Table 2: Stereoselectivity on bicyclo[3.1.1]heptane ring system

entry	10	R	*endo/exo*[a]
1	10a	H	100/0
2	10c	TES	78/22
3	10d	Ac	100/0
4	10e	Bz	88/12
5	10f	3,5-$(NO_2)_2C_6H_3CO$	88/12

a) The ratio of *endo/exo* was determined

b) by ^1H NMR.

It is interesting to note that with the *cross*-adduct 10a or 10d, the ratio of the two epimers at C-6 position on the bicyclo[3.1.1]ring has a value of 100:0 (Table 2, entry 1, 3). And the preference of *endo*-stereochemistry at C-6 bridged head was observed in other *cross*-adducts. So as to the stereoselectivity on bicyclo[3.2.0]heptane ring 11, the stereoselectivity increased giving rise to a 87:13 mixture of two epimers *endo*-11f and *exo*-11f (Table 3, entry 5).

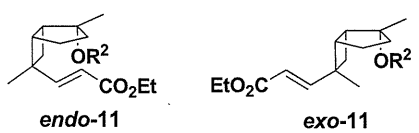


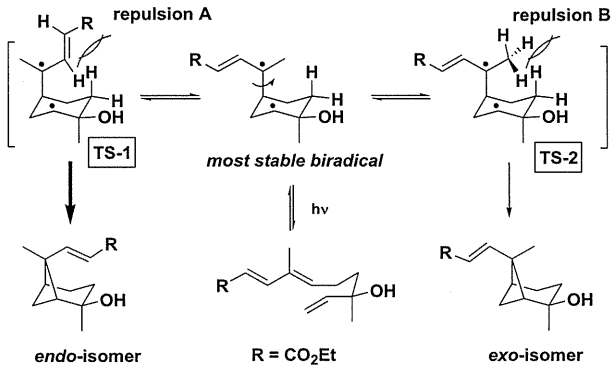
Table 3: Stereoselectivity on bicyclo[3.2.0]heptane ring system

entry	11	R	*endo/exo*[a]
1	11a	H	51/49
2	11c	TES	53/47
3	11d	Ac	76/24
4	11e	Bz	77/23
5	11f	3,5-$(NO_2)_2C_6H_3CO$	87/13

a) The ratio of *endo/exo* was determined by ^1H NMR.

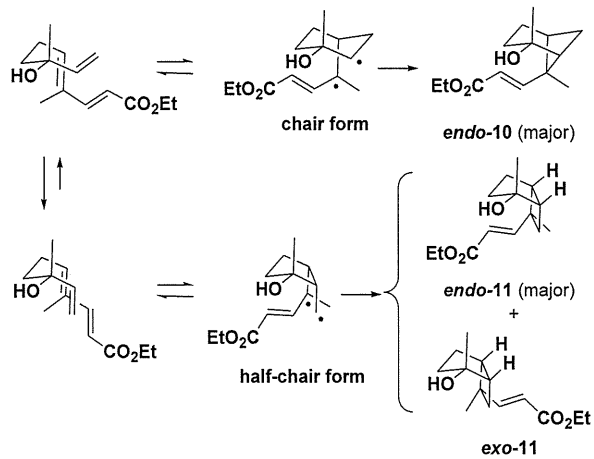
We assume that the preference of *endo*-stereochemistry at C-6 bridged head is due to fast rotation in the 1,4-biradical intermediate and the selectivity in the ring closure step reflects steric interactions in the transition state. The first bond is formed between the terminal double bond and excited diene. Rotation around the single bond in the most stable 1,4-diradical intermediate was found to be much faster than cyclization. Therefore *Z* or *E* trisubstituted olefin moiety of diene leads to the same product mixture.

The conformational preference of TS-1 over TS-2 may result from the 1,3-diaxial repulsion B between the axial hydrogen on cyclohexane ring and the methyl substituent being larger than that of repulsion A between the axial hydrogen on cyclohexane ring and the 2-ethoxycarbonyl vinyl group as shown in Scheme 3.



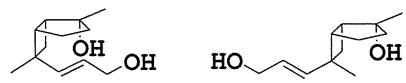
Scheme 3.

Srinivasan suggested that the initial step, which gives a diradical, involves preferential formation of a five-membered ring ("rule of five") on intramolecular [2+2] photocycloaddition reactions of 1,6-heptadiene [9]. However, irradiation of 9a gave the cross photoadduct *endo*-10 and some parallel adducts. This mode of the cross addition observed here is against the "rule of five" for intramolecular [2+2] photocycloadditions and points to the fact that no strict generalization can be made for such reactions [12]. We assumed the stable biradical of chair form may be attributed to the extra stabilization being called *the captodative effect* [13] which is synergistic stabilization of carboncentered radicals by both an electron-withdrawing (captive) and an electron-donating (dative) substituent as shown in Scheme 4. Thus, it may be due to the stabilization of the radical on tertiary carbon by both an ester vinylogue (captive) and a methyl (dative) substituent.



Scheme 4.

On the other hand, using of 9b instead of 9a, no cycloadducts were observed on exposure with the low pressure Hg lamp in each of hexane, diethyl ether, MeOH or benzene solutions. However, when 9b was irradiated with the high pressure Hg lamp in acetone, two parallel adducts 14 originated through [2+2] cycloaddition according to the "rule of five" was obtained in 39% yield. The structure of photoadducts 14 was confirmed by the sequential hydrogenation to afford a 50:50 mixture of two 1,2-bridged cyclobutanes *endo*-13 and *exo*-13.



