enamine precursor, which determines the stability of the β-enaminyl radical and its ability to transfer the electron to **1a**. Therefore, various aldehydes and ketones were screened as the enamine precursors. As the results in Table 4 show, aldehyde **5a** proved to be the best enamine precursor. *para*-Substituted 3-phenylpropanals **5b** and **5c** are much less effective than **5a** (Table 4). In contrast, pentanal and acrylaldehyde are not effective at all (Table 4), probably because the β-enaminyl radical of the former is not stable enough and an enamine can't be formed from the latter. Only trace amount of product was obtained when 2-butanone was used, again maybe because the β-enaminyl radical derived from this compound is not stable enough. However, cyclohexanone (**5g**) is much more effective, especially at 40 °C. At this temperature, a 40% yield of product **4a** was obtained (Table 4). Nonetheless, the other cyclic ketones we screened all led to poorer yields than that of cyclohexanone (Table 4).

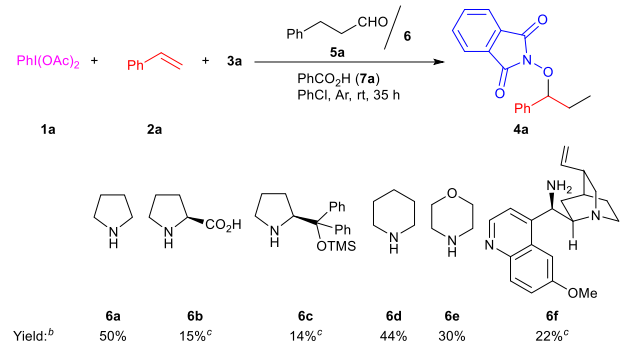
Next, we screened other common organic solvents (Table 1, entries 9-17) with the optimal enamine precursor, catalyst, and co-catalyst. Nevertheless, except for 1,4-dioxane (entry 12), which was almost as effective as chlorobenzene (entry 8), all of these solvents were inferior to chlorobenzene. Since water is produced during the formation of the enamine intermediate, we also tested whether an additive like molecular sieves or water would help this reaction and found both additives diminished the yield of **4a** (entries 18-19). Finally, it was found

Table 2 Screening of acid co-catalysts **7**[a]



[a] All reactions were carried out using NHPI (**3a**, 1.0 mmol), styrene (**2a**, 3.0 equiv.), $PhI(OAC)_2$ (**1a**, 2.0 equiv.), aldehyde **5a** (3.0 equiv.), the amine catalyst **6** (0.3 equiv., 10 mol % of **5a**), and acid **7** (0.3 equiv., 10 mol % of **5a**) in toluene (5.0 mL) under argon at the room temperature for 35 h. [b] Yield of product **4a** after column chromatography.

Table 3 Screening of the amine catalyst **6**[a]

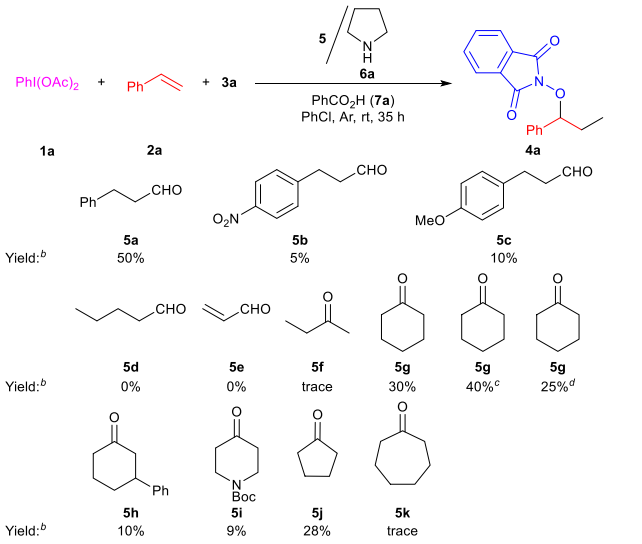


[a] All reactions were carried out using NHPI (**3a**, 1.0 mmol), styrene (**2a**, 3.0 equiv.), $PhI(OAC)_2$ (**1a**, 2.0 equiv.), aldehyde **5a** (3.0 equiv.), the amine catalyst **6** (0.3 equiv., 10 mol % of **5a**), and benzoic acid (**7a**, 0.3 equiv., 10 mol % of **5a**) in chlorobenzene (4.0 mL) under argon at the room temperature for 35 h. [b] Yield of product **4a** after column chromatography. [c] A racemic product was obtained.

a lower yield of **4a** was obtained when the reaction was carried at either a slightly higher (40 °C) or a slightly lower temperature (0 °C) (entries 20-21). As expected for a radical reaction, a lower yield of **4a** was obtained when the reaction was carried out under air instead of argon (entry 22).

