Enantioselective Diels–Alder Reaction Catalyzed by Chiral Ammonium Salts: The Synthetic Applications and the Design of New Dienophiles

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Contents

Chapter 1	Introduction and General Summary	1
Chapter 2	The First Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines with α-Acyloxyacrolein Catalyzed by Chiral Primary Ammonium Salt	23
Chapter 3	α-Heterosubstituted β-Alkylacroleins as Useful Multisubstituted Dienophiles for Enantioselective Diels–Alder Reactions	55
Chapter 4	Enantioselective Diels–Alder Reaction with β-Substituted/Unsubstituted α-(Acylthio)acroleins	81
Publication List		114
Ackowledgments		115

Chapter 1

Introduction and General summary

1-1. General Summary

Enantioselective organocatalysis is an important field in the asymmetric synthesis of chiral molecules. Over the past 10 years, this field has grown at an extraordinary pace. Our laboratory has developed an enantioselective cyclization with α-heterosubstituted acroleins catalyzed by a chiral ammonium catalyst (Figure 1.1).[1] These reactions are useful for constructing a chiral hetero-substituted quaternary carbon moiety, but the substrates have been limited to β-unsubstituted α-(oxy or amino)acroleins.

In this thesis, we describe the Diels–Alder reaction with α-heterosubstituted acroleins catalyzed by a chiral primary ammonium salt. Chapter 1 describes that a new asymmetric synthesis of chiral isoquinuclidine (2-azabicyclo[2.2.2]octane), which is a key skeleton of natural products via the enantioselective DA reaction of 1,2-dihydropyridines with α-(acyloxy)acroleins. Chapters 2 and 3 describe new syn methods for the synthesis of β-substituted α-heteroacroleins and the enantioselective DA reaction with β-substituted α-heteroacroleins.

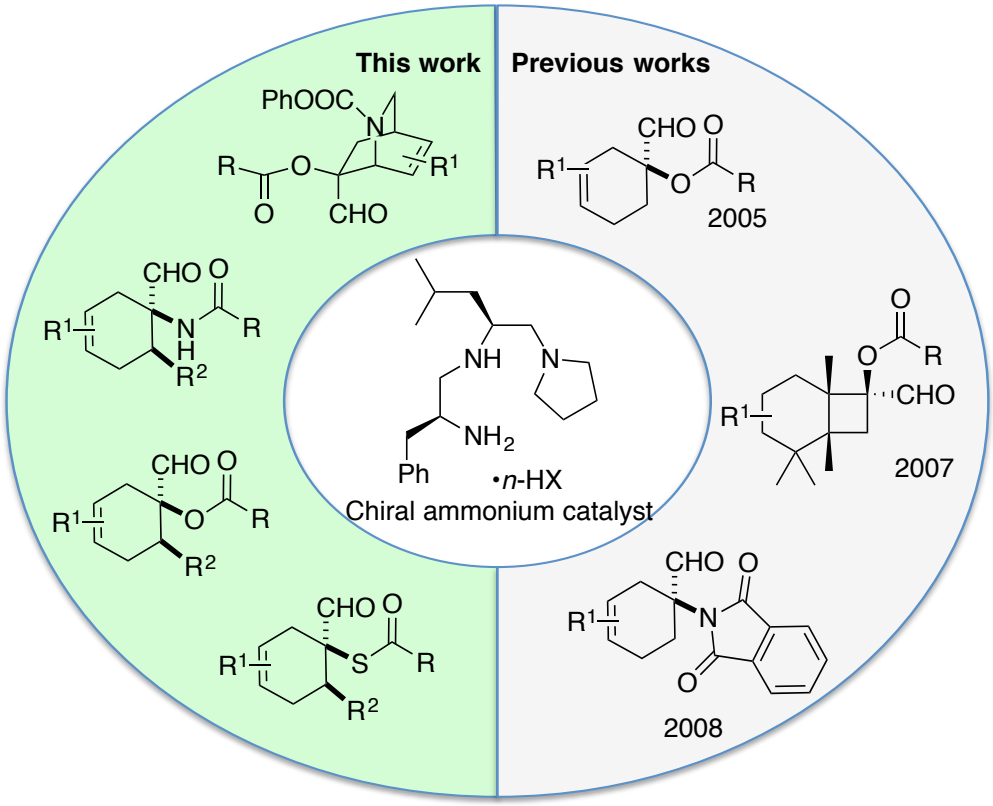


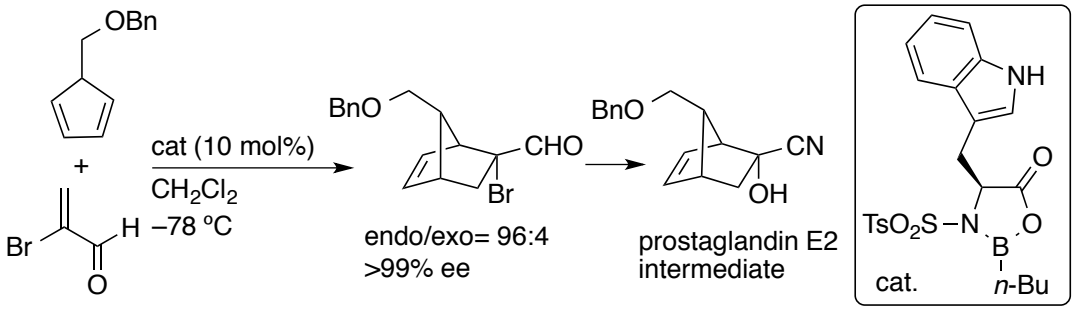
Figure 1.1. Enantioselective cycloaddition catalyzed by a chiral ammonium catalyst

1-2. Introduction

Chiral compounds with heteroatom-substituted quaternary carbons are valuable and versatile synthetic intermediates, particularly in the synthesis of complex molecules like drugs and natural products. Therefore, there is a strong need for the development of methods for the synthesis of a chiral heteroatom-substituted quaternary carbon moiety in organic synthesis.

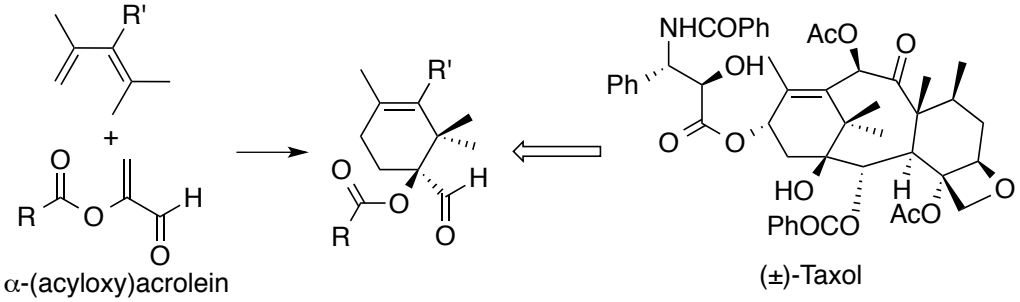
One of the most powerful methods for constructing a chiral heteroatom-substituted quaternary carbon moiety is the enantioselective Diels–Alder (DA) reaction with α-heterosubstituted acroleins. For example, α-bromoacrolein is well known to be a useful dienophile. In 1991, Corey and co-workers reported the chiral Lewis acid-catalyzed enantioselective DA reaction with α-bromoacrolein (Scheme 1.1).[2,3] The corresponding bromide DA adducts could be converted to cyanohydrine, which is a key intermediate for bioactive compounds such as prostaglandin E2, under basic conditions with high enantioselectivity.[4]

Scheme 1.1. Enantioselective Diels–Alder Reaction with α-Bromoacrolein



α-(Acyloxy)acroleins are also useful as synthetic equivalents of α-haloacroleins. In 1996, Funk and Yost reported the first example of the DA reaction with α-(acyloxy)acroleins, which represents an exceptionally facile synthesis of Taxol A-ring synthons (Scheme 1.2).[5]

Scheme 1.2. Synthesis of Taxol A-Ring Synthons via the Diels–Alder Reaction



Although α-haloacroleins have high reactivity and utility, they are irritants and are unstable at ambient temperature. In contrast, α-(acyloxy)acrolein is relatively stable, and its reactivity can be controlled by switching the acyloxy group (Figure 1.2).

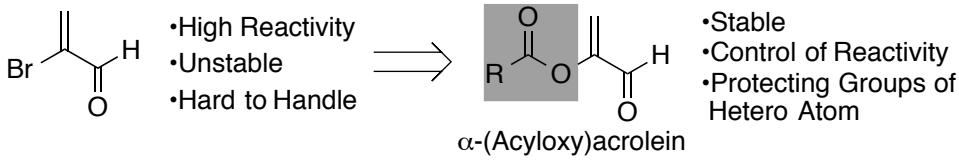
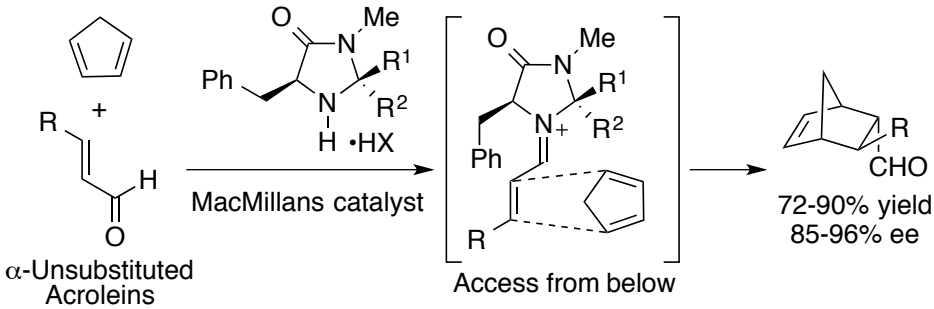


Figure 1.2. α-Heterosubstituted acroleins

The DA reaction of dienes with α-(acyloxy)acroleins is considered to be useful and versatile because the adducts can be converted to α,α-disubstituted α-hydroxycarbonyl compounds. However, there have been no reports on the enantioselective version of the DA reaction.