[3.2.0] *endo*-14 [3.2.0] *exo*-14

It is noteworthy that the optically active 1,3-bridged cyclobutanes 10 of the bicyclo[3.1.1]heptane ring system and 1,2-bridged cyclobutanes 11 of the bicyclo[3.2.0]heptane ring system were produced by UV irradiation of α,β,γ,δ-unsaturated esters 9a and 9c-f. These results suggest that a chirality on the C-8 atom can control the stereoselectivity of the cycloaddition reaction. The preference of *endo*-stereochemistry at C-6 bridged head was observed in *cross*-adducts 10. On the other hand, the regioselectivity was found to proceed exclusively in the parallel fashion when conjugated dienol 9b was irradiated.

We expect that this methodology will be useful for the synthesis of a wide range of bergamotene family, and further work toward this goal is in progress.

Supplementary data: Spectroscopic and analytical data for *endo*-10, *endo*-11 and *exo*-11 (6 pages).

Acknowledgments –
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[11] Isolated compounds were identified as follows:

endo-12: Y. 16.1%, MP: 78.8 °C. $[\alpha]_D^{20}$: -24.8 (*c* 1.00, $CHCl_3$). Rf: 0.40 (diethyl ether). IR (KBr): 3286, 2948, 2863, 1462, 1374, 1197, 1182, 1112, 1075, 1057, 916 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 1.13 (3H, s, H-11), 1.22 (3H, s, H-12), 1.16-1.47 (5H, m, H-9 , H-8, H_{cis}-7), 1.62-1.73 (4H, m, H-4, H_{trans}-7, H-3a), 1.79-1.90 (1H, m, H-3e), 2.36-2.45 (2H, m, H-5, H-1), 3.62 (2H, t, J= 6.6 Hz, H-10). ^{13}C NMR (100 MHz $CDCl_3$): 22.1(CH_3), 24.8(CH_2), 27.4(CH_2), 28.2(CH_3), 33.3(CH_2), 34.6(C), 35.6(CH_2), 39.9(CH_2), 44.8(CH), 47.7(CH), 63.6(CH_2), 81.5(C).

exo-13: Y.6.5%, MP: 93.3 °C. $[\alpha]_D^{20}$:+25.2 (*c* 1.00, $CHCl_3$). Rf: 0.33(diethyl ether). IR (KBr): 3244, 2946, 2864, 1453, 1373, 1170, 1066, 980 cm^{-1}. ^1H NM R (400 MHz, $CDCl_3$): 0.88 (3H, s, H-12), 1.20 (3H, s, H-8), 1.44-1.72 (9H, m, H-3a, H-4, H_{trans}-7, H_{cis}-7, H-9 , H-10), 1.90-1.97 (1H, m, H-3e), 2.20 (1H, t, *J*= 7.2 Hz, H-5), 2.32 (1H, dd, *J*= 15.5 Hz, 6.8 Hz ,H-1), 3.65 (2H, t, *J*= 6.1 Hz, H-11). ^{13}C NMR (100 MHz $CDCl_3$): 20.6(CH_3), 24.4(CH_2), 27.4(CH_3), 27.6(CH_2), 32.1(CH_2), 35.0(C), 39.0(CH_2), 39.9(CH_2), 42.6(CH), 44.4(CH), 63.4(CH_2), 79.0(C).

endo-13: Y.54.1%, $[\alpha]_D^{20}$: +23.0(*c* 1.00, $CHCl_3$). Rf: 0.28 (diethyl ether). IR (neat): 3336, 2948, 2865, 1455, 1372, 1169, 1143, 1058, 977, 916, 917 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 1.06 (3H, s, H-12), 1.14 (3H, s, H-8), 1.18-1.60 (9H, m, H-4, H-3a, H_{trans}-7, H_{cis}-7, H-9, H-8), 1.81-1.89 (1H, m, H-3e), 2.12 (1H, t, *J*= 7.6 Hz, H-5), 2.30 (1H, dd, *J*= 15.2 Hz, 7.2 Hz ,H-1), 3.64 (2H, t, *J*= 6.4 Hz, H-11). ^{13}C NMR (100 MHz $CDCl_3$): 24.1(CH_2), 27.2(CH_2), 27.3(CH_3), 28.4(CH_3), 32.5(CH_2), 32.6(CH_2), 34.8(C), 39.1(CH_2), 42.2(CH), 46.2(CH), 63.3(CH_2), 81.5(C).

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Vanadium-Catalyzed Oxidation of *tert*-Butyl *N*-Hydroxycarbamate to Nitrosoformate and Its Diels-Alder Reaction with Simple and Functionalized Dienes

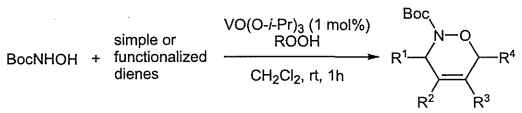
Abstract: A general and efficient vanadium-catalyzed oxidation of *tert*-butyl *N*-hydroxycarbamate to *tert*-butyl nitrosoformate using alkyl hydroperoxides as the terminal oxidants has been developed. The intermediate nitroso compound was trapped by in situ Diels□Alder reaction with simple and functionalized dienes, providing general access to a variety of functionalized 3,6-dihydro-2*H*-1,2-oxazines.

Key words: nitroso Diels-Alder reaction, catalysis, oxidation, functionalized dienes, vanadium catalyst

Nitroso Diels-Alder (NDA) reaction is an intriguing method for synthetic organic chemists due to the selective 1,4-incorporation of amino and hydroxy functionalities into 1,3-dienes in a single step.[1] Among nitroso compounds nitrosocarbonyl compounds, RCONO, are well known to be very powerful dienophiles[2] and are typically generated in situ by the stoichiometric oxidation of hydroxamic acids, using organic or inorganic periodates,[1a,3] Dess-Martin periodinane,[4] oxalyl chloride,[5] *N*-bromosuccinimide,[6] silver oxide,[6] lead oxide,[6] or by thermally liberation from their NDA adducts with 9,10-dimethylanthracene in refluxing solvent.[1] In view of green chemistry, catalytic reaction and more safe reagents are preferable. Therefore, metal-catalyzed oxidations involving peroxides as the terminal oxidants have recently emerged for the generation of nitrosocarbonyl compounds.[7] Late transition metals, especially Ru and Cu, have been extensively examined as a catalyst for these reactions.

