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Catalytic Oxygenative Allylic Transposition of Alkenes into Enones with an Azaadamantane-Type Oxoammonium Salt Catalyst

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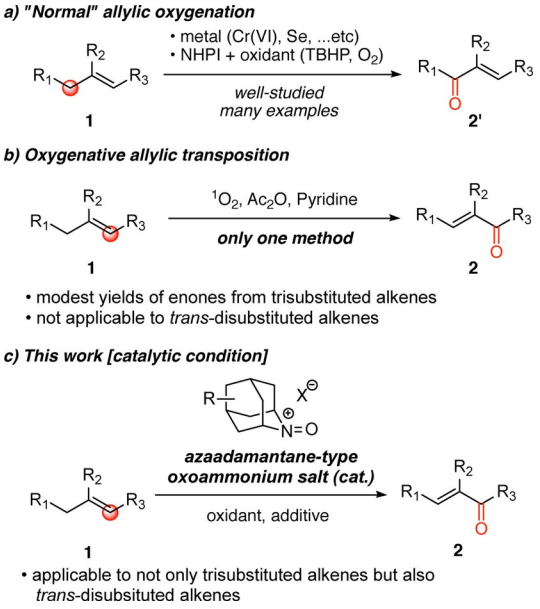
Abstract: The first catalytic oxygenative allylic transposition of unactivated alkenes into enones has been developed using an oxoammonium salt as the catalyst. This reaction converts various tri- and *trans*-disubstituted alkenes into their corresponding enones with transposition of their double bonds at ambient temperature in good yields. The use of a less-hindered azaadamantane-type oxoammonium salt as the catalyst and a combination of two distinct stoichiometric oxidants, namely, iodobenzene diacetate and magnesium monoperoxyphthalate hexahydrate (MMPP·6 H_2O) are essential to facilitate the enone formation efficiently.



Scheme 1. Enone synthesis from alkenes.

Alkene is a ubiquitous and readily-accessible structural motif in organic chemistry, and selective modifications of alkenes have been extensively investigated to develop various methods.[1] Those methods are applied to the synthesis of valuable chemical products, including pharmaceuticals, agrochemicals, and polymer materials. The selective oxygenation of alkenes at the periphery of the double bond poses attractive opportunities to access useful molecules, such as allylic alcohols and enones, spurring chemists to achieve these transformations efficiently.[2]

Schematically, two possible ways can be drawn for oxygenation of an alkene to give an enone (Scheme 1). One is a direct oxygenation at the allylic position of alkene substrate **1** to give enone **2**′ ("normal" allylic oxygenation, Scheme 1 a). This type of reaction has been investigated for a long time to establish numbers of reliable methods to synthesize complex molecules.[2d] The other is an oxygenative allylic transposition that involves a migration of the alkene functionality of **1** to give regioisomeric enone **2** (Scheme 1 b). To the best of our knowledge, a sequence of an ene reaction of an alkene and singlet oxygen (Schenck ene reaction) and subsequent acetylation–dehydroacetoxylation of the resulting allyl hydroperoxide[3] is the only known single-step method for this transformation.[4] Although some successful applications of this method to the synthesis of complex molecules have been demonstrated,[5] this method has some major drawbacks: it is potentially dangerous due to the explosive nature of the hydroperoxide intermediate, it gives modest yields of enones from trisubstituted alkenes due to poor regioselectivity of the singlet oxygen ene reaction, and it is generally not applicable to *trans*-disubstituted alkenes due to lack of the reactivity of singlet oxygen toward them.[6] Here, we describe the first catalytic oxygenative allylic transposition of alkenes into enones, featuring the use of a less-hindered azaadamantane-type oxoammonium salt as a catalyst (Scheme 1 c). This novel method is applicable to not only trisubstituted alkenes but also *trans*-disubstituted alkenes.

