Dehydrogenation

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Synthesis of 1,3-Cycloalkadienes from Cycloalkenes: Unprecedented Reactivity of Oxoammonium Salts

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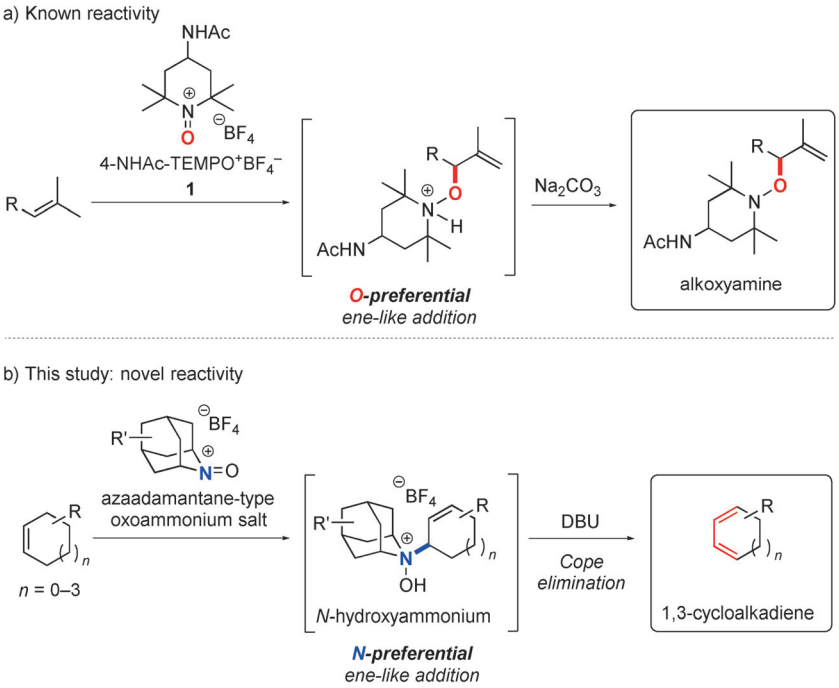
Abstract: *Few methods allow for the direct conversion of cycloalkenes into cycloalkadienes with high chemo- and regioselectivity. Herein, we report a convenient one-pot process for this transformation that involves the unprecedented N-preferential group transfer of N-oxoammonium salts to cycloalkenes, followed by Cope elimination, to afford cycloalkadienes at room temperature and pressure.*

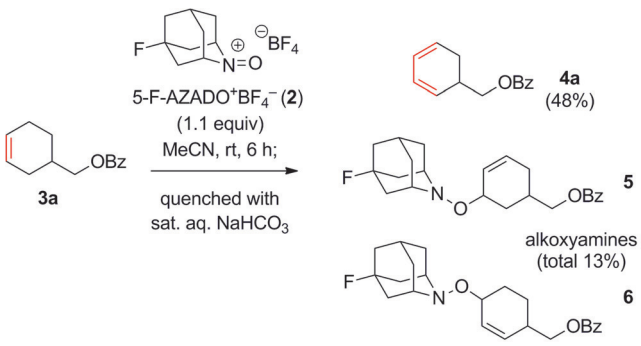
1,3-Cycloalkadiene is a versatile structural motif in organic chemistry. This conjugated diene system is found in various natural products, including biologically significant compounds,[1] and is regarded as a useful building block in organic synthesis, especially for the Diels–Alder reaction.[2] Among numerous methods for the construction of 1,3-cycloalkadienes,[3–5] the most straightforward is the dehydrogenation of cycloalkenes, which are readily available.[6] However, conditions for this transformation are limited. A dibromination–dehydrobromination sequence has predominantly been used for this transformation,[7] but this method often suffers from low regioselectivity and/or a low yield in the dehydrobromination step.[7d,f]

We herein describe a new way of synthesizing 1,3-cycloalkadienes from cycloalkenes on the basis of unprecedented reactivity of oxoammonium salts with cyclic alkenes.[8] The reaction of oxoammonium salts with alkenes was introduced in 2006 by Bobbitt and co-workers, who reported that the 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO)-derived oxoammonium salt **1** reacted with trisubstituted alkenes to afford alkoxyamines through O-preferential ene-like addition (Scheme 1 a).[9] In contrast, we report herein that less-hindered azaadamantane-type oxoammonium salts react with cycloalkenes to afford 1,3-cycloalkadienes through N-preferential ene-like addition (Scheme 1 b).