Acylnitroso Diels-Alder reactions with 1,3-dienes having functional groups would directly furnish functionalized 3,6-dihydro-1,2-oxazines, which possess a great potential for the synthesis of nitrogen-containing natural products.[2b,e,8] However, since the first reports by Whiting[7a], and Iwasa and Nishiyama[7b], only simple 1,3-dienes have been examined in the metal-catalyzed oxidation of hydroxamic acids to nitroso compounds and their Diels-Alder reaction.[9] Herein we describe the vanadium-catalyzed oxidation of *tert*-butyl *N*-hydroxycarbamate using alkyl hydroperoxides as terminal oxidants and in situ Diels-Alder trapping of nitrosoformate with simple and functionalized dienes, which potentially allows access to polyfunctionalized 1,2-oxazines in a single step, which are versatile intermediates

for preparing nitrogen containing bioactive compounds (Scheme 1).



(1)

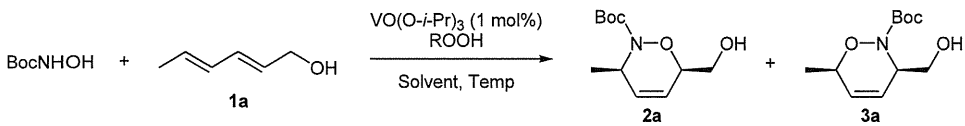
Scheme 1

Our studies began with the reaction of *t*-butyl *N*-hydroxycarbamate (BocNHOH) with hexa-2,4-dien-1-ol (**1a**) in the presence of cumyl hydroperoxide (CHP) as a terminal oxidant. In the absence of any catalyst, no Diels-Alder adduct was detected and BocNHOH was quantitatively recovered (Table 1, entry 1). On the other hand, when a catalytic amount (1 mol%) of $VO(O\text{-}i\text{-}Pr)_3$ was added to the reaction mixture (at -20 °C for 1 hr), the [4+2]cycloadducts **2a** and **3a** were obtained in 65% yield (entry 2).[10] Increasing the amount of BocNHOH and CHP (1.5 and 2.0 equiv) led to improve the yields of Diels-Alder adducts (entries 3 and 4). When commercial grade or water-saturated CH_2Cl_2 was used as the solvent, the yield of adducts was slightly decreased (72% yield). It is noteworthy that raising the temperature from -20°C to rt resulted in a complete conversion of dienol **1a**, affording the Diels-Alder adduct in quantitative yield (entry 5). It is well-known that epoxidation of allylic alcohols smoothly proceed in the above reaction conditions except in the presence of excess amount of hydroxamic acids.[11] Indeed, ^{1}H-NMR analysis of the reaction mixture, which was obtained from the vanadium-catalyzed reaction of hexadienol **1a** with CHP at rt for 1 hr, showed the exclusive formation of the corresponding epoxide (see Supporting Information). On the other hand, in the presence of 2 equiv of BocNHOH the cycloadducts were quantitatively obtained with no observation of oxidized byproducts such as epoxides and aldehydes.[12] Thus, these results imply a formation of stable hydroxamate complexes from vanadium ion and hydroxamic acid, which substantially forbids the concurrent coordination of dienol **1a** and oxidant to vanadium, leading to the inhibition of epoxidation of dienol **1a**. Interestingly, compared to the literature result (80% yield, regioisomer ratio of **2a**/**3a** = 67:33) in

which tetrabutylammonium periodate was used as an stoichiometric oxidant, our oxidation system gave the adducts in quantitative yield with slightly higher regioselectivity (99% yield, **2a**/**3a** = 72:28).[13] These results suggest that some involvement of concurrent coordination of the nitrosoformate and hexadienol **1a** to vanadium would exist in Diels-Alder reaction, which would control their orientation in the bond forming step and would enhance the regioselectivity. Even 0.1 mol% of $VO(O\text{-}i\text{-}Pr)_3$ could also give the desired Diels-Alder adduct in good yield (entry 6). While the use of 1.1 equiv of BocNHOH and 2 equiv of oxidant gave a satisfactory result (rt, 1 h, 80% yield, entry 7), the reverse case (2 equiv of BocNHOH and 1 equiv of oxidant, entry 8) afforded the complete conversion of starting material to give the

desired product in high yield (1 h, 99% yield). Other non-polar solvents, e.g. toluene and cyclopentylmethylether (CPME), are also used as a solvent (entries 9 and 10). The reaction catalyzed by titanium complex, instead of vanadium catalyst, also proceeded in satisfactory yield but needed much longer reaction time (12 h) (Table 1, entry 11). The reaction using *tert*-butyl hydroperoxide (TBHP, 5.5 M in decane) as an oxidant gave the almost same result with CHP (entry 12). Hydrogen peroxide (30%) was not an effective oxidant for this reaction (entry 13).