In 2000, MacMillan and co-workers developed an enantioselective DA reaction with α,β-unsaturated aldehydes catalyzed by chiral secondary amines derived from L-phenylalanine and Brønsted acid (Scheme 1.3).[6]

Scheme 1.3. MacMillan's Secondary Amine-Catalyzed Diels–Alder Reaction



MacMillan's catalysts are effective for α-nonsubstituted acroleins, and activate them via the formation of iminium ions. According to our preliminary experimental results and other reports,[7] it is difficult for secondary amines to activate α-substituted acroleins. This is probably due to poor generation of the corresponding iminium ion, although the secondary amines have relatively strong basicity. It is assumed that the difficulty of the formation of iminium ion is due to steric hindrance between substituents adjacent to the secondary amine in the catalyst and the α-substituent of acroleins. Otherwise, a primary ammonium salt can activate the acrolein because of less steric hindrance (Figure 1.3).

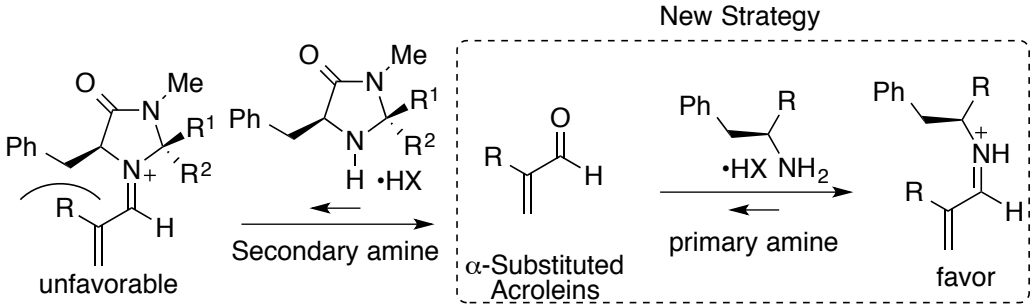
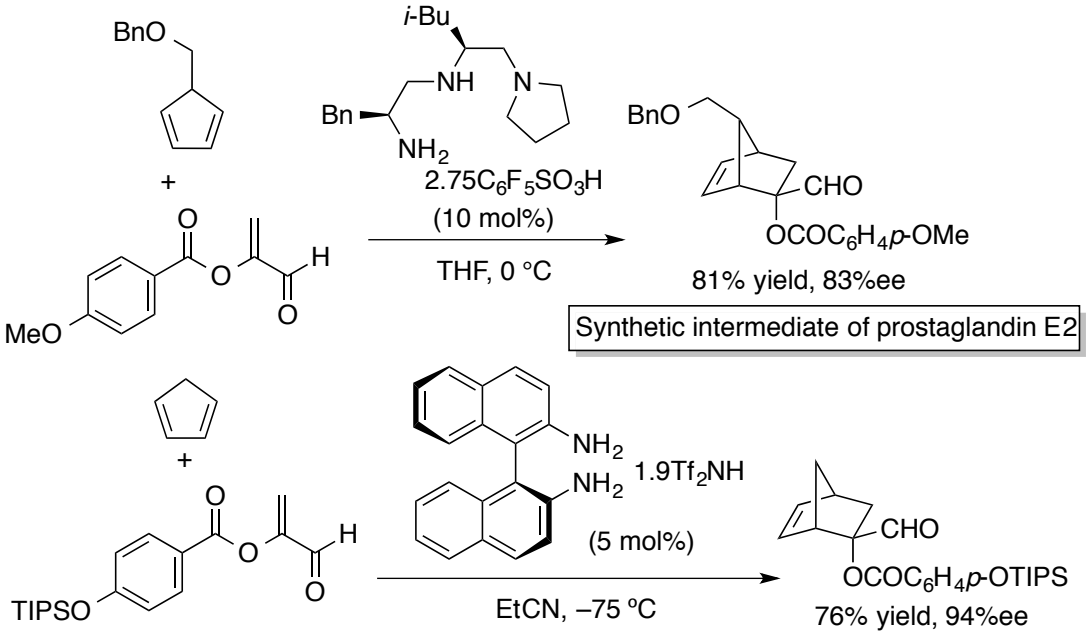


Figure 1.3. Activation of α-substituted acroleins with primary vs. secondary amine

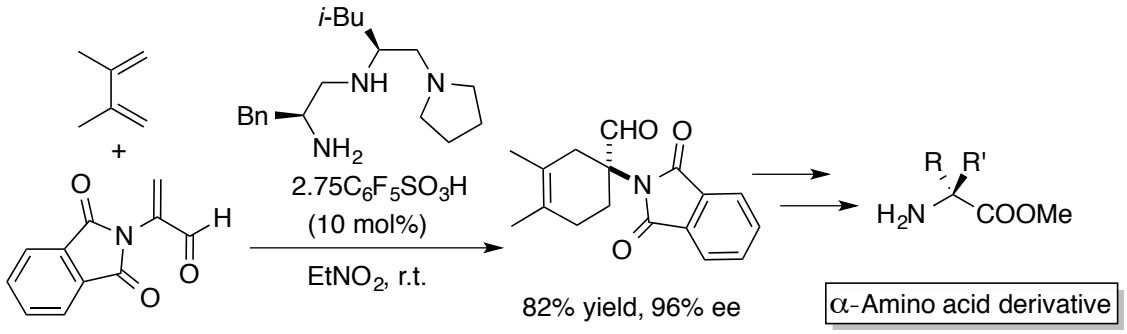
Thus, our laboratory developed the first catalytic enantioselective DA reaction with α-substituted acroleins catalyzed by primary ammonium salts (Scheme 1.4). We succeeded in the enantioselective synthesis of the key intermediate of prostaglandin E2 (PG E2) through the DA reaction with α-(acyloxy)acroleins catalyzed by a chiral triammonium salt.[8] (*S*)-1,1'-Binaphthyl-2,2'-diammonium salt was a useful catalyst for the DA reaction of cyclic dienes.[9,10]

Scheme 1.4. Enantioselective Diels–Alder Reacion with α-(Acyloxy)acroleins Catalyzed by Chiral Primary Ammonium Salts



The DA reaction with α-acylaminoacroleins also has significant synthetic versatility, because the corresponding DA adducts are optically active cyclic α-quaternary α-amino acid precursors (Scheme 1.5).[11]

Scheme 1.5. Enantioselective Diels–Alder Reaction with α-(*N*,*N*'-Diacylamino)acroleins Catalyzed by Chiral Primary Ammonium Salts



A proposed transition-state assembly is shown in Figure 1.4. α-Substituted acroleins are activated through the corresponding aldimines by the use of primary amines and Brønsted acids as ammonium salt catalysts. Furthermore, it seems that the

formation of strong hydrogen bonding between the acyl group and an ammonium proton of the catalyst stabilizes the conformation of the transition state. Therefore, the basicity and structure of the acyl group are important for inducing good enantioselectivity.

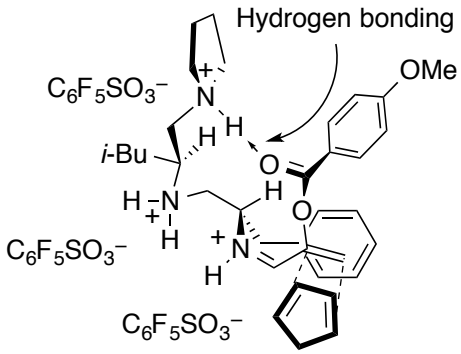


Figure 1.4. Proposed transition-state assembly

1-3. Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines with α-(Acyloxy)acroleins Catalyzed by a Chiral Primary Ammonium Salt

The 2-Azabicyclo[2.2.2]octane structure is called isoquinuclidine. This structure can be found in a wide range of natural products like (+)-catharanthine among the *Iboga* family[12] and (–)-dioscorine, which is a toxic central nervous system depressant and a modulator of the nicotinic acetylcholine receptor (Figure 1.5).[13] Moreover, isoquinuclidine compounds are not only useful in themselves but can also be converted to other optically active compounds.