Scheme 1. Reactivity of oxoammonium salts toward alkenes. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

The novel reactivity of these oxoammonium salts was discovered unexpectedly during an investigation of 2-azadamantane *N*-oxyl (AZADO)-derived oxoammonium salts.[10] We examined the reaction between cyclohexene **3a** and the 5-F-AZADO-derived oxoammonium salt **2** (5-F-AZADO$^+$BF$_4^-$;[11] Scheme 2). The mixture of **2** and **3a** in acetonitrile was stirred at room temperature until **3a** was no



Scheme 2. Unexpected 1,3-cyclohexadiene formation.

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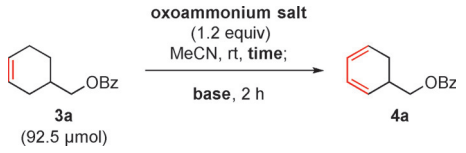
longer detectable by TLC. After quenching of the reaction with saturated aqueous $NaHCO_3$, 1,3-cyclohexadiene **4a** was isolated unexpectedly in 48% yield along with alkoxyamines **5** and **6**, which were obtained in 13% combined yield.[12]

We were interested in the potential of this unexpected reaction and began to study it (Table 1). By TLC of the reaction mixture, we found that cyclohexene **3a** reacted with oxoammonium salt **2** to form a highly polar intermediate. This intermediate was partially converted into 1,3-cyclohexadiene **4a** after treatment with aqueous $NaHCO_3$. We hypothesized that the basicity of $NaHCO_3$ causes the conversion of the highly polar intermediate into 1,3-cyclohexadiene **4a** and that a different base would improve the conversion of the highly polar intermediate into **4a**. Indeed, the screening of bases identified DBU as the ideal base, with the yield increasing from 48 to 60% (Table 1, entry 2). When no base was used to quench the reaction, a marked decrease in yield was observed (Table 1, entry 3). Next, we compared the reactivity of various oxoammonium salts (Table 1, entries 4–7). Almost no reaction was observed with the TEMPO-derived oxoammonium salt 4-NHAc-TEMPO$^+$ BF_4^- (**1**), which oxidizes trisubstituted alkenes (entry 4).[9] 1-Me-AZADO$^+$ BF_4^- (**7**), which bears a methyl group adjacent to the oxoammonium moiety, also showed very low reactivity (entry 5). Unsubstituted AZADO$^+$ BF_4^- (**8**) afforded the desired diene in good yield but required a longer reaction time (entry 6). These results indicate that the steric accessibility of the oxoammonium moiety is essential to induce dehydrogenation and that electron-withdrawing groups at a remote position from the oxoammonium moiety enhance the reactivity of oxoammonium salts. However, we thought that the ideal oxoammonium salt 5-F-AZADO$^+$ BF_4^- (**2**) would be unsuitable for widespread use owing to its low availability.[13] Instead, we envisioned that more readily available 4-halo-substituted azaadamantane-type oxoammonium salts would also show high reactivity. Gratifyingly, we found that 4-Cl-AZADO$^+$ BF_4^- (**9**) exhibited modestly improved reactivity as compared with 5-F-AZADO$^+$ BF_4^- (**2**; Table 1, entry 7).[14–16]

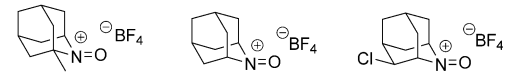
Table 1: Optimization of the reaction conditions.