Table 1 Optimization of vanadium-catalyzed oxidation of BocNHOH using CHP and in situ Diels-Alder reaction with (*E*,*E*)-hexa-2,4-dien-1-ol (**1a**)



Entry	BocNHOH (equiv)	ROOH (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]	Ratio of **2a** to **3a**[b]
1[c]	2	CHP (2)	CH_2Cl_2	-20	1	0	-
2	1	CHP (1)	CH_2Cl_2	-20	1	65	83:17
3	1.5	CHP (1.5)	CH_2Cl_2	-20	1	94	79:21
4	2	CHP (2)	CH_2Cl_2	-20	1	95	77:23
5	2	CHP (2)	CH_2Cl_2	rt	0.5	99	72:28
6[d]	2	CHP (2)	CH_2Cl_2	rt	1	71	74:26
7	1.1	CHP (2)	CH_2Cl_2	rt	1	80	78:22
8	2	CHP (1)	CH_2Cl_2	rt	1	99	77:23
9	2	CHP (2)	Toluene	rt	0.5	99	79:21
10	2	CHP (2)	CPME	rt	2	80	71:29
11[e]	2	CHP (2)	CH_2Cl_2	rt	12	85	78:22
12	2	TBHP (2)	CH_2Cl_2	rt	1	91	77:23
13	2	H_2O_2 (2)	CH_2Cl_2	rt	2	27[f]	80:20[g]

[a] Isolated yield of **2a** and **3a** after silica gel chromatography.

[b] The ratio is based on the isolated yields of the regioisomers.

[c] The reaction was carried out in the absence of vanadium catalyst. BocNHOH was recovered quantitatively.

[d] $VO(O\text{-}i\text{-}Pr)_3$ (0.1 mol%) was used.

[e] $Ti(O\text{-}i\text{-}Pr)_4$ (1 mol%) was used.

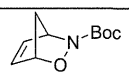
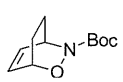
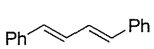
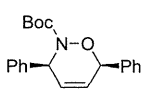
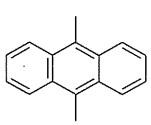
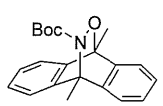
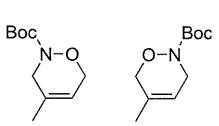
[f] The adduct **2a** was obtained as a mixture with BocNHOH. The yield of **2a** was calculated on

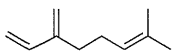
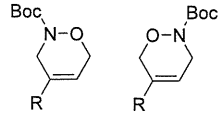
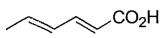
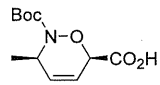
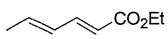
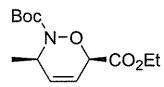
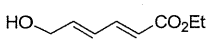
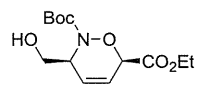
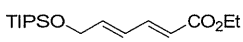
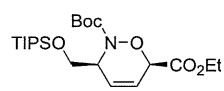
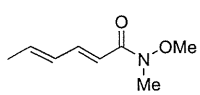
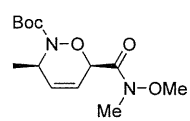
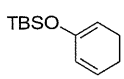
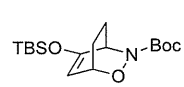
the basis of ^{1}H NMR analysis of the mixture.

[g] The ratio determined by ^{1}H NMR.

With optimized reaction conditions (1 mol% of VO(O-*i*-Pr)$_3$ and 2 equiv of oxidant and BocNHOH at rt for 1 h) in our hands, various simple or functionalized dienes were subjected to this optimized conditions.[14] Our oxidation system proved to be general for a variety of simple dienes (Table 2, entries 1-5). Cyclic and acyclic conjugated dienes afforded the desired 3,6-dihydro-1,2-oxazines in good yields (entries 1-3). The reaction with 9,10-dimethylanthrathene, which is frequently used to mask of nitrosocarbonyl compounds,[1] gave the nitroso Diels-Alder adduct **2e** in moderate yields (entry 4). The reaction with 2-substituted diene **1f** afforded the desired 1,2-oxadines in 1:1 ratio of regioisomers **2f** and **3f** (entry 5), which was consistent with the literature result.[15] The 1:1 mixture of regioisomers was also obtained from myrcene (**1g**), having a trisubstituted double bond, in low yield due to the lability to polymerization under work-up conditions (entry 6).

Table 2Carbonylnitroso Diels-Alder reaction with various simple and functionalized dienes

Entry	Diene	Oxidant	Products	Yield (%)[a]
1[b]	 **1b**	CHP	 **2b**	62
2[c]	 **1c**	CHP	 **2c**	86
3	 **1d**	CHP	 **2d**	77
4	 **1e**	TBHP	 **2e**	40
5	 **1f**	TBHP	 **2f** **3f**	46[d]

6	 **1g**	CHP	 R = $(CH_3)_2C=CHCH_2CH_2$ **2g** **3g**	20[d]
7	 **1h**	CHP	 **2h**	44
8	 **1i**	TBHP	 **2i**	70
9	 **1j**	CHP	 **2j**	62
10	 **1k**	TBHP	 **2k**	20
11	 **1l**	TBHP	 **2l**	79
12	 **1m**	CHP	 **2m**	13[e]

[a] Isolated yield.

[b] The reaction temperature is -20 °C.

[c] Toluene was used as solvent.

[d] The ratio of regioisomers is 1:1.

[e] *N*-Boc-6-hydroxyamino-2-hexenone was produced in 24% yield.

A single isomeric adduct was obtained in moderate yield from the reaction with sorbic acid as a functionalized diene (entry 7). The reaction with sorbic acid derivatives **1i-l** also gave exclusively the 1,2-oxadines **2i-l** as single stereoisomers (entries 8-11). Interestingly, the Diels-Alder reaction with silyl protected dienoate ester **1k** gave a lower yield compared to unmasked hydroxy dienoate ester **1j**, implying the steric repulsion between triisopropylsilyl group and *tert*-butoxycarbonyl group. Weinreb amide **1l** is also a good substrate for this reaction, giving the desired adduct **2l** in a good yield (entry 11). When 2-silyloxy substituted cyclohexadiene **1m** was used as a functionalized diene, Diels-Alder adduct **2m** was obtained in low yield (entry 12). This adduct is likely to desilylation on silica gel column chromatography, giving □-hydroxyaminocyclohexenone.