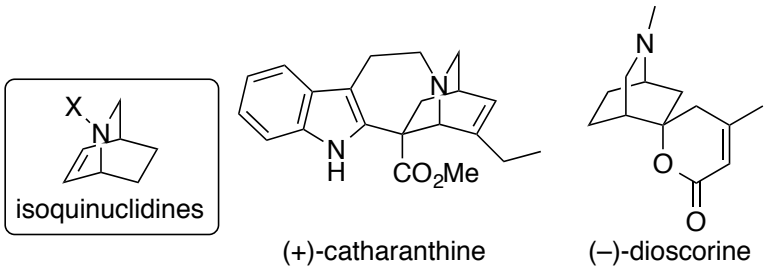
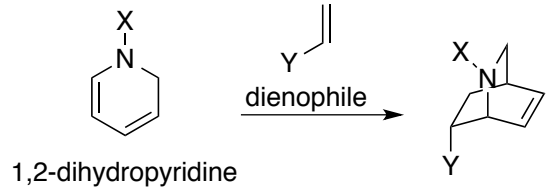


Figure 1.5. Isoquinuclidine moiety in natural products

Some methods for the synthesis of chiral isoquinuclidine derivatives have already been reported. In particular, the enantioselective DA reaction of 1,2-dihydropyridine[14] with dienophile is one of the most efficient methods (Scheme 1.6).

Scheme 1.6. Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines



In 1988, Marazano and coworkers described the diastereoselective DA reaction of chiral *N*-substituted 1,2-dihydropyridine, but the diastereoselectivity was moderate (Figure 1.6). Two years later, they improved the diastereoselectivity by using sugar derivatives as chiral auxiliaries.[15] In 2000, Matsumura *et al.* synthesized a new chiral 1,2-dihydropyridine that originated from L-lysine, and the corresponding adducts could be obtained with high diastereoselectivity.[16]

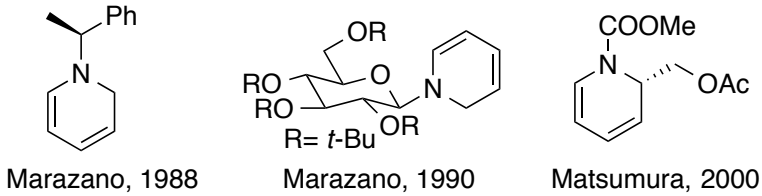
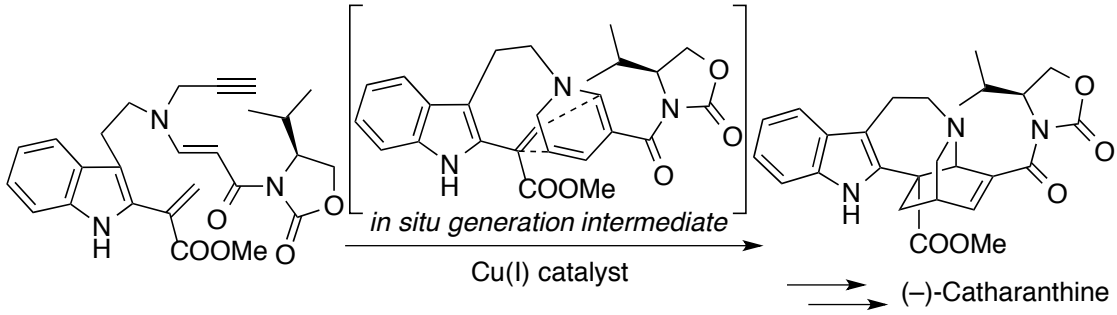


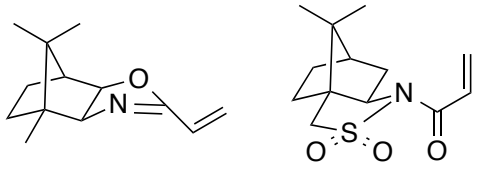
Figure 1.6. Chiral 1,2-dihydropyridines for asymmetric Diels–Alder reaction

Recently, Oguri and coworkers reported a biogenetically inspired synthesis of (–)-catharantine with *in situ*-generated chiral 1,2-dihydropyridine (Scheme 1.7).[17]

Scheme 1.7. Diastereoselective Diels–Alder Reaction of *In Situ*-Generated 1,2-Dihydropyridine



In 1990, Langlois and co-workers proved that α,β-unsaturated oxazolines activated with trifluoroacetic anhydride were useful as chiral dienophiles for the construction of chiral isoquinuclidines (Figure 1.7).[18] Campbell *et al.* also demonstrated a total synthesis of (–)-homogabaculinate via the diastereoselective DA reaction with a chiral dienophile.[19]

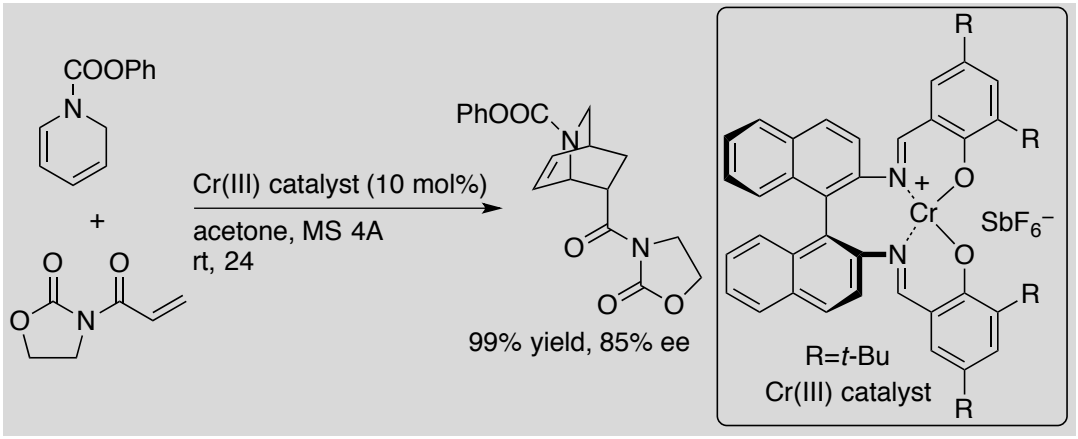


Langlois, 1990 Campbell, 1992

Figure 1.7. Chiral dienophiles for the asymmetric Diels–Alder reaction

The first enantioselective DA reaction with a chiral catalyst was reported by Rawal and co-workers (Scheme 1.8).[20] In the presence of a chiral Cr(III) salen complex catalyst, the DA reaction of 1,2-dihydropyridine with *N*-acryloyloxazolidinone proceeded in excellent yield and with good ee. Since then, some Lewis acid catalysts have been reported.[21,22]

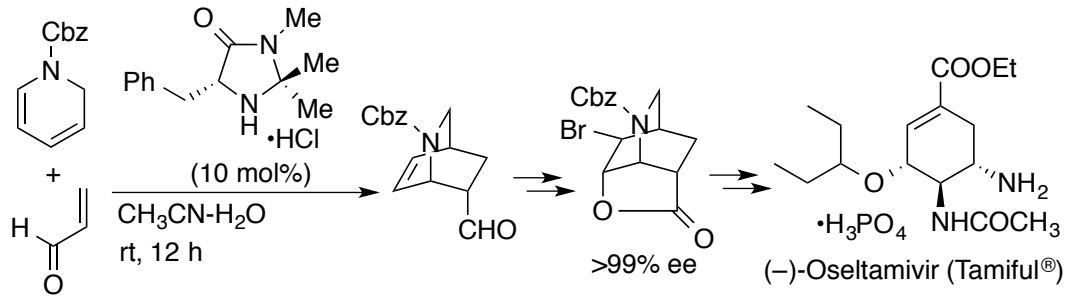
Scheme 1.8. Enantioselective Diels–Alder Reaction with Chiral Cr(III) Catalyst



Chiral organocatalysts are also useful for the DA reaction. In 2007, Fukuyama and co-workers synthesized (–)-oseltamivir phosphate, widely known as Tamiflu®, via the enantioselective DA reaction of 1,2-dihydropyridine with acrolein with MacMillan's catalyst (Scheme 1.9).[23] Enantiopure bromolactone could be obtained in moderate yield from pyridine (26% yield, 4 steps). Due to the use of mild conditions, this

synthetic method has potential for a bulk-scale operation. To improve this reaction, some new organocatalysts have been investigated.[23,24]

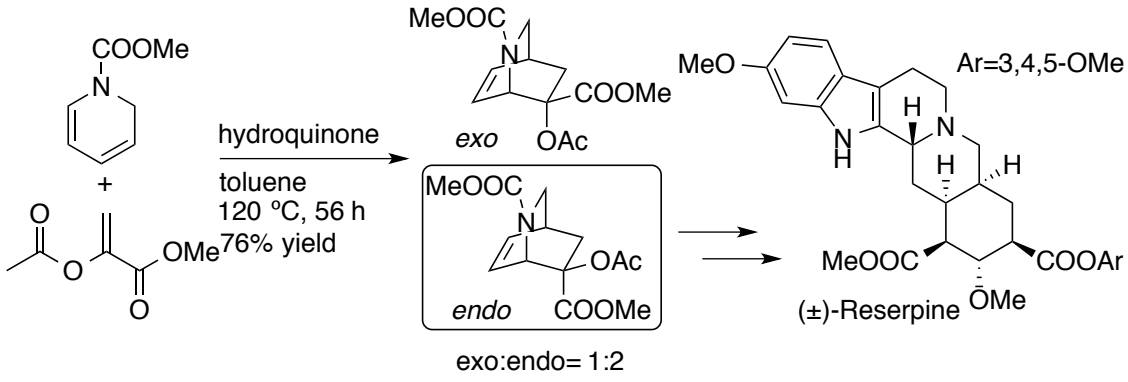
Scheme 1.9. Total Synthesis of (–)-Oseltamivir (Tamiflu®) via the Enantioselective Diels–Alder Reaction



While there are many methods available for the construction of chiral isoquinuclidines, to the best our knowledge there have been no reports on the enantioselective DA reaction with α-hydrosubstituted dienophiles.