3a (92.5 μmol) **4a**

Entry	Oxoammonium salt	Base (equiv)	*t* [h]	Yield [%][a]
1	5-F-AZADO$^+$ BF_4^- (**2**)[b]	sat. aq. $NaHCO_3$	6	48
2	5-F-AZADO$^+$ BF_4^- (**2**)	DBU (3)	6	60
3	5-F-AZADO$^+$ BF_4^- (**2**)	none	6	18
4	4-NHAc-TEMPO$^+$ BF_4^- (**1**)	DBU (3)	48	<2[c]
5	1-Me-AZADO$^+$ BF_4^- (**7**)	DBU (3)	48	8[c]
6	AZADO$^+$ BF_4^- (**8**)	DBU (3)	48	58
7	4-Cl-AZADO$^+$ BF_4^- (**9**)	DBU (3)	2	65

[a] Yield of the isolated product. [b] The reaction was carried out with 1.1 equivalents of **2**. [c] The yield was determined by ^{1}H NMR spectroscopy.



1-Me-AZADO$^+$$BF_4^-$ (**7**) AZADO$^+$$BF_4^-$ (**8**) 4-Cl-AZADO$^+$$BF_4^-$ (**9**)

Having optimized the reaction conditions, we evaluated the scope of the reaction in terms of possible substrates (Scheme 3). The O-protected cyclohexenemethanols **3a–c** were efficiently dehydrogenated to give their corresponding 1,3-cyclohexadienes **4a–c**. In contrast, it was confirmed that a mixture of regioisomers **4c** and **4c′** was obtained in low yield by the conventional dibromination–dehydrobromination sequence (Scheme 4).[17] The 4-Cl-AZADO$^+$ BF_4^--promoted dehydrogenation tolerated azide (product **4d**), phthalimide (product **4e**), carbamate (product **4f**), and sulfonamide (product **4g**) functional groups. This reaction proceeded well with both *trans*- and *cis*-4,5-disubstituted cyclohexenes **3h–j**, even on a gram scale (see **4h**). Notably, these *cis*-4,5-disubstituted cyclohexenes were converted into 5,6-disubstituted 1,3-cyclohexadienes as single regioisomers; however, the conventional dibromination–dehydrobromination sequence converts these substrates into a mixture of 1,6-disubstituted (major) and 5,6-disubstituted (minor) 1,3-cyclohexadiene regioisomers.[7d] The bicyclic substrates **3k** and **3l** were also dehydrogenated by 4-Cl-AZADO$^+$ BF_4^- in moderate yield. Whereas cyclohexene **3m**, which bears a methyl group at its allylic position, gave the 1,3-cyclohexadiene product **4m** in modest yield, cyclohexene **3n**, which instead bears a phenyl group, gave the product **4n** in good yield. Unfortunately, 1-substituted and 1,2-disubstituted cyclohexenes **3o** and **3p** were not converted into the desired cyclohexadienes, but rather into the corresponding alkoxyamines, which are generated by the O-preferential addition of oxoammonium species to alkenes (Scheme 1a).[17] The 4,4-disubstituted cyclopentenes **3q** and **3r** were smoothly converted into the corresponding 5,5-disubstituted cyclopentadienes **4q** and **4r** in good yield. *O*-Benzoyl cyclopentenol **3s** gave a complex mixture, and the desired cyclopentadiene **4s** was not isolated. Cycloheptenes **3t** and **3u** were dehydrogenated in moderate yield. The 4-Cl-AZADO$^+$ BF_4^--promoted dehydrogenation of cyclooctene **3v** was also possible, but only in a low yield of 16%.[18]