In summary we have demonstrated the vanadium-catalyzed oxidation of *tert*-butyl *N*-hydroxycarbamate using alkyl hydroperoxides and its Diels-Alder reaction with simple and functionalized dienes. This useful reaction proceeds rapidly under mild conditions (1 mol% catalyst loading, room temperature, 1 hr), leading to good yields of functionalized 1,2-oxadines, which was considered as the promising synthetic intermediates for highly functionalized compounds. Synthetic studies to access useful natural products are currently underway and will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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Typical Procedure for the vanadium-catalyzed oxidation of *tert*-butyl *N*-hydroxycarbamate and in situ Diels-Alder reaction with (*E,E*)-hexa-2,4-dien-1-ol (1a):

To a solution of *tert*-butyl *N*-hydroxycarbamate (0.564 g, 4.1 mmol), (*E,E*)-hexa-2,4-dien-1-ol (0.246 mL, 2.1 mmol), and $VO(O\text{-}i\text{-}Pr)_3$ (5.0 μL, 0.021 mmol) in CH_2Cl_2 (4.2 mL) was added 80% CHP (0.39 mL, 2.1 mmol) at ambient temperature. After stirring for 1 h, water (2 mL) was added to the mixture. Saturated sodium sulfite solution was slowly added to the resulting mixture. After stirring for 1 h, the reaction mixture was transferred to separatory funnel, and the aqueous phase was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatographic purification (eluent: hexane/diethyl ether = 3:1 to 2:1) of the residue provided **2a** and **3a** (0.480 g, 99%) as a mixture of two regioisomers. The mixture was separated by column chromatography on silica gel (hexane/ethyl acetate = 9:1) to give pure **2a** and **3a**. The structure was deduced from two-dimensional NMR

spectroscopies (HMBC and HMQC).[13]

(3*R,6*R**)-*N*-*tert*-butoxycarbonyl-6-hydroxymethyl-3-methyl-3,6-dihydro-2*H*-1,2-oxazine (2a):**[13] TLC (hexane/ethyl acetate = 1:1) R_f = 0.26. IR (neat): 3407, 2978, 1698, 1369, 1169, 1119, 1066, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, *J* = 9 Hz, 3H), 1.47-1.49 (m, 1H), 1.50 (s, 9H), 3.67 (dd, *J* = 6.6, 12.6 Hz, 1H), 3.77 (dd, *J* = 3.0, 12.3 Hz, 1H), 4.41-4.46 (m, 1H), 4.64-4.68 (m, 1H), 5.69 (dt, *J* = 10.2, 1.8 Hz, 1H), 5.92 (ddd, *J* = 10.2, 4.5, 2.4 Hz, 1H).

(3*S,6*S**)-*N*-*tert*-butoxycarbonyl-3-hydroxymethyl-6-methyl-3,6-dihydro-2*H*-1,2-oxazine (3a):**[13] TLC (hexane/ethyl acetate = 1:1) R_f = 0.38. IR (neat) 3445, 2979, 1704, 1369, 1166, 1113, 1088 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.6 Hz, 3H), 1.50 (s, 9H), 1.65 (s, 1H), 3.72-3.77 (m, 2H), 4.47-4.52 (m, 1H), 4.65-4.68 (m, 1H), 5.78 (ddd, *J* = 10.2, 4.2, 2.1 Hz, 1H), 5.85 (td, *J* = 1.5, 10.2 Hz, 1H).

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***N*-*tert*-butoxycarbonyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (2b):**[16] TLC (hexane/diethyl ether = 1:2) R_f = 0.33. IR (neat) 2978, 1739, 1702, 1165 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.73 (d, *J* = 8.6, 1H), 1.99 (td, *J* = 2.4, 8.6 Hz, 1H), 4.98 (br s, 1H), 5.21 (br s, 1H), 6.40-6.42 (m, 2H).

***N*-*tert*-butoxycarbonyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (2c):**[16] TLC (hexane/ethyl acetate = 3:1) R_f = 0.51. IR (neat) 2976, 2936, 1736, 1695, 1158, 1073 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27-1.54 (m, 2H), 1.47 (s, 9H), 2.06-2.23 (m, 2H), 4.73-4.75 (m, 2H), 6.50-6.59 (m, 2H).

(3*S,6*R**)-*N*-*tert*-butoxycarbonyl-3,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine (2d):** TLC (hexane/ethyl acetate = 5:1) R_f = 0.39. IR (neat) 2978, 1700, 1392, 1368, 1166, 1094, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 5.56 (br s, 1H), 5.59 (br s, 1H), 6.09 (d, *J* = 10.5 Hz, 1H), 6.16 (ddd, *J* = 10.8, 4.5, 2.1 Hz, 1H), 7.26-7.53 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 79.0, 81.7, 126.4, 127.7, 127.8, 128.2, 128.5, 128.7, 129.0, 137.2, 139.2, 154.2.

***N*-*tert*-butoxycarbonyl-1,8-dimethyl-15-oxa-16-azatetracyclo[6.6.2.0.^{2,7}0^{9,14}]hexadec-2,4,6,9,11,13-hexaene (2e):**[4] mp 106-109 °C. TLC (hexane/ethyl acetate = 5:1) R_f = 0.33. IR (KBr) 2981, 1707, 1460, 1288, 1159, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 9H), 2.23 (s, 3H), 2.56 (s, 3H), 7.23-7.27 (m, 4H), 7.34-7.38 (m, 2H), 7.43-7.46 (m, 2H).