The reaction design is shown in Scheme 2. We set a member of 2-azaadamantane *N*-oxyl (AZADO)-derived oxoammonium salts as the key catalyst for the catalytic oxygenative allylic transposition, which we have investigated as catalysts for oxidation of alcohols[7] and silyl enol ethers.[8] Based on some preliminary results in our pioneering study of the reactivity of the azaadamantane-type oxoammonium salts toward alkenes, we envisioned that a trisubstituted or acyclic alkene reacts with an azaadamantane-type oxoammonium salt through an O-preferential ene-like addition to afford an allylic alkoxyamine (the first reaction).[9] We envisaged that connecting this alkoxyamine formation with two transformations, namely, alkoxyamine oxidation-oxy-Cope elimination giving a carbonyl compound and a hydroxylamine (the second reaction),[10] and oxi-

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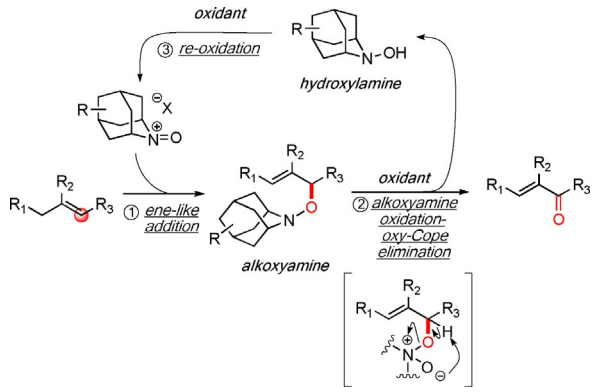
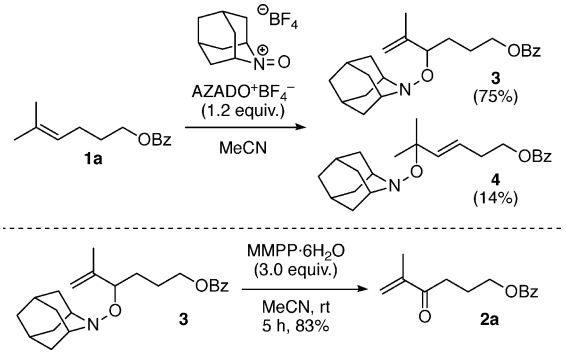


Scheme 2. Reaction design.

dation of a hydroxylamine into an oxoammonium ion (the third reaction), would form a catalytic system to convert an alkene into an enone with the transposition of the alkene functionality. Although a 2,2,6,6-tetramethylpiperidine-type oxoammonium salt is also known to lead the first ene-like reaction, which was reported by Bobbitt and co-workers,[11] we anticipated that this highly hindered oxoammonium salt is much less suitable for the catalyst than the azaadamantane-type oxoammonium salts. To develop the catalytic system, competing direct oxidation of the alkene substrate by a stoichiometric oxidant (e.g., epoxidation) is anticipated as a problem. We expected that the less-hindered azaadamantane-type oxoammonium salts and alkoxyamine/hydroxylamine intermediates should react more readily with alkene substrates and stoichiometric oxidants, respectively, than tetramethylpiperidine-type ones. Therefore, the use of the azaadamantane-type oxoammonium salts would increase the efficiency of the catalytic cycle to eventually suppress the problematic side reaction. Furthermore, the less-hindered azaadamantane-type oxoammonium salts would exhibit broader substrate scope, whereas the tetramethylpiperidine-type ones would react with only electron-rich trisubstituted alkenes.

To evaluate the feasibility of the reaction design, we examined the first and second reactions separately using stoichiometric amounts of reagents (Scheme 3). The ene-like addition of 2-azaadamantane *N*-oxoammonium tetrafluoroborate (AZADO$^+$BF$_4^-$) to trisubstituted alkene **1a** proceeded smoothly

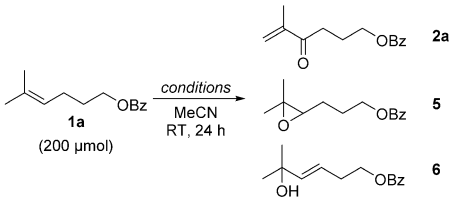


Scheme 3. Stoichiometric reaction of AZADO$^+$BF$_4^-$ and alkene **1a** (top); oxidative conversion of alkoxyamine **3** (bottom).