The DA reaction with α-hydrosubstituted dienophiles is a powerful tool for the construction of stereoselective hydrosubstituted isoquinuclidines. In 1980, Wender *et al.* synthesized (±)-reserpine via the DA reaction of 1,2-dihydropyridine with an α-acetoxy acrylic acid methyl ester (Scheme 1.10).[25] The corresponding exo and endo isomeric mixture of DA adducts was obtained in moderate yield. However, the exo/endo ratio was low, and only the endo-adduct could be used for synthesis.

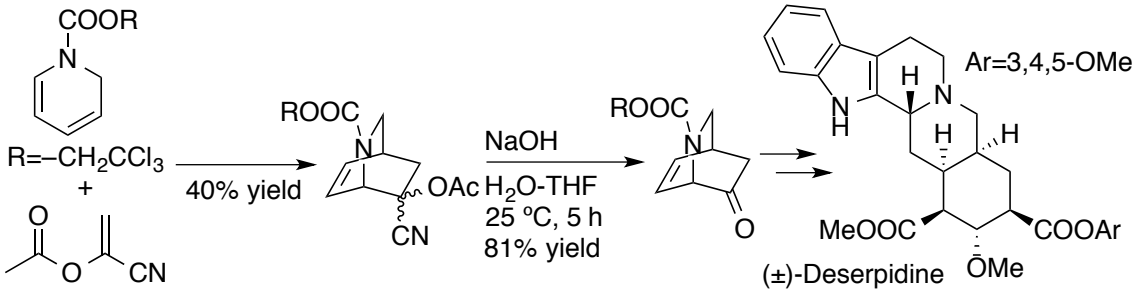
Scheme 1.10. Wender's Method for the Synthesis of (±)-Reserpine



Based on this result, Mariano and co-workers focused on the DA reaction with α-acetoxy acrylonitrile[26] and described a total synthesis of (±)-deserpidine (Scheme

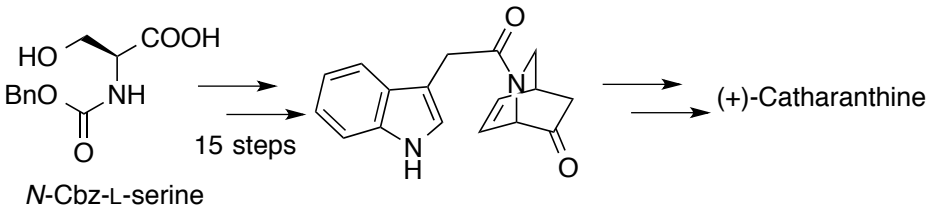
1.11). The *exo*/*endo* mixture could be converted to isoquinuclidin-7-one in good yield via Oku's procedure.[27] In contrast, the yield of the DA reaction step was low.

Scheme 1.11. Mariano's Method for the synthesis of (±)-Deserpidine



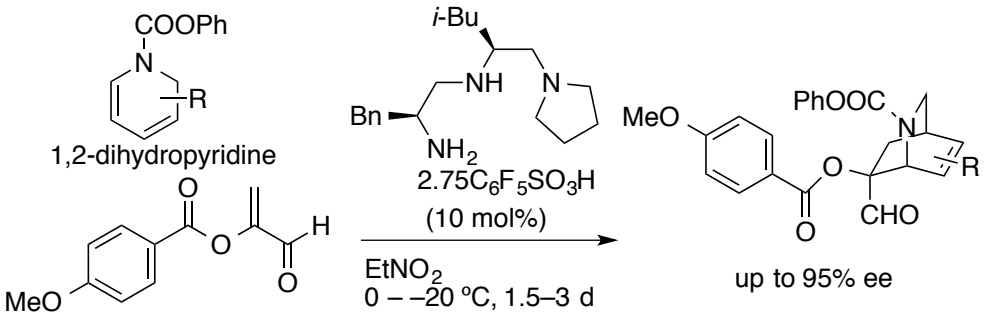
Chiral isoquinuclidin-7-one is also a key intermediate for natural products. Doris and co-workers reported a formal synthesis of (+)-catharantine from L-serine derivative through a chiral isoquinuclidin-7-one intermediate (Scheme 1.12).[28] The intermediate was synthesized from *N*-Cbz-L-serine in 15 steps.

Scheme 1.12. Formal Synthesis of (+)-Catharanthine



Based on our strategy, we developed a catalytic enantioselective DA reaction of 1,2-dihydropyridines with α-(acyloxy)acroleins for the synthesis of chiral isoquinuclidine derivatives. As a result, the corresponding DA adducts were successfully obtained in good yields and with high enantioselectivities, and the adducts were converted to key intermediates of natural products (Scheme 1.13).

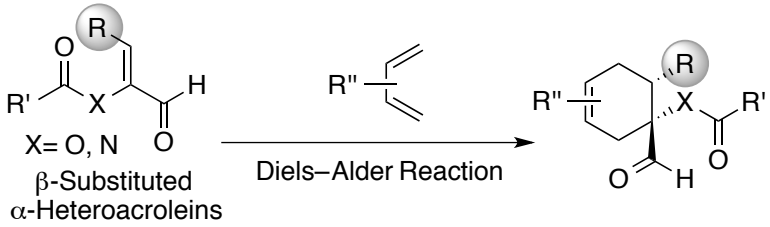
Scheme 1.13. Enantioselective Diels-Alder Reaction of 1,2-Dihydropyridines with α-(Acyloxy)acroleins



1-4. Enantioselective Diels–Alder Reaction of β-Substituted α-(Acyloxy/Acylamino)acroleins

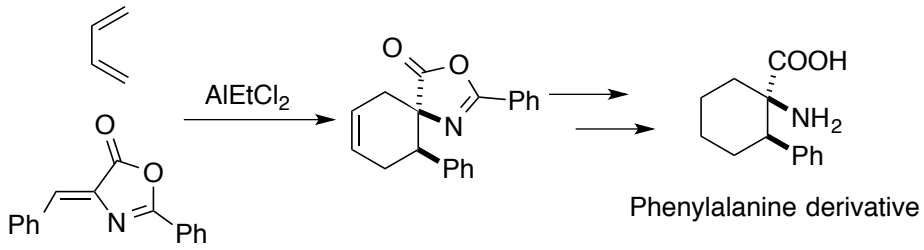
With respect to the synthesis of multisubstituted chiral cyclohexenes, α-heterosubstituted β-alkylacroleins are useful dienophiles for the enantioselective Diels–Alder reaction, since the corresponding adducts are useful chiral building blocks for the synthesis of a variety of bioactive natural compounds (Scheme 1.14).

Scheme 1.14. Enantioselective Diels–Alder Reaction with β-Substituted α-Heteroacroleins



Cativiela Díaz-de-Villegas reported an interesting DA reaction with a multisubstituted dienophile for the construction of a phenylalanine derivative (Scheme 1.15).[29] Readily available (*Z*)-2-phenyl-4-benzylidene-5-(4*H*)-oxazolone was used as a dienophile, and the dienophile was activated by Lewis acid. The corresponding adducts were spirooxazolone compounds, which could be easily converted to an amino acid structure. Especially, the β-phenyl moiety of the adducts is oriented on the same side as the amino moiety. This result indicates that two enantiomeric centers can be controlled by one reaction with a stereopure multisubstituted dienophile.

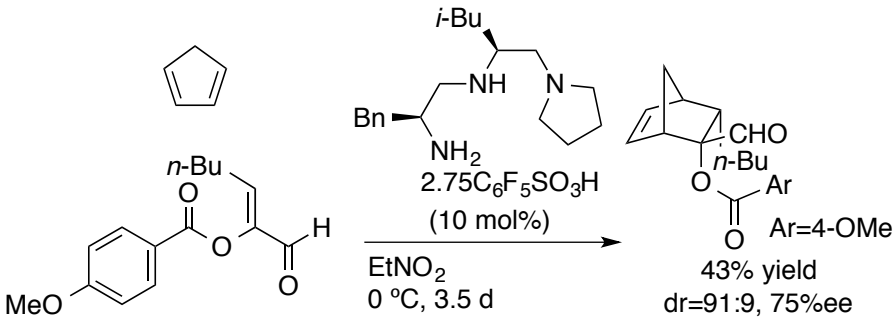
Scheme 1.15. Synthesis of a Phenylalanine Derivertive via Diels–Alder Reaction



To the best of our knowledge there have been no reports on the synthesis of stereopure β-substituted α-(acyloxy/acylamino)acroleins syntheses. Therefore, we primarily focused on new efficient methods for the synthesis of these acroleins.

First, we synthesized β-substituted α-(benzyloxy)acroleins by a modification of Funk's method[30] and tried an enantioselective DA reaction with an ammonium catalyst. The corresponding adduct was obtained in low yield and with moderate ee (Scheme 1.16).

Scheme 1.16. Enantioselective Diels–Alder Reaction with β-Substituted α-(Benzoxy)acroleins



We expected that the electron-donating nature of the *O*-acyl groups might be very important for obtaining high enantioselectivity in the DA reaction of α-(acyloxy)acroleins. Thus, we planned a method for the synthesis of α-(carbamoyloxy)acroleins with a more basic acyl moiety as a directing group (Figure 1.8).