1:1 mixture of *N*-*tert*-butoxycarbonyl-4-methyl-3,6-dihydro-2*H*-1,2-oxazine (2f) and *N*-*tert*-butoxycarbonyl-5-methyl-3,6-dihydro-2*H*-1,2-oxazine (3f):[13] TLC (hexane/ethyl acetate = 6:1) R_f = 0.66. IR (neat) 2978, 2933, 1705, 1683, 1392, 1368, 1243, 1166, 1102 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H, 3×CH_3 (3f)), 1.51 (s, 9H, 3×CH_3), 1.67 (br s, 3H, CH_3-5 (3f)),

1.74 (br s, 3H, CH_3-4), 3.94 (br s, 2H, H-3), 4.02-4.05 (m, 2H, H-3 (**3f**)), 4.26 (br s, 2H, H-6 (**3f**)), 4.35-4.38 (m, 2H, H-6), 5.51-5.55 (m, 1H+1H, overlapped with H-5 and H-4 (**3f**)).

1:1 mixture of *N*-*tert*-butoxycarbonyl-4-(4-methylpent-3-enyl)-3,6-dihydro-2*H*-1,2-oxazine (2g) and *N*-*tert*-butoxycarbonyl-5-(4-methylpent-3-enyl)-3,6-dihydro-2*H*-1,2-oxazine (3g): TLC (hexane/ethyl acetate = 6:1) R_f = 0.64. IR (neat) 2976, 2929, 1727, 1703, 1366, 1162, 1092 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H+9H), 1.60 (s, 3H+3H), 1.69 (s, 3H+3H), 1.98-2.12 (m, 4H+4H), 3.97 (br s, 2H), 4.05 (br s, 2H), 4.29 (br s, 2H), 4.39 (br s, 2H), 5.05-5.12 (m, 1H+1H), 5.52 (br s, 1H+1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 25.6, 25.8, 25.9, 28.3, 32.7, 33.9, 44.9, 47.6, 68.0, 70.4, 81.4, 116.0, 117.6, 123.3, 132.3, 134.2, 135.5, 155.0.

***N*-*tert*-butoxycarbonyl-6-carboxy-3-methyl-3,6-dihydro-2*H*-1,2-oxazine (2h):** TLC (methanol) R_f = 0.68. IR (KBr) 2977, 1748, 1686, 1370, 1156, 1121 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, J = 6.6 Hz, 3H), 1.51 (s, 9H), 4.43 (br s, 1H), 5.16 (s, 1H), 5.93-6.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 28.3, 50.8, 75.9,
82.8, 121.9, 130.6 154.5, 170.5.

***N*-*tert*-butoxycarbonyl-6-ethoxycarbonyl-3-methyl-3,6-dihydro-2*H*-1,2-oxazine (2i):**[17] TLC (hexane/ethyl acetate = 6:1) R_f = 0.63. IR (neat) 2980, 1760, 1738, 1705, 1369, 1312, 1196, 1169, 1076, 1032, 716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.50 (s, 9H), 4.27 (q, J = 7.2 Hz, 2H), 4.46-4.48 (m, 1H), 5.14-5.16 (m, 1H), 5.90 (td, J = 1.3, 10.4 Hz, 1H), 5.98 (ddd, J = 10.2, 4.3, 2.5 Hz, 1H).

***N*-*tert*-butoxycarbonyl-6-methoxycarbonyl-3-hydroxymethyl-3,6-dihydro-2*H*-1,2-oxazine (2j):** TLC (hexane/ethyl acetate = 1:1) R_f = 0.24. IR (neat) 3446, 2979, 1737, 1707, 1475, 1251, 1157, 1071, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 3.73-3.88 (m, 2H), 3.82 (s, 3H), 4.51-4.55 (m, 1H), 5.52 (s, 1H), 6.00 (ddd, J = 10.2, 3.9, 2.1 Hz, 1H), 6.06 (td, J = 1.5, 10.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 52.8, 56.6, 63.0, 74.3, 82.8, 124.3, 125.7, 155, 167.6.

***N*-*tert*-butoxycarbonyl-3-((triisopropylsilyloxy)methyl)-6-methoxycarbonyl-3,6-dihydro-2*H*-1, 2-oxazine (2k):** TLC (hexane/ethyl acetate = 1:1) R_f = 0.77. IR (neat) 2943, 2867, 1766, 1740, 1710, 1367, 1109, 881, 681 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.02-1.13 (m, 3H), 1.06 (d, J = 3.9 Hz, 18H), 1.49 (s, 9H), 3.80 (s, 3H), 3.82 (dd, J = 9.6, 7.8 Hz, 1H), 3.97 (dd, J = 9.3, 6.6 Hz, 1H), 4.48-4.49 (m, 1H), 5.16-5.19 (m, 1H), 6.02 (td, J = 1.8, 10.2 Hz, 1H), 6.16 (ddd, J = 10.2, 4.2, 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 17.9, 28.3, 52.6, 55.8, 64.1, 74.7, 82.1, 123.2, 127.3, 154.1, 167.9.

***N*-*tert*-butoxycarbonyl-6-(*N*'-methoxy-*N*'-methylcarbamoyl)-3-methyl-3,6-dihydro-2*H*-1,2-oxazine (2l):** TLC (hexane/ethyl ether = 1:2) R_f = 0.25. IR (neat) 3592, 2979, 2934, 1681, 1369, 1172, 992, 714 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 6.6 Hz, 3H), 1.51 (s, 9H), 3.24 (br s, 3H), 3.84 (s, 3H), 4.45-4.47 (m, 1H),

5.53 (br s, 1H), 5.86 (br s, 1H), 5.99 (ddd, J = 10.5, 5.1, 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 28.4, 32.4, 50.7, 62.2, 74.3, 81.7, 122.3, 130.0, 154.2.