Once the reaction conditions were optimized, the substrate scope of this alkylation-aminoxidation reaction was established. As summarized in Table 5, besides the more challenging methyl radical derived from $PhI(OAc)_2$ (**1a**), alkyl radicals derived from other phenyliodine(III) dicarboxylates (**1b-1f**) also participated in this reaction and, as expected, better yields were obtained for the products of secondary and tertiary radicals, such as those of cyclopentyl (**1c**), cyclohexyl (**1d**), t-butyl (**1e**), and

Table 4 Screening of the enamine precursor **5**[a]

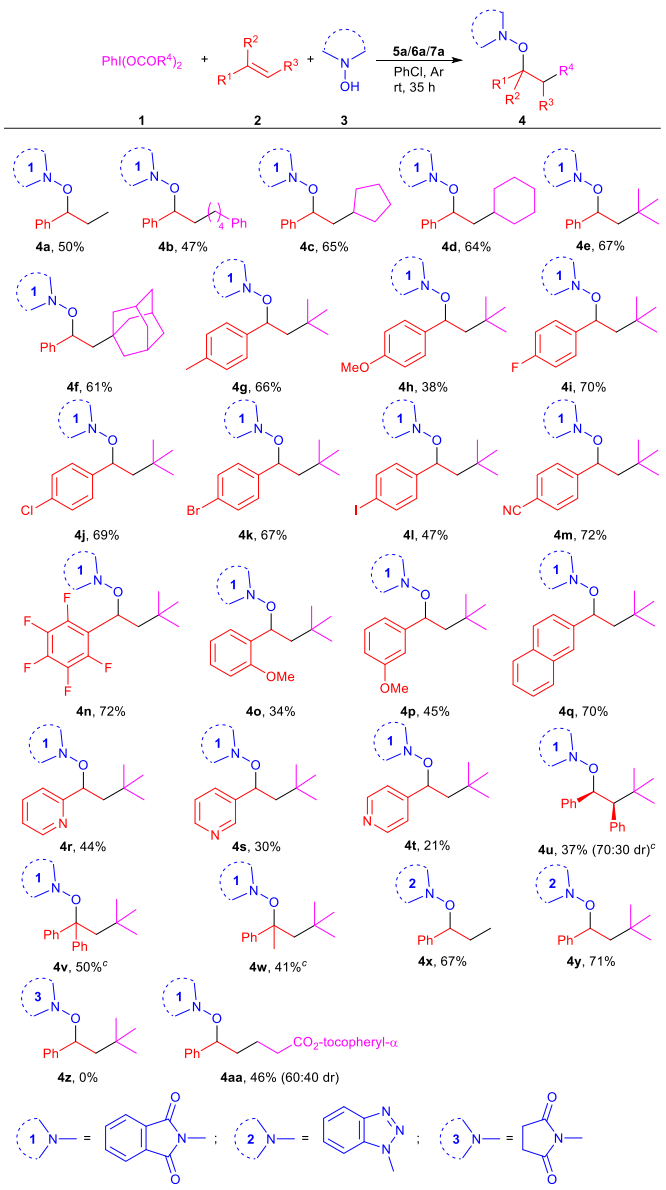


[a] Unless otherwise indicated, all reactions were carried out using $PhI(OAC)_2$ (**1a**, 2.0 equiv.), NHPI (**3a**, 1.0 mmol), styrene (**2a**, 3.0 equiv.), aldehyde **5** (3.0 equiv.), pyrrolidine (**6a**, 0.30 equiv., 10 mol % of **5**), and benzoic acid (**7a**, 0.30 equiv., 10 mol % of **5**) in chlorobenzene (4.0 mL) under argon at the room temperature for 35 h. [b] Yield of product **4a** after column chromatography. [c] The reaction was carried out at 40 °C. [d] The reaction was carried out at 80 °C.