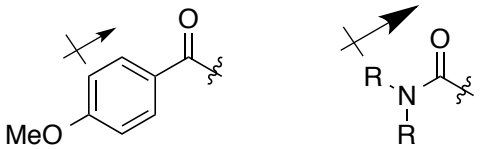
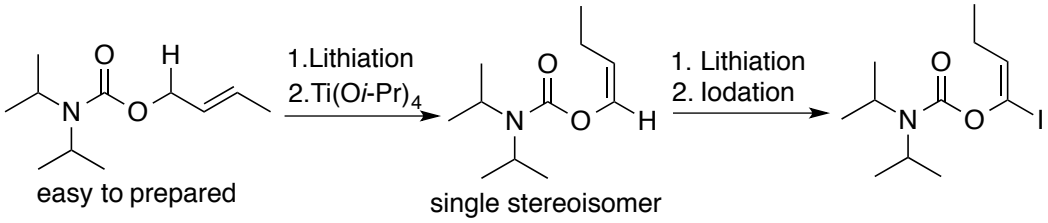


Figure 1.8. Comparison of a carbamoyl moiety to an acyl moiety

Hoppe and co-workers developed an interesting *N*,*N*-diisopropyl carbamate chemistry. In their reports, allylic carbamates successfully gave the corresponding *Z*-vinyl carbamates as single stereoisomers with a titanium reagent. Moreover, the proton α-position of carbamate could be converted to iodine with an alkyl lithium reagent (Scheme 1.17).[31]

Scheme 1.17. Stereoselective Carbon–Carbon Double Bond Migration and Iodation



According to this result, we planned a retrosynthesis of β-substituted α-(acyloxy)acroleins by C–C bond formation between anionic *Z*-vinyl carbamates and formyl cations (Figure 1.9).

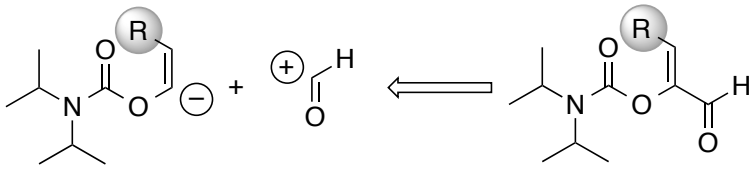
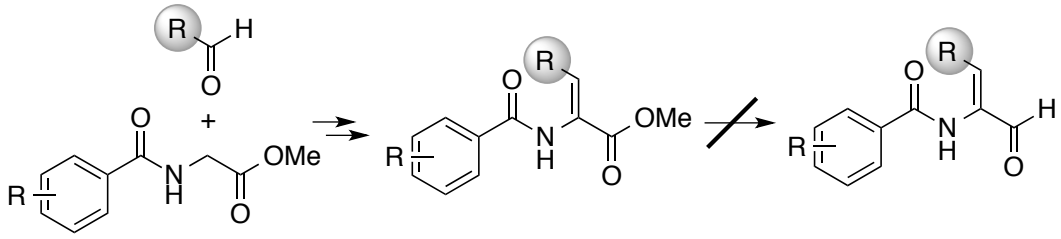


Figure 1.9. Retrosynthesis of β-substituted α-(acyloxy)acroleins

Subsequently, we tried to synthesize β-substituted α-(acylamino)acroleins. *N*-Arylcarbonylglycine methyl ester was chosen as a starting material. According to the method reported by Burk and co-workers,[32] a variety of β-alkyl and β-aryl derivatives could be synthesized with complete *Z*-selectivity with changes in the starting aldehyde. However, the corresponding HWE reaction products could not be converted to aldehydes (Scheme 1.18). Other strategies were needed.

Scheme 1.18. First Approaching to Synthesize β-Substituted α-(Acylamino)acroleins



Next, we focused on a strategy of *N*-protection by changing from Boc to Bz (Figure 1.10). A method for the synthesis of *Z*-selective β-substituted α-(*tert*-butoxycarbonylamino)acroleins has already reported.[32] From this known compound, we expected that the *N*-Boc group could be converted to an *N*-benzoyl group by a modification of Martin's method,[33] and removed only the *N*-Boc group with acid.

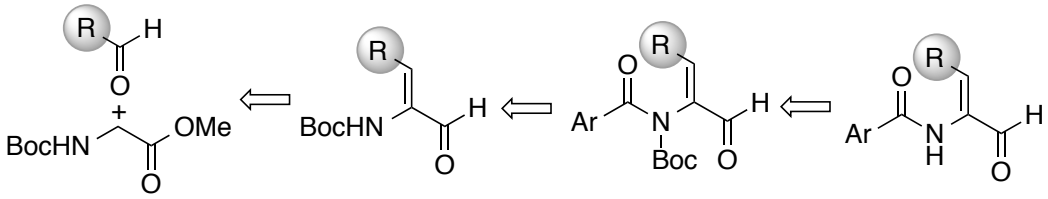
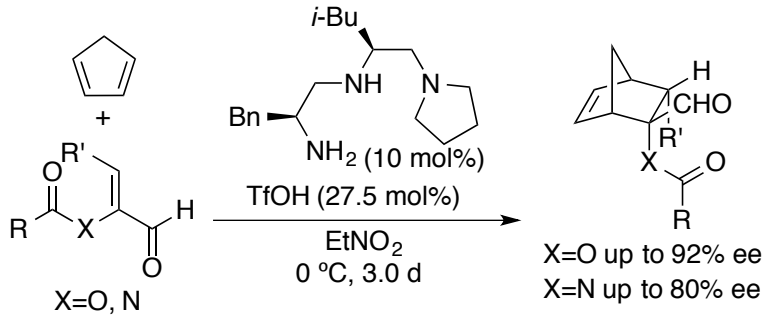


Figure 1.10. Retrosynthesis of β-substituted α-(acylamino)acroleins

With these dienophiles in hand, we investigated the chiral triammonium salt-catalyzed DA reaction (Scheme 1.19).[34] As a result, the corresponding DA adducts were successfully obtained in good yields with high enantioselectivities.

Scheme 1.19. Enantioselective Diels–Alder Reaction of β-Substituted α-(Acyloxy/Acylamino)acroleins with a Chiral Ammonium Catalyst



1-5. Enantioselective Diels–Alder Reaction with α-(Acylthio)acroleins

Chiral quaternary carbons bearing sulfur atoms can be widely found in bioactive compounds (Figure 1.11).

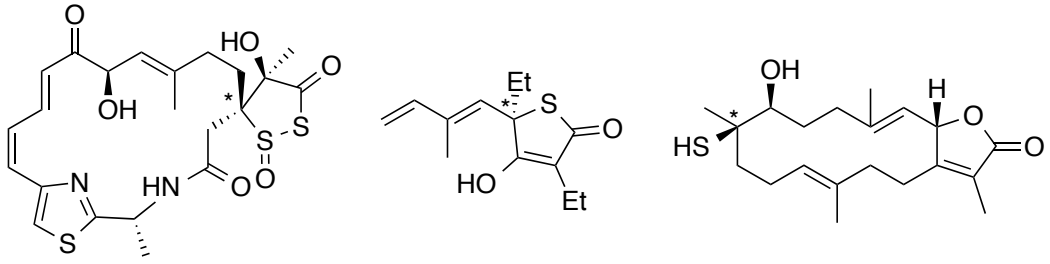


Figure 1.11. Bioactive compounds containing quaternary carbons bearing sulfur atoms

Considerable effort has been devoted to the development of methods for their construction including stereoselective reactions such as (a) the alkylation of chiral thioenolates,[35] (b) the alkylation of chiral thioalkyllithiums,[36] (c) the S_N2 reaction of chiral *tert*-alcohols,[37] and (d) the rearrangement of chiral thiooxazolines (Figure 1.12).[38,39] Although some catalytic reactions have also been reported, phenyl or benzyl thiol is often used as a nucleophile. The corresponding adduct cannot be converted from benzyl or alkyl thioether to thiol.[40]