The synthetic use of the cycloalkadienes is exemplified by the synthesis of carbasugar derivatives.[19] Thus, upon exposure to $^1O_2$, **4h** was converted into endoperoxide **10**, and the O–O bond was cleaved with thiourea to give diol **11** (Scheme 5a). After dibenzoylation of the diol **11**, the resulting tetrabenzoate was subjected to OsO_4-catalyzed dihydroxylation, followed by acetonization to give **12** as a single diastereoisomer. On the other hand, when **4i** was subjected to a hetero-Diels–Alder reaction with *tert*-butyl nitrosoformate, generated in situ from *tert*-butyl *N*-hydroxycarbamate, adducts **13** and **13′** were formed in a 9:1 mixture (Scheme 5b). This mixture was subjected to dihydroxylation, benzoylation, and N–O bond cleavage to give the aminocarbasugar derivative **14** and an isomer as an inseparable 9:1 mixture.

To gain insight into the mechanism of this novel dehydrogenation reaction, we identified the reaction intermediates. First, the treatment of O-bound alkoxyamines **5** and **6** with DBU did not afford 1,3-diene **4a**, which suggests that

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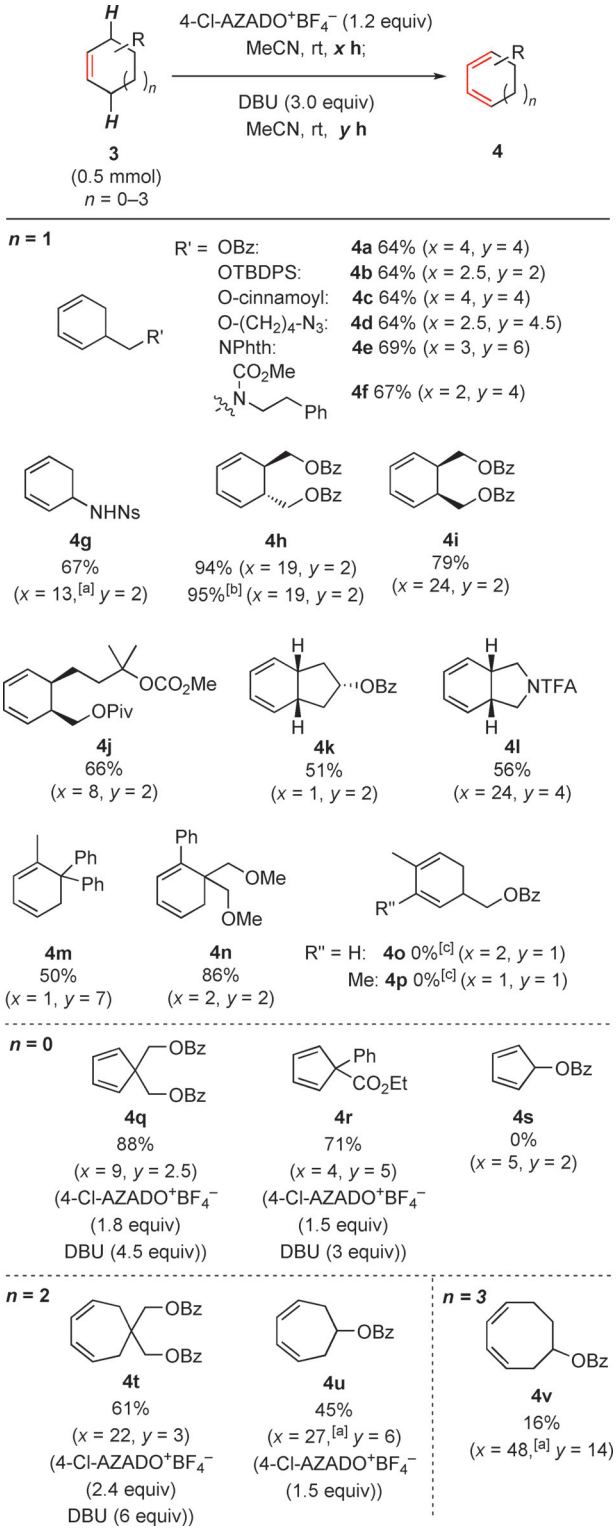
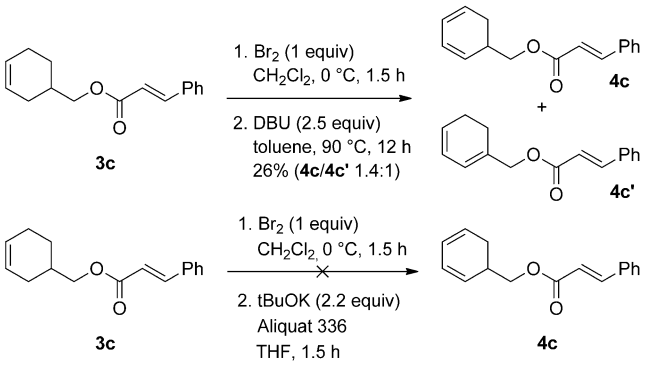
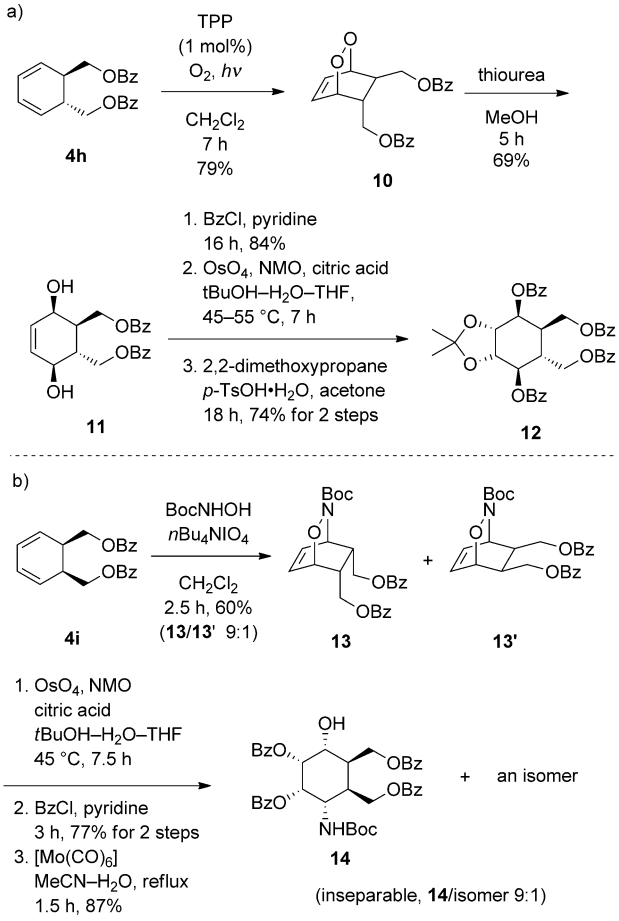