1-adamantyl (**1f**). Similarly, good yields of the alkylation-aminoxidation reaction of styrene derivatives with a *para*-substituent on the phenyl group, and electronic effects of these substituents almost have no effects on the product yields (**4g-4m**), except that a lower yield was obtained with the 4-methoxy-substituted styrene (**4h**). Pentafluoro-substituted styrene is also a good substrate for this reaction (**4n**). Moreover, as compared with that of 4-methoxy-substituted styrene (**4h**), similar yields were obtained for 2-methoxy- and 3-methoxy-substituted styrenes (**4o-4p**), indicating that the reaction is not sensitive to the substitution pattern of the substituents. Desired products were also obtained for 2-vinylnaphthalene and 2-, 3- and 4-vinylpyridines in 70%, 44%, 30%, and 21% yield, respectively (**4q-4t**). Besides styrenes, *trans*-stilbene, α-phenylstyrene, α-methylstyrene all participated in this reaction when cyclohexanone (**5g**) was used as the enamine precursor and the desired products (**4u-4w**) were obtained in moderate yields. Moreover, a moderate diastereoselectivity of 70:30 was obtained for the product of *trans*-stilbene (**4u**). Cyclohexene is a very challenge substrate for radical alkylation reaction and, not surprisingly, no desired product could be obtained from this substrate (data not shown). Besides NHPI, HOBt was found to be also a good source of the radical needed for the enamine HAT reaction, and good yields were obtained for both products derived from the methyl and *t*-butyl radicals (**4x-4y**). Nonetheless, the related *N*-hydroxysuccinimide (NHS) failed to participate in this reaction as a source of the required radical (**4z**).

To further demonstrate the utility of this method, we synthesized a phenyliodine(III) dicarboxylate derived from α-tocopheryl acid succinate (For details, please see Scheme S-1 in

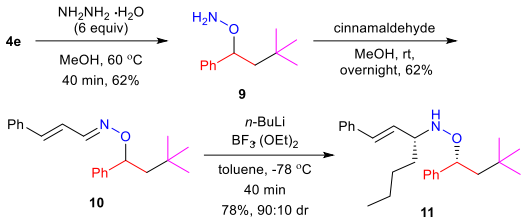
Table 5 Substrate scope of the alkylation-aminoxidation of alkenes.[a,b]



[a] Unless otherwise indicated, all reactions were carried out using **3** (1.0 mmol), alkene **2** (3.0 equiv.), phenyliodine(III) dicarboxylate **1** (2.0 equiv.), aldehyde **5a** (3.0 equiv.), pyrrolidine (**6a**, 0.3 equiv., 10 mol % of **5a**), and benzoic acid (**7a**, 0.3 equiv., 10 mol % of **5a**) in chlorobenzene (4.0 mL) under argon at the room temperature for 35 h. [b] Yield of the isolated product after column chromatography. [c] The reactions was carried out using **3a** (1.0 mmol), alkene 2 (3.0 equiv.), phenyliodine(III) dicarboxylate **1e** (2.0 equiv.), cyclohexanone (**5g**, 3.0 equiv.), pyrrolidine (**6a**, 0.3 equiv., 10 mol % of **5g**), and benzoic acid (**7a**, 0.3 equiv., 10 mol % of **5g**) in chlorobenzene (4.0 mL) under argon at 40 °C for 24 h.

the supporting information). When this phenyliodine(III) dicarboxylate was applied in the reaction, the desired product **4aa** was obtained with a dr of 60:40 and the major diastereomer was isolated in 46% yield.[30]

The product obtained in this alkylation-aminoxidation reaction is very synthetically useful, since it can be regarded as a protected alcohol or *O*-alkylhydroxylamine, both of which are very useful in synthetic and medicinal chemistry.[31] For example, the phthalimide group in compound **4e** could be easily removed by reacting with hydrazine. The resulting hydroxylamine **9** reacted with aldehyde to give the imine **10**, which diastereoselectively reacted with *n*-BuLi to give product **11**



Scheme 4 Derivatization of the reaction product **4e**.