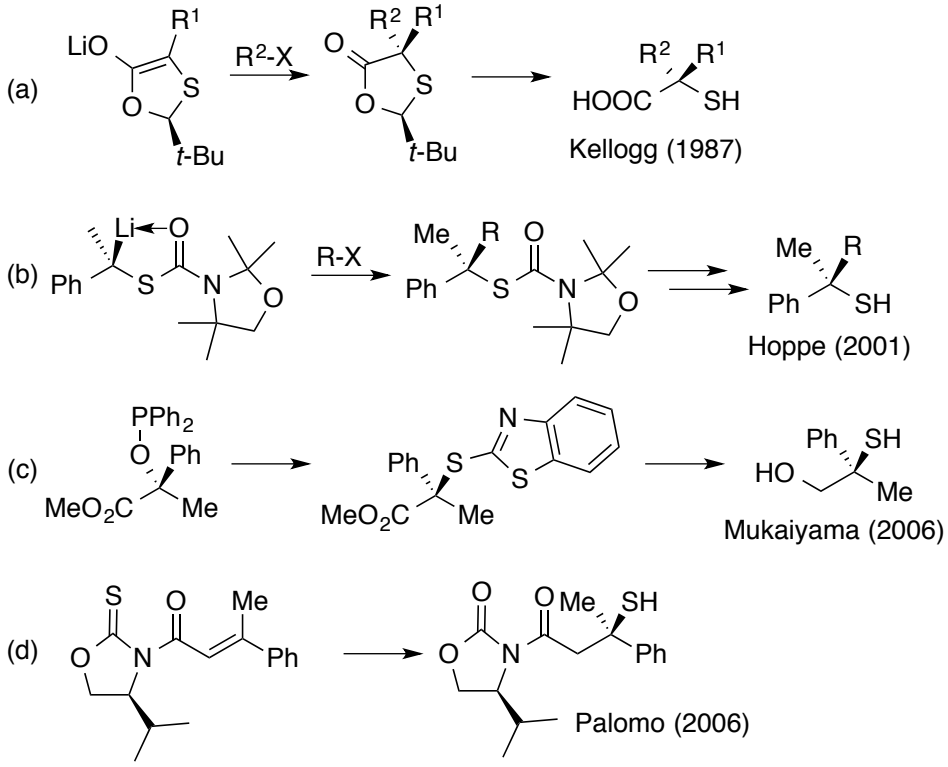
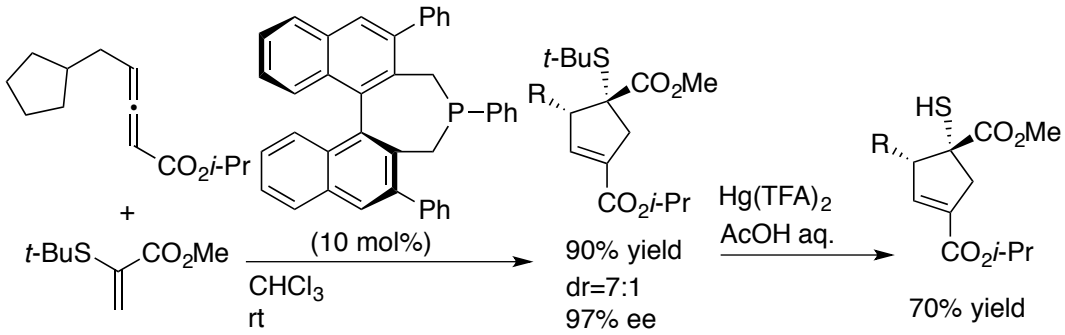


Figure 1.12. Stereoselective synthesis of chiral *tert*-thiols

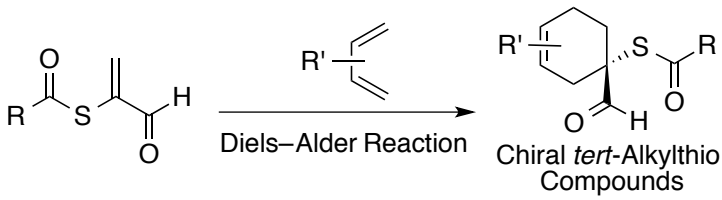
In 2011, a rare example was reported (Scheme 1.20).[41] Fu and Fujiwara developed the enantioselective [3+2] cycloaddition of α-heterosubstituted acrylic acid ester derivatives with a chiral phosphine catalyst. In their report, they described the reaction of α-(*tert*-butylthio)acrylic acid methyl ester as a substrate. The *tert*-butyl group of a cyclized product could be deprotected, and chiral *tert*-thiol was obtained in good yield.

Scheme 1.20. *tert*-Thiol Synthesis via [3+2] Cyclization



The enantioselective DA reaction of α-(acylthio)acroleins is a useful method for the construction of sulfur-containing quaternary carbons. We expected that the acyl group of the corresponding adducts could be easily removed with base reagents (Scheme 1.21).

Scheme 1.21. Enantioselective Diels–Alder Reaction with α-(Acylthio)acroleins



Based on our previous results, the enantioselectivity depends on the acyl moiety. Therefore, we planned methods for the synthesis of two types of α-(acylthio)acroleins. For the synthesis of α-(benzoylthio)acroleins, the reaction between nucleophilic thiirane and acyl chloride or carboxylic anhydride was examined.[42,43] After the acetal was converted to aldehyde with acid, the desired α-(benzoylthio)acroleins were obtained (Figure 1.13).

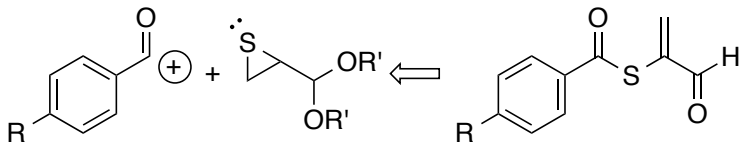


Figure 1.13. Retrosynthesis of α-(benzoylthio)acroleins

As another acyl candidate of α-(acylthio)acroleins, we focused on thiocarbamate which is a stronger electron donor than benzoyl groups (Figure 1.14). Since bis(carbamoyl)disulfide[44] was expected to be an *S*-carbamoyl synthon, we planned to combine a cationic synthon and a vinyl anion synthon from acroleins. Compared with the synthesis of α-(benzoylthio)acroleins, β-substituted acroleins also could be synthesized in a regiospecific manner.

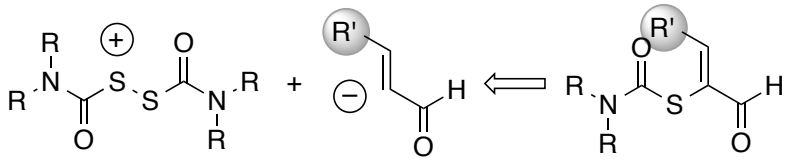
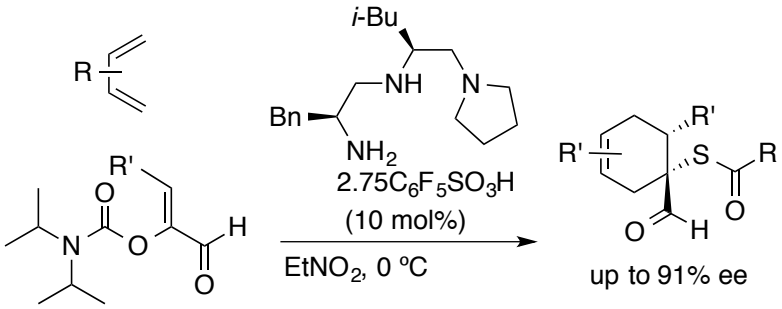


Figure 1.14. Retrosynthesis of α-(carbamoylthio)acroleins

We developed an organocatalytic and enantioselective DA reaction with α-(carbamoylthio) acroleins to provide chiral tertiary thiol precursors for the first time. β-Unsubstituted or β-substituted α-(carbamoylthio)acroleins were designed and synthesized as new sulfur atom-containing dienophiles (Scheme 1.22).[45]

Scheme 1.22. Enantioselective DA Reaction with α-(Carbamoylthio)acroleins catalyzed by a Chiral Ammonium Catalyst



References and Notes

1. For a review reaction catalyzed by chiral ammonium catalyst; Sakakura, A.; Ishihara, K. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 313.
2. Corey, E. J.; Loh, T. -P. *J. Am. Chem. Soc.* **1991,** *113,* 8966.
3. (a) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987. (b) Corey, E. J.; Cywin, C. L. *J. Org. Chem.* **1992**, *57*, 7372. (c) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979. (d) Ishihara, K.; Qingzhi, G.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917. (e) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. (f) Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611. (g) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049. (h) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920. (i) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.
4. Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397.
5. Funk, R.L.; Yost, K. J. III *J. Org. Chem.* **1996**, *61*, 2598.
6. (a) Ahrendt, K. A.; Borths, C. J. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (c) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.
7. Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.
8. Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. Additions and corrections: Ishihara, K; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 13079.
9. Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457.
10. Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229.
11. Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893.
12. Sundberg, R. J.; Smith, S. Q. *The Alkaloids* **2002**, *59*, 281.
13. (a) Page, C. B.; Pinder, A. R. *J. Chem. Soc.* **1964**, 4811. (b) Fruk Khan, M. O.; Levi, M. S.; Clark, C. R.; Ablordeppey, S. Y. *Stud. Nat. Prod. Chem.* **2008**, *34*, 753.
14. (a) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321. (b) For a recent review of 1,2-dihydropyridine syntheses: Silva, E. M.; Varandas, P. A. M. M.; Silva, A. M. S. *Synthesis* **2013**, *45*, 3053.