***N*-*tert*-butoxycarbonyl-3-((*tert*-butyldimethylsilyloxy)methyl)-6-methoxycarbonyl-3,6-dihydro-2*H*-1,2-oxazine (2m):** TLC (hexane/ethyl acetate = 1:1) R_f = 0.66. IR (neat) 2954, 2930, 2857, 1766, 1741, 1710, 1253, 1106, 834, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.49 (s, 9H), 3.73 (dd, J= 9.9, 7.2 Hz, 1H), 3.81 (s, 3H), 3.88 (dd, J= 10.2, 7.2 Hz, 1H), 4.46 (br s, 1H), 5.16-5.19 (m, 1H) , 6.01 (td, J= 1.5, 10.2 Hz, 1H), 6.11 (ddd, J= 10.5, 4.2, 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -5.3, 18.2, 25.6, 25.8, 28.3, 52.6, 55.8, 63.6, 74.7, 82.1, 123.5, 127.0, 154.2, 167.8.

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1,2-oxazinane　dihydro-1,2-oxazine

2. 学会発表

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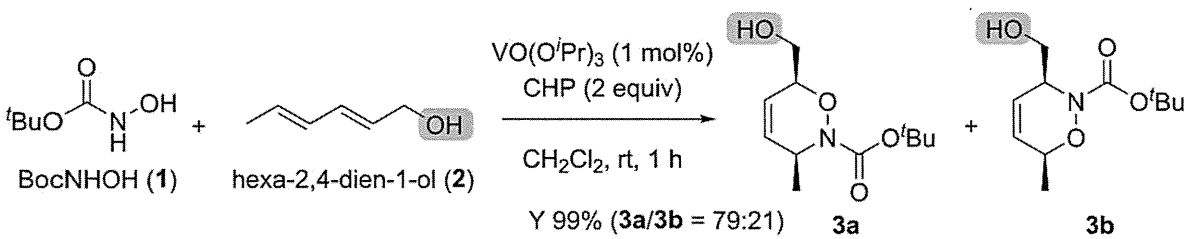
ニトロソカルボニル Diels-Alder 反応を用いた官能性 1,2-オキサジンの合成

1. はじめに

1,2-オキサジナンは、官能基化された□□□-アミノアルコールやピロリジンなどの有用合成中間体として有望であり、また、生理活性化合物の一部としてしばしば見られる骨格でもあり、官能基化された 1,2-オキサジナンやその不飽和体のジヒドロ-1,2-オキサジンの効率的合成法の開発が望まれる。ニトロソカルボニル化合物は Diels-Alder 反応において良好な親ジエン体として働き、

ジヒドロ-1,2-オキサジンを与えることが知られている [1]。しかし、単離が困難なため系中で発生させて反応を行う必要がある。代表的従来法としては、一旦 Diels-Alder 付加体を合成し、それを加熱して逆 Diels-Alder 反応によりニトロソカルボニル化合物を発生させる方法と、ヒドロキサム酸を過ヨウ素酸塩によって酸化して得る方法の二種類が知られている。これらの方法では多段階や、大量の副生成物を発生するといった問題点が指摘されている。グリーンケミストリーの観点から、触媒を用いる環境にやさしい酸化反応系の構築が望まれており、過酸化物を酸化剤とする金属触媒を用いたヒドロキサム酸の酸化が、ニトロソカルボニル化合物を発生させる有望な方法として近年注目を集めている [2]。



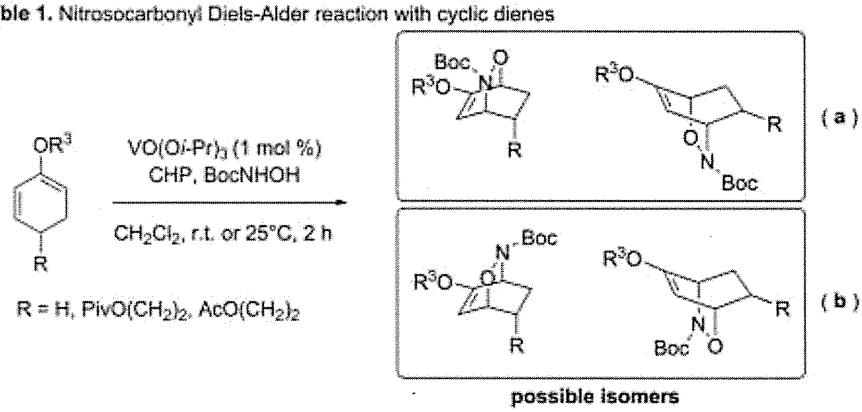
Scheme 1. Vanadium-catalyzed oxidation of N-hydroxycarbamate.
CHP: cumene hydroperoxide

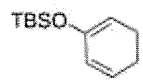
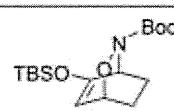
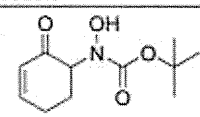
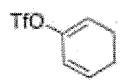
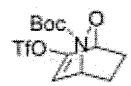
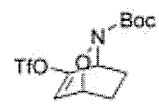
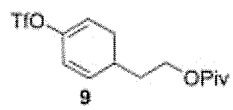
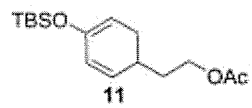
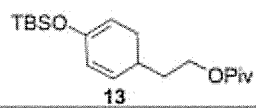
我々は酸素との親和力が高い前周期遷移金属に着目し、バナジウム錯体を触媒とした *N*-ヒドロキシカルバミン酸誘導体の酸化反応を検討したところ、室温で高選択的に酸化反応が進行し、速やかにニトロソ化合物が発生することを見出した（**Scheme 1**）[3]。アルコール官能基が存在しても高い選択性でヒドロキサム酸を酸化し、アルデヒドなどの副生成物は全く見られないことが大きな特色であり、官能基化されたジヒドロ-1,2-オキサジン合成法として期待がもたれる。今回我々は天然物合成などに応用できる、環状ジエンとのニトロソカルボニル Diels-Alder 反応を検討したので、それらの結果について報告する。