(Scheme 4).[32]

Based on the results of our control reactions (Tables 1 and S-1), the following mechanism was proposed to explain the outcome of this alkylation-aminoxidation reaction of alkenes. As shown in Scheme 5, aldehyde **5a** reacts with pyrrolidine (**6a**) and the acid co-catalyst to form the enamine intermediate **12a**. Meanwhile, NHPI is oxidized by phenyliodine(III) diacetate (**1a**) to yield the PINO radical (Scheme 5, top right corner). A HAT reaction between the PINO and **12a** yields the key β-enaminyl radical **13a**. The single-electron transfer from **13a** to **1a** results in the formation of the acetoxy radical from **1a**, which decarboxylates to yield the methyl radical. The addition of the methyl radical to **2a** yields the benzylic radical **16a**, which combines with the PINO radical to give the observed product **4a**. On the other hand, after the SET oxidation, **13a** is converted to the iminium intermediate **14a**, which hydrolyzes to give **15a** and completes the organocatalytic cycle. According to this mechanistic proposal, phenyliodine(III) diacetate (**1a**) functions as the oxidant for NHPI (**3a**), the single-electron acceptor for **13a**, and the source of the methyl radical, while the PINO radical functions both as the HAT agent for the formation of **13a** and as a reagent for **16a** in the formation of the final product **4a**. As a further support of this radical mechanism, when the reaction was conducted in the presence of TEMPO under the optimized conditions, no desired product was obtained (data not shown).

Conclusion

In summary, we have developed novel organocatalytic method to access the β-enaminyl radicals via a HAT process. The resulting β-enaminyl radicals can be used as SET reductant for phenyliodine(III) dicarboxylates to release the alkyl radicals from the latter. *N*-Oxyl radicals, such as the PINO and BTO (benzotriazole-1-oxyl) radicals, generated in situ from the oxidation of NHPI and BtOH by phenyliodine(III) dicarboxylates, are used to achieve the synthesis of the β-enaminyl radicals via the HAT reaction. The alkyl radical species generated in the SET reduction of phenyliodine(III) dicarboxylates and the *N*-oxyl radicals can be trapped by styrene derivatives to give the alkylation-aminoxidation products of the corresponding alkenes in moderate to good yields.

Experimental Section

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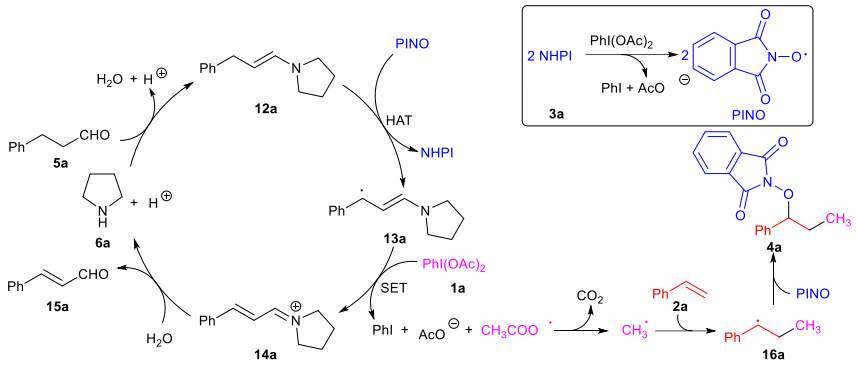

Scheme 5 Proposed mechanism for the radical alkylation-aminoxidation of alkenes.

General procedure for the one-pot alkylation-aminoxidation of styrenes:

An oven-dried round-bottom flask was evacuated and backfilled with argon. This procedure was repeated for three times. To this flask, chlorobenzene (5.0 mL), 3-phenylpropionaldehyde (**5a**, 402 mg, 3.0 mmol), pyrrolidine (**6a**, 21 mg, 0.30 mmol, 10 mol %), and benzoic acid (**7a**, 36 mg, 0.30 mmol, 10 mol %) were added under argon. The resulted solution was allowed to stir for 15 min at room temperature. Styrene (**2a**, 312 mg, 3.0 mmol) and $PhI(OAc)_2$ (**1a**, 644 mg, 2.0 mmol) were then added, followed by NHPI (**3a**, 163 mg, 1.0 mmol). The reaction mixture was further stirred under the same conditions. After completing of the reaction (monitored by TLC), the organic volatiles were evaporated under reduced pressure. The resulted crude reaction mixture was purified by flash column chromatography using 2 to 5% EtOAc in hexane to give product 4a as a white solid (165 mg, 59% yield).

Products **4s**, **4t**, and **4u** were synthesized from **3a**, $PhI(OCOBu\text{-}t)_2$ (**1e**), and the corresponding alkenes by following the above general procedure using cyclohexanone (**5g**, 294 mg, 3.0 mmol) instead of **5a** at 40 °C.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

This research is financially supported by the Welch Foundation (AX-1593). The authors also thank the National Science Foundation (CHE 1664278) for a post-doctoral fellowship (to N. Sakkani).

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