at room temperature to give alkoxyamines **3** and **4** in a high combined yield (89%) with good regioselectivity (5.4:1). In contrast, the ene reaction of singlet oxygen and **1a** gave poor regioselectivity (1:1).[12] The oxidative conversion of alkoxyamine **3** into enone **2a** was examined using various oxidants. The screening of oxidants indicated that only organic peracids promoted this reaction in high yield, and identified magnesium monoperoxyphthalate hexahydrate (MMPP·6H$_2$O) as the most promising oxidant for the catalytic reaction. MMPP·6H$_2$O converted **3** into **2a** in 83% yield, which proceeded selectively even in the presence of an equimolar amount of alkene **1a**.[12]

Encouraged by the aforementioned promising results, we proceeded to investigate the catalytic conditions (Table 1). The conditions consisting of AZADO$^+$BF$_4^-$ (20 mol%), MMPP·6H$_2$O (1.5 equiv), and LiBF$_4$ (2 equiv) in acetonitrile, which was established for a catalytic oxygenation of silyl enol ethers into 1,2-diketones,[8] afforded the expected enone **2a**, but its yield (43%) was unsatisfying (entry 1). The close analysis of the reaction identified epoxide **5** and tertiary alcohol **6** as byproducts, which would be generated by the direct oxidation of alkene **1a** with MMPP·6H$_2$O and by the oxidative elimination of the azaadamantane moiety from alkoxyamine **4**, respectively. We considered that minimization of the amount of MMPP·6H$_2$O by using another oxidant that selectively promotes the third reaction in Scheme 2 (a hydroxylamine to an oxoammonium ion) would suppress the generation of epoxide **5** to improve the yield of **2a**. Gratifyingly, we found that the use of 0.55 equiv of MMPP·6H$_2$O with 1.0 equiv of PhI(OAc)$_2$ suppressed the generation of **5** below our detectable limit and increased the yield of **2a** to 64% (entry 2). Note that molecular sieves were necessary to ensure good reproducibility.

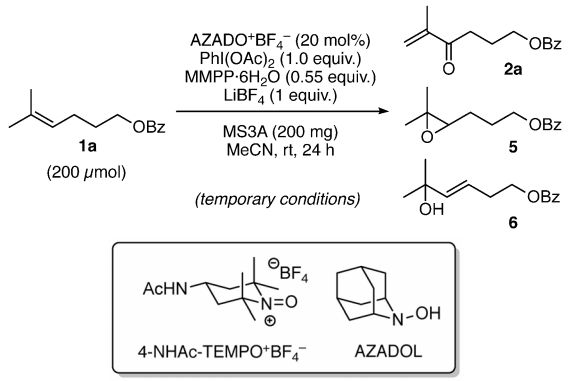
Table 1. Initial investigation of the catalytic conditions[a]



Entry	Conditions	^{1}H NMR yield [%][b] 2a	5	6	1a
1	AZADO$^+$BF$_4^-$ (20 mol%) MMPP·6H$_2$O (1.5 equiv) LiBF$_4$ (2 equiv)	43	17	11	N.D.
2	AZADO$^+$BF$_4^-$ (20 mol%) **PhI(OAc)$_2$ (1.0 equiv)** MMPP·6H$_2$O **(0.55 equiv)** LiBF$_4$ (1 equiv) *powdered MS3A (200 mg)*	**64**	N.D.	13	N.D.

[a] All of the reactions were conducted with slow addition of the solution of alkene **1a** into the mixture of the other reagents in solvent over 2 h using a syringe pump. [b] Yields were determined by ^{1}H NMR of crude products using 1,3,5-trimethoxybenzene as an internal standard. N.D. = not detected.