15. (a) Mehmandoust, M.; Marazano, C.; Singh, R.; Gillet, B.; Ce´sario, M.; Fourrey, J.-L.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4423. (b) Marazano, C.; Yannic, Y.;Mehmandoust, M.; Das, B. C. *Tetrahedron Lett.* **1990**, *31*, 1995.
16. Matsumura, Y.; Nakamura, Y.; Maki, T.; Onomura, O. *Tetrahedron Lett.* **2000**, *41*, 7685.
17. Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nature Chem.* **2014**, *6*, 57.
18. Kouklovsky, C.; Pouilhès, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672.
19. Campbell, M. M.; Sainsbury, M.; Searle, P. A. *Tetrahedron Lett.* **1992**, *33*, 3181.
20. Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58*, 8299.
21. (a) Nakano, H.; Tsugawa, N.; Fujita, R. *Tetrahedron Lett.* **2005**, *46*, 5677. (b) Nakano, H.; Tsugawa, N.; Takahashi, K.; Okuyama, Y.; Fujita, R. *Tetrahedron* **2006**, *62*, 10879.
22. Seki, C.; Hirama, M.; Hutabarat, N. M. D. R.; Takada, J.; Suttibut, C.; Takahashi, H.; Takaguchi, T.; Kohari, Y.; Nakano, H.; Uwai, K.; Takano, N.; Yasui, M.; Okuyama, Y.; Takeshita, M.; Matsuyama, H. *Tetrahedron* **2012**, *68*, 1774.
23. (a) Satoh, N.; Akiba, T.; Yokoshima, S. and Fukuyama, T. *Angew. Chem.*, *Int. Ed.*, **2007**, *46*, 5734. (b) Satoh, N.; Akiba, T.; Yokoshima S.; Fukuyama, T. *Tetrahedron*, **2009**, *65*, 3239.
24. (a) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y. *Chem. Commun.* **2010**, *46*, 4827. (b) Suttibut, C.; Kohari, Y.; Igarashi, K.; Nakano, H.; Hirama, M.; Seki, C.; Takeshita, M.; Kwon, E. *Tetrahedron Lett.* **2011**, *52*, 4745. (c) Okuyama, Y.; Osone, K.; Nakano, H.; Takeshita, M. *Heterocycles* **2012**, *84*, 1209. (d) Nakano, H.; Okuyama, Y.; Kwon, E. *Heterocycles* **2014**, *89*, 1.
25. (a) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157. (b) Wender, P. A.; Schaus, J. M.; White, A. W. *Heterocycles* **1987**, *25*, 263.
26. (a) Baxter, E. W.; Labaree, D.; Chao, S.; Mariano, P. *J. Org. Chem.* **1989**, *54*, 2893. (b) Baxter, E. W.; Labaree, Ammon, H. L.; Mariano, P. *J. Am. Chem. Soc.* **1990**, *112*, 7682.
27. (a) Oku, A.; Hasegawa, H.; Shimazu, H.; Nishimura, J.; Harada, T. *J. Org. Chem.* **1981**, *46*, 4152. (b) Magee, D. I.; Lee, M. *Synlett* **1997**, *7*, 786.

28. Moisan, L.; Thuéry, P.; Nicolas, M.; Doris, E.; Rousseau, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 5334.
29. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron* **1993**, *49*, 10987.
30. Aungst, R. A. Jr.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3553.
31. (a) Chedid, R. B.; Brümmer, M. Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 3131.; (b) Chedid, R. B.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Eur. J. Org. Chem.* **2007**, 3179.
32. Burk, M. J.; Johnson, N. B.; Lee, J. R. *Tetrahedron Lett.* **1999**, *40*, 6685.
33. Hernández, J. N.; Martin,V. S. *J. Org. Chem.* **2004**, *69*, 3590.
34. Sakakura, A.; Yamada, H.; Ishihara, K. *Asian J. Org. Chem.* **2012**, *1*, 133.
35. Strijtveen, B.; Kellogg, R. M. *Tetrahedron* **1987**, *43*, 5039.
36. (a) Stratmann, O.; Kaiser, B.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Chem. Eur. J.* **2001**, *7*, 423. (b) Marr, F.; Hoppe, D. *Org. Lett.* **2002**, *4*, 4217. (c) For an example of the arylation of chiral thioalkyllithiums: MacLellan, P.; Clayden J. Chem. Commun. **2011**, *47*, 3395.
37. Ikegai, K.; Pluempanupat, W.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 780.
38. Palomo, C.; Oiarbide, M.; Dias, F.; Lopez, R. T.; Gonzalez, P. B.; Gomez-Bengoa, E.; Saa, J. M.; Linden, A. *J. Am. Chem. Soc.* **2006**, *128*, 15236.
39. MacLellan, P.; Clayden, J. *Chem. Commun.* **2011**, *47*, 3395.
40. Recent examples: (a) Lu, H.; Zhang, F.; Meng, X.; Duan, S.; Xiao, W. *Org. Lett.* **2009**, *11*, 3946. (b) Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jørgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 5689.
41. Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293.
42. Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897.
43. Silvestri, M. G.; Wong, C.-H. *J. Org. Chem.* **2001**, *66*, 910.
44. (a) Barany, G.; Schroll, A. L.; Mott, A. W.; Halsrud, D. A. *J. Org. Chem.* **1983**, *48*, 4750. (b) Kobayashi, N.; Osawa, A.; Fujisawa, T. *Chem. Lett.* **1973**, *2*, 1315.
45. Sakakura, A.; Yamada, H.; Ishihara, K. *Org. Lett.* **2012**, *14*, 2972.

Chapter 2

The First Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines with α-Acyloxyacrolein Catalyzed by Chiral Primary Ammonium Salt

Abstract:

We have developed the first example of a catalytic and highly enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-(acyloxy)acroleins catalyzed by the chiral ammonium catalyst, and their derivatization to some key synthetic intermediates of biologically active compounds. Furthermore, a plausible mechanism via an aqua complex can explain all previous results with the use of the chiral ammonium catalyst.

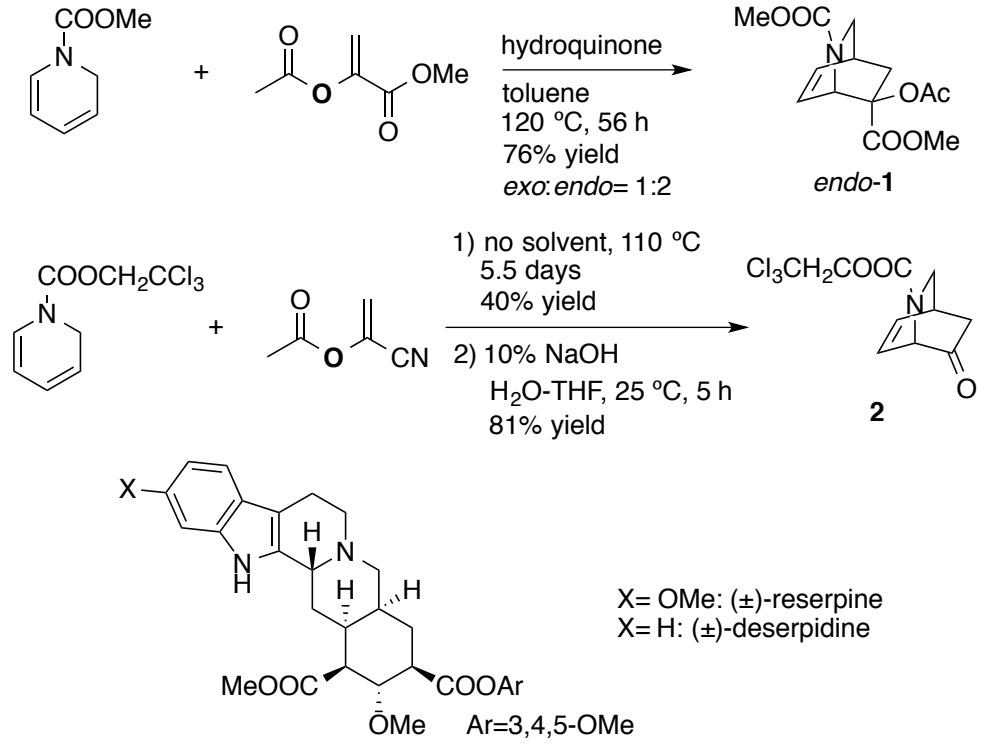
2-1. Introduction

The isoquinuclidine skeleton is found in a wide range of alkaloids, and optically active functionalized isoquinuclidines, as chiral synthons, can be transformed to versatile alkaloids.[1] The enantioselective Diels–Alder reaction of 1,2-dihydropyridines with acryloyl derivatives is one of the most straightforward methods for the construction of optically active isoquinuclidines.

For example, in 1980, Wender *et al*. achieved the total synthesis of (±)-reserpine from (±)-*endo*-Diels–Alder adduct **1** of *N*-methoxycarbonyl-1,2-dihrdropyridine with methyl α-acetoxyacrylate (Scheme 1).[2]

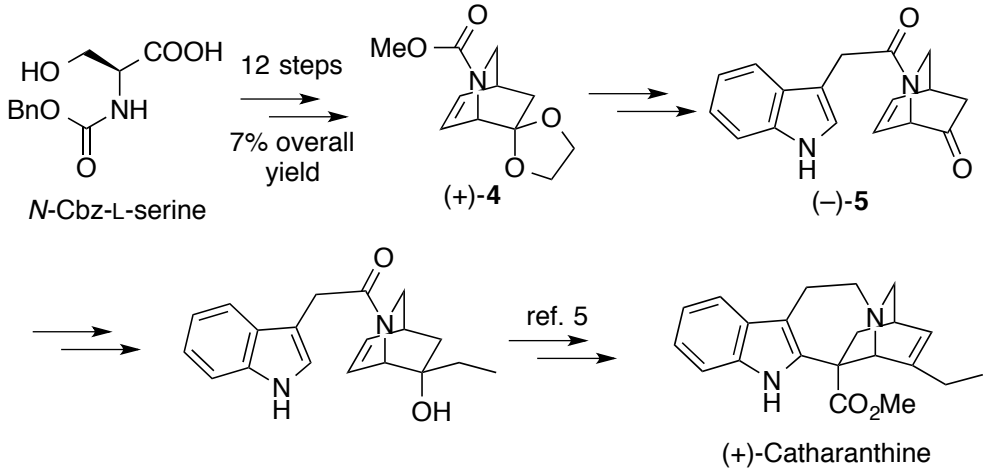
In 1990, Mariano *et al*. achieved the formal total synthesis of (±)-deserpidine from (±)-Diels–Alder adduct **2** of *N*-(2,2,2-trichloroethoxycarbonyl)-1,2-dihydropyridine with α-acetoxyacrylonitrile. However, these Diels–Alder reactions were very slow and the *endo*-selectivity was low (Scheme 1).[3]