Scheme 3. Scope of the reaction. Yields are for the isolated product. [a] The reaction was carried out at 50 °C. [b] The reaction was carried out with 1.23 g of **3h**. [c] The corresponding alkoxyamine was obtained (see the Supporting Information). Bz = benzoyl, Ns = 2-nitrobenzenesulfonyl, Piv = pivaloyl, TBDPS = *tert*-butyldiphenylsilyl, TFA = trifluoroacetyl.



Scheme 4. Dibromination–dehydrobromination sequence.



Scheme 5. Functionalization of the obtained 1,3-cyclohexadienes. Boc = *tert*-butoxycarbonyl, NMO = 4-methylmorpholine *N*-oxide, TPP = 5,10,15,20-tetraphenylporphyrin, Ts = toluenesulfonyl.

alkoxyamine adducts **5** and **6** are not relevant intermediates (Scheme 6a). Second, we observed reaction intermediates in the dehydrogenation of *meso*-alkene **3i** in [D$_3$]MeCN by NMR spectroscopy (Scheme 6b).[17] We observed a peak characteristic of a hydroxy functionality in the ^{1}H NMR spectrum, which suggests that the highly polar intermediate observed by TLC could be the *N*-hydroxyammonium species **15**.[20] Although this intermediate was too unstable under ambient conditions to be isolated, the tertiary amine **16** was

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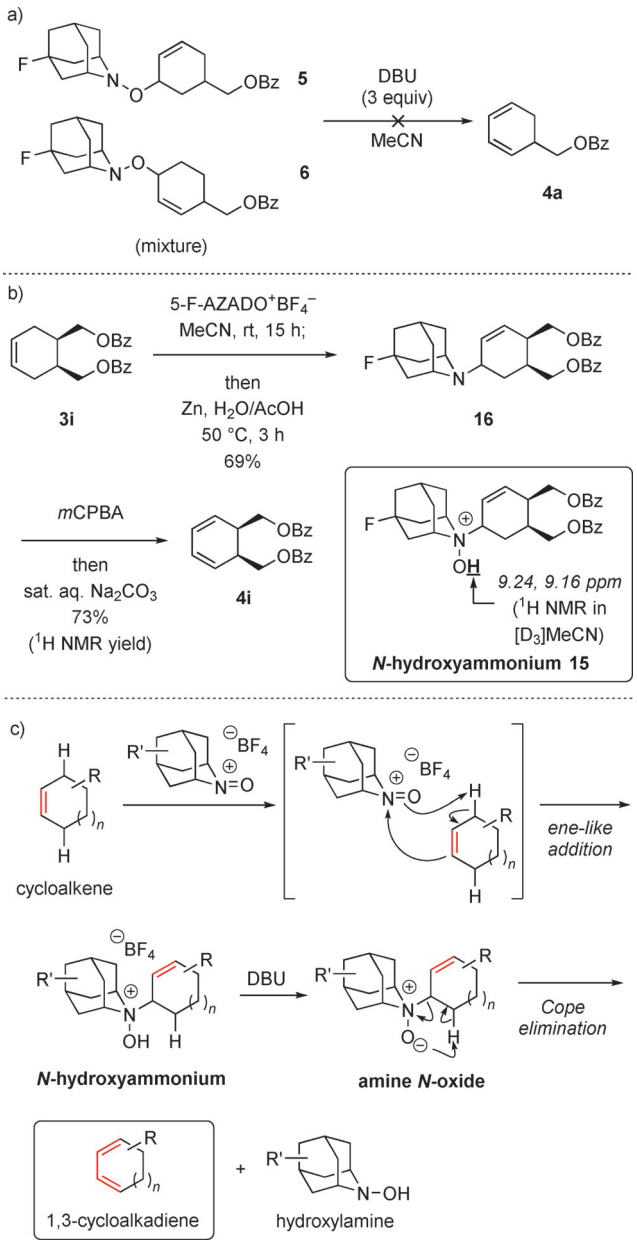

Scheme 6. a) Attempt to convert alkoxyamines **5** and **6** into diene **4a**. b) Isolation of **16**. c) Plausible reaction mechanism. *m*CPBA = *m*-chloroperoxybenzoic acid.

successfully isolated after in situ reduction by zinc in AcOH. The reoxidation of amine **16** with *m*CPBA and subsequent treatment with aqueous Na_2CO_3 afforded 1,3-diene **4i** in 73% yield. These results indicate that **15** is the pertinent reaction intermediate.