Table 2. Further optimization of the reaction conditions[a]

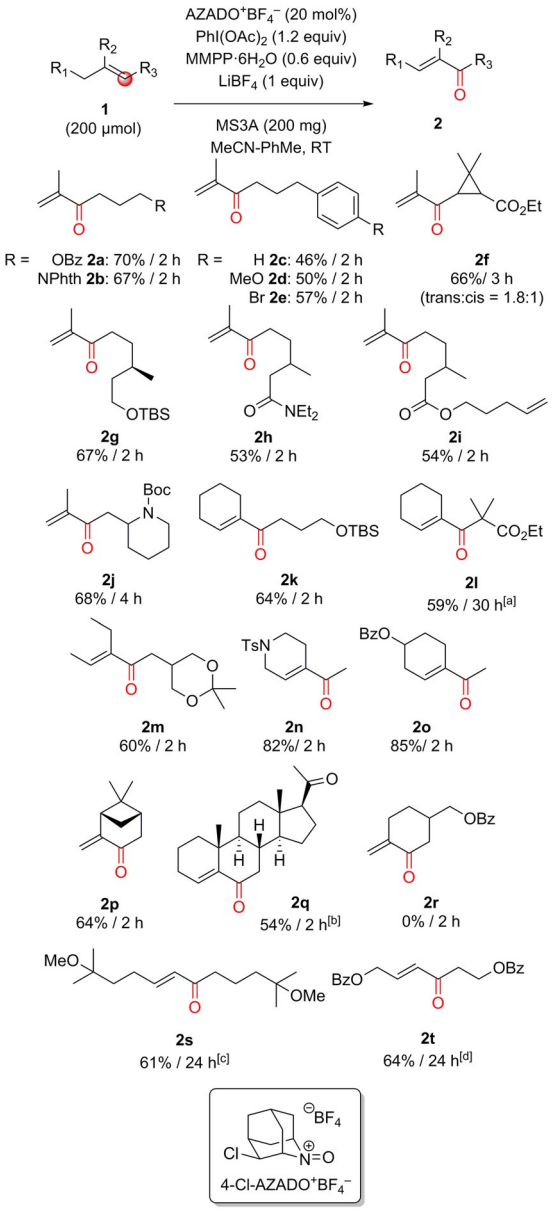


Entry	Change(s) from the initial conditions	^{1}H NMR yield [%][b] 2a	5	6	1a
1	none	64	N.D.	13	N.D.
2	4-NHAc-TEMPO$^+$BF$_4^-$ instead of AZADO$^+$BF$_4^-$	26	28	N.D.	11
3	**MeCN-PhMe (1:4) instead of MeCN**	**71**	N.D.	10	N.D.
4[c,d]	AZADOL instead of AZADO$^+$BF$_4^-$	52	N.D.	7	25
5[d]	AZADO$^+$BF$_4^-$ (10 mol%)	62	12	8	N.D.
6[d]	LiBF$_4$ (0 equiv)	17	11	N.D.	55

[a] All of the reactions were conducted with slow addition of the solution of alkene **1a** into the mixture of the other reagents in solvent over 2 h using a syringe pump. [b] Yields were determined by ^{1}H NMR of crude products using 1,3,5-trimethoxybenzene as an internal standard. [c] 1.2 equiv of PhI(OAc)$_2$ and LiBF$_4$ were used. [d] MeCN-PhMe (1:4) was used as solvent. N.D. = not detected.

On the basis of these key findings, other reaction parameters were optimized (Table 2).[12] The screening of oxoammonium salts with various steric and electronic properties indicated that AZADO$^+$BF$_4^-$ showed the best catalytic efficiency. It is noteworthy that 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (4-NHAc-TEMPO$^+$BF$_4^-$), which is known to react with trisubstituted alkenes to give alkoxyamines,[11] hardly catalyzed the reaction (entry 2). This result indicates that the less-hindered structure of an oxoammonium salt is essential to realize the catalytic reaction. The screening of solvents revealed that the mixed solvent of acetonitrile and toluene (1:4 *v*/*v*) gave the best yield of **2a** (71%; entry 3). Note that this mixed solvent promoted the reaction much more efficiently than acetonitrile alone, consuming the alkene substrate within two hours. The conditions that generate AZADO$^+$BF$_4^-$ in situ from commercially available hydroxylamine AZADOL did not achieve the full conversion of alkene **1a**. (entry 4). Reducing the amount of AZADO$^+$BF$_4^-$ to 10 mol% afforded enone **2a** in good yield (62%), and a detectable amount of undesired epoxide **5** (Table 1, entry 5). A significant decrease of the reaction efficiency was observed under the conditions without LiBF$_4$ (entry 6). Eventually, we identified the conditions shown in entry 3 as the optimal conditions.