2. 結果および考察

まず、無置換のシクロヘキセノンから誘導されるジエン **4** と **7** を用いてニトロソカルボニル Diels-Alder 反応を検討した（**Table 1**）。シリロキシ基が置換したジエン **4** からの付加体は比較的不安定であり、カラムクロマトグラフィーにより単離したところ付加体 **5b** が収率 13%で得られた。その付加体の分解生成物と思われるヒドロキシアミノケトン **6** も得られてきたことから、後処理の段階で付加体が次第に化合物 **6** へと分解していることが示唆された。一方、トリフラート化体では、Diels-Alder 反応がそれほど進行せず、低収率であったが、先ほどとは逆の位置選択性で付加体 **8a** を高選択的に与えた。続いて、5-アルキル置換体を用いて選択性を検討したところ、位置選択性に若干の低下が見られたものの、大きな変化は見られなかった。この場合、5位のアルキル基に対して面選択性が現れ、1.2：1 から 1.6：1 程度の選択性であることが分かった。

Table 1. Nitrosocarbonyl Diels-Alder reaction with cyclic dienes



Entry	Reactant	Products	Yield (%)
1 [a]	 **4**	 **5b**  **6**	**5b:** 13 **6:** 24
2	 **7**	 **8a**  **8b**	**8a:** 16 **8b:** trace
3	 **9**	**10a, 10b**	**10a:** 67 (37 : 30) **10b:** 13
4	 **11**	**12b**	**12b:** 60 (37 : 23)
5	 **13**	**14a, 14b**	**14a:** 11 **14b:** 29 (17 : 12)

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ビシクロ[3.2.0]ヘプタン環の環拡大反応を用いるビシクロ[4.2.1]ノナン環の合成

【諸言】

天然にはビシクロ[4.2.1]ノナン環骨格を有する化合物が知られている。例えば Mediterraneols はマウス白血病細胞に抗白血病作用を示し、Culmorin は抗カビ作用を持つことが知られている(**Figure 1**)。

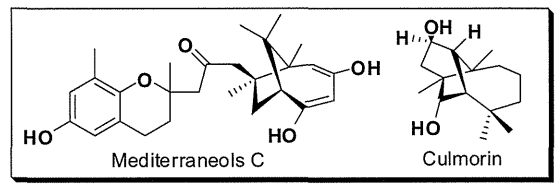
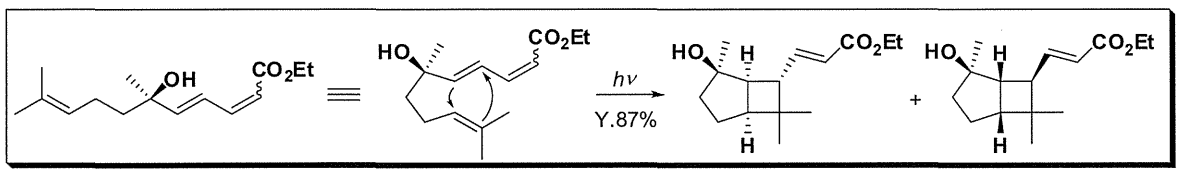


Figure 1

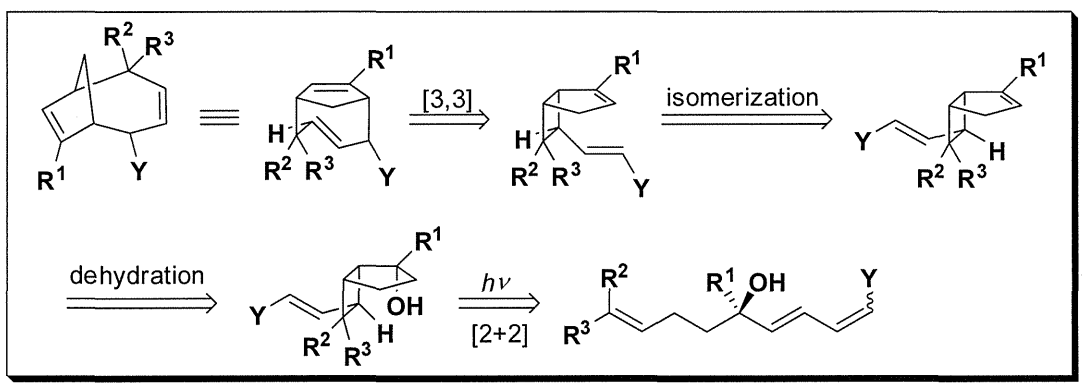
これらの化合物に共通するビシクロ[4.2.1]ノナン環骨格の合成は過去にいくつか報告されているが、工程数や収率、立体選択性に問題を有する。

当研究室では電子求引基を有するトリエン化合物に対して光照射を行い、パラレル配向の[2+2]環化付加物であるビシクロ[3.2.0]ヘプタン環骨格を構築できることを見出した(**Scheme 1**)[1]。



Scheme 1

本研究では、この方法を利用してビシクロ[3.2.0]ヘプタン環骨格を構築したのち環拡大反応に Cope 転位を用いた、ビシクロ[4.2.1]ノナン環骨格の新規合成法について報告する。以下に逆合成を示す(**Scheme 2**)。



Scheme 2