Considering the above results, we propose the reaction mechanism shown in Scheme 6c. A cycloalkene reacts with an oxoammonium salt through a group-transfer reaction to form an *N*-hydroxyammonium species. In this step, C–N bond formation occurs preferentially: the regioselectivity of this addition is opposite to that of the ene-like addition of TEMPO-derived oxoammonium salt **1** to trisubstituted alkenes, in which C–O bond-formation occurs (see Scheme 1). The difference in selectivity could be defined by the steric hindrance around the nitrogen atom of the oxoammonium species. After treatment with DBU, the *N*-hydroxyammonium species forms an amine *N*-oxide, which undergoes Cope elimination to give the corresponding 1,3-cycloalkadiene and hydroxylamine.[21,22]

In summary, we have discovered an unprecedented N-preferential ene-like addition of an oxoammonium ion onto a cyclic alkene to give an *N*-hydroxyammonium species. 4-Cl-AZADO$^+$BF$_4^-$ was used for this novel group-transfer reaction, which was followed by a base-induced Cope elimination. This process constitutes an expedient method for the chemo- and regioselective conversion of cycloalkenes into 1,3-cycloalkadienes. The key reagent 4-Cl-AZADO$^+$BF$_4^-$ can be readily prepared on a multigram scale and is recyclable.[23] We expect that this unprecedented reactivity of oxoammonium species will lead to new avenues for designing oxidative molecular transformations. Further mechanistic investigation and expansion of the substrate scope are under way.

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Keywords: alkenes · dehydrogenation · ene reaction · regioselectivity · synthetic methods

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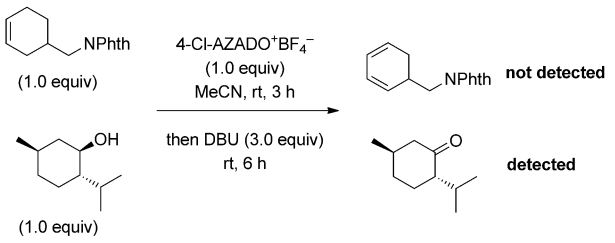
[12] In the course of the optimization of the reaction, we observed another alkoxyamine product that may be generated by Meisenheimer rearrangement (see the Supporting Information for details).

[13] 5-F-AZADO$^+$BF$_4^-$ (**2**) was prepared from commercially available 2-adamantanone in nine steps, including steps involving a rare ruthenium salt and an expensive fluorination reagent (see Ref. [11] and the Supporting Information).

[14] See the Supporting Infomation for detailed optimization results.

[15] 4-Cl-AZADO$^+$BF$_4^-$ (**9**) was prepared in six steps from 2-adamantanone (see the Supporting Information).

[16] To clarify the reactivity of 4-Cl-AZADO$^+$BF$_4^-$, we conducted a competition experiment between a cycloalkene and a secondary alcohol (see scheme). In this reaction, the corresponding cycloalkadiene was not detected, and the ketone was detected in the crude mixture by ^{1}H NMR spectroscopy. Therefore, we concluded that secondary alcohols react with the AZADO-derived oxoammonium salt much faster than cycloalkenes.



[17] See the Supporting Information for details.

[18] We tested a few acyclic alkene substrates. The desired dienes were not obtained, but the corresponding alkoxyamines formed in high yield (see the Supporting Information for details).

[19] For a review about carbasugars, see: O. Arjona, A. M. Gómez, J. C. López, J. Plumet, *Chem. Rev.* **2007**, *107*, 1919 – 2036.

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[21] 4-Chloro-2-azaadamantane-2-ol (4-Cl-AZADOL) was recovered from this reaction system (see the Supporting Information for details).
[22] To develop catalytic reaction conditions, we tested the compatibility of the oxoammonium salt with DBU. When DBU was added at the beginning of the reaction, however, the reaction did not proceed (other bases, such as 2,6-lutidine and Na_2CO_3, gave the same result). Additionally, we found that the generated cyclohexadiene reacted with the oxoammonium salt to give the corresponding arene. From these observations, we consider that a catalytic reaction would be difficult with this particular system.
[23] The recovered 4-Cl-AZADOL was converted into 4-Cl-AZADO$^+BF_4^-$ in 95% yield (see Ref. [21] and the Supporting Information).

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