With the optimized conditions in hand, we evaluated their substrate scope (Scheme 4). The functional group tolerance was evaluated by using isopropylidene-type substrates **1a–j**.



Scheme 4. Substrate scope. All of reactions were conducted with slow addition of the solution of alkene **1** into the mixture of other reagents in solvent over 2 h using a syringe pump except for **1t**. Yields are of isolated product. [a] 30 mol% of AZADO$^+$BF$_4^-$, 1.5 equiv of PhI(OAc)$_2$, and 0.75 equiv of MMPP·6H$_2$O were used. [b] 30 mol% of AZADO$^+$BF$_4^-$ was used. [c] 30 mol% of 4-Cl-AZADO$^+$BF$_4^-$, 1.5 equiv of PhI(OAc)$_2$, and 0.75 equiv of MMPP·6H$_2$O were used. [d] Reaction conditions: 4-Cl-AZADO$^+$BF$_4^-$ (30 mol%), PhI(OAc)$_2$ (1.5 equiv), MMPP·6H$_2$O (0.75 equiv), LiNTf$_2$ (1.25 equiv), MS3A (200 mg), MeCN-PhMe (1:4), RT. **1t** was added to a suspension of 4-Cl-AZADO$^+$BF$_4^-$, PhI(OAc)$_2$, MMPP·6H$_2$O, LiNTf$_2$ and MS3A in MeCN-PhMe in one portion.

The optimal conditions tolerated various functional groups including esters (**2a**, **2f**, and **2i**), a phthalimide (**2b**), electron-rich and -deficient aryl groups (**2c–e**), a cyclopropane (**2f**), a silyl ether (**2g**), an amide (**2h**), and a carbamate (**2j**). Note that a terminal alkene was intact in this reaction condition (**2i**). The optimal conditions allowed for the oxidation of other types of trisubstituted alkenes, namely, cyclohexylidenes (**2k** and **2l**), a 3-pentylidene (**2m**), and others (**2n** and **2o**) to give

their corresponding enones in good to high yields. Furthermore, α-pinene and a pregnenolone derivative were also converted into enones **2p** and **2q**, respectively. Unfortunately, a simple cyclohexene-type substrate gave not its corresponding enone **2r**, but a complex mixture. Less electron-rich *trans*-disubstituted alkenes that are difficult to be oxidized by the conventional method using singlet oxygen were also examined. Although the optimal conditions for trisubstituted alkene **1a** did not convert the *trans*-disubstituted alkenes into enones **2s** and **2t**, the use of a more electrophilic oxoammonium salt, namely, 4-chloro-2-azaadamantane *N*-oxoammnium tetrafluoroborate (4-Cl-AZADO$^{+}BF_4^{-}$),[9] effectively converted these alkenes into enones **2s** and **2t** in 61 and 64% yields, respectively. Note that $LiNTf_2$, instead of $LiBF_4$, is especially effective for synthesis of **2t**.

In summary, we have developed the first catalytic oxygenative allylic transposition of alkenes using an oxoammonium salt as a catalyst, which poses an alternative synthetic method to obtain enones from alkenes. This reaction tolerates and works efficiently with various functional groups and structurally diverse alkenes including *trans*-disubstituted ones. The use of the less-hindered azaadamantane-type oxoammonium salt as the catalyst and the combination of the two distinct stoichiometric oxidants play key roles for facilitating the catalytic reaction efficiently. This is a rare example of oxoammonium salt-catalyzed oxidative transformation of alkenes.[13] We believe that the reaction developed here will contribute to the synthesis of new enones and facilitate the research of applied chemistry focusing on unique the reactivity of oxoammonium salts.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · enones · organocatalysis · oxygenation · synthetic methods

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