Scheme 2.1. Total Synthesis of (±)-Reserpine[2] and (±)-Deserpidine[3]



In 2006, Doris *et al.* reported the formal synthesis of (+)-catharanthine using optically active isoquinuclidine **4** as a key intermediate, which was derived from *N*-benzyloxycarbonyl-L-serine (**3**) in 7% overall yield over 12 steps (Scheme 2.2).[4,5]

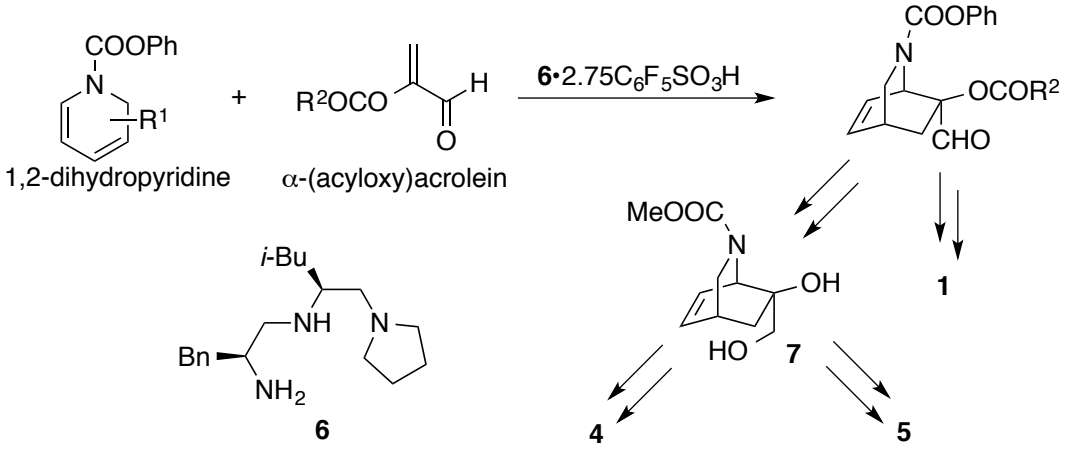
Scheme 2.2. Doris's Formal Total Synthesis of (+)-Catharanthine[4]



In 2002, Rawal *et al.* reported the first catalytic enantioselective Diels–Alder reaction of 1,2-dihydropyridine with *N*-acryloyloxazolidinone.[6a] Since then, Nakano *et al.* have intensively studied on the development of an asymmetric catalysis.[6b–k] In 2005, Fukuyama *et al.* reported that MacMillan's catalyst[7] was also effective for the enantioselective Diels–Alder reaction of *N*-benzyloxycarbonyl-1,2-dihydropyridine with acrolein to give optically active isoquinuclidine.[8]

Against this backgroud, we expected that we could prepare optically active synthons **1**, **2** and **4** through the enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-(acyloxy)acroleins as a key step. However, there have been no reports on the highly enantioselective Diels–Alder reaction of dihydropyridines with α-substituted acryloyl derivatives.[9] Along these lines, we have developed the enantioselective Diels–Alder reaction of simple dienes with α-heterosubstituted acroleins catalyzed by chiral primary ammonium salts.[10] In this report we describe the first enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-(acyloxy)acroleins catalyzed by **6**•2.75$C_6F_5SO_3H$, and their derivatization to *endo*-**1**, **7**, **4**, and **5** (Scheme 2.3).

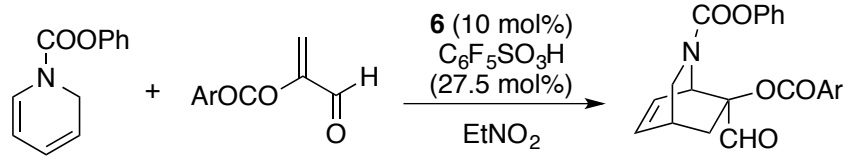
Scheme 2.3. This work



2-2 Results and discussion

First, the Diels–Alder reaction of *N*-phenoxycarbonyl-1,2-dihydropyridine (**9a**) with α-(benzoyloxy)acrolein (**10a**) was examined in the presence of 10 mol% of **7**•2.75$C_6F_5SO_3H$ in nitroethane (Table 2.1).

Table 2.1. Enantioselective Diels–Alder Reaction of **9a** with **10**



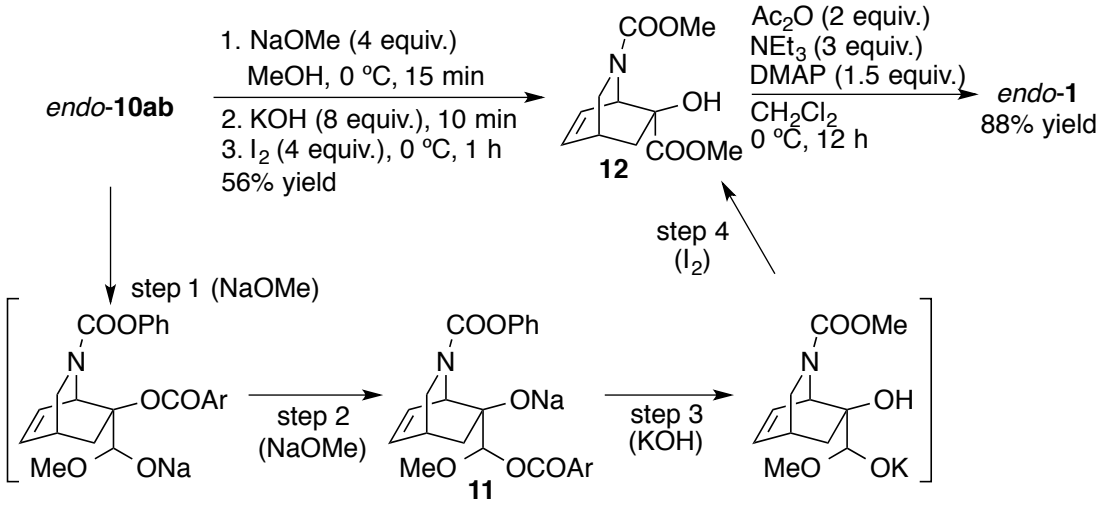
8a (1.1 equiv.) **9** *endo*-**10**, >95% *endo*

entry	**9** (Ar)	conditions	**10** yield (%)	**10** ee (%)[b]
1[c]	**9a** (Ph)	–78 °C, 5 min to 0 °C, 3 days	**10aa**, 58	88
2[c]	**9b** (C_6H_4(OMe)-*p*)	–78 °C, 5 min to 0 °C, 1.5 days	**10ab**, 88	91
3[c]	**9b**	0 °C, 12 h	**10ab**, 88	69
4[d]	**9b**	–78 °C, 5 min to –20 °C, 4 days	**10ab**, 61	95
5[e]	**9b**	–20 °C, 5 min to 0 °C, 2.5 days	**10ab**, 81	92

[a] See the experimental section in detail. [b] Ee of *endo*-**10**. [c] 0.1 mmol scale of **9** (0.8 M) in $EtNO_2$. [d] 0.1 mmol scale of **9b** (0.4 M) in $EtNO_2$. 1.5 equiv of **8a** was used. [e] 2.4 mmol scale of **9b** (0.8 M) in $EtNO_2$.

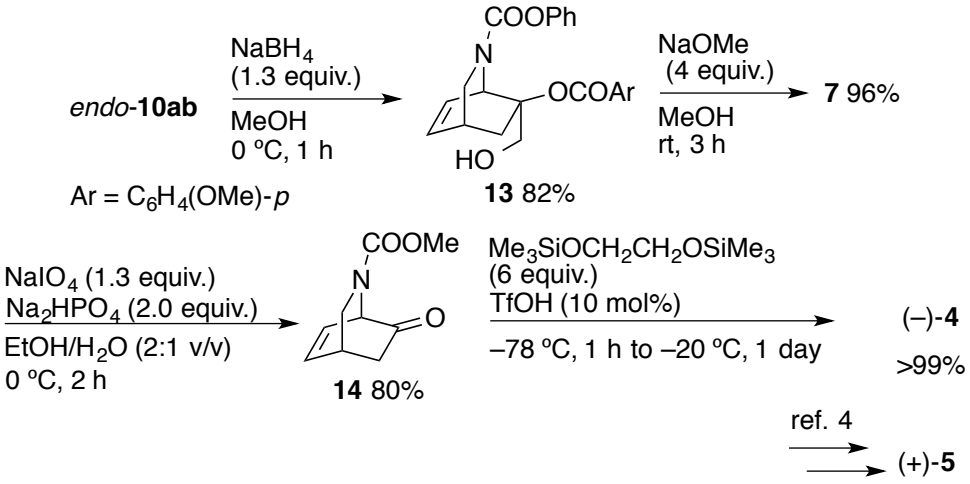
The reaction temperature was gradually increased from –78 °C to 0 °C, and the reaction mixture was further stirred at 0 °C for 3 days. The desired isoquinuclidine **10aa** was obtained in 58% yield with >95% *endo*-selectivity. The enantioselectivity of *endo*-**10aa** was 88% ee (entry 1). Since a hydrogen-bonding interaction between an α-acyl moiety of **9** and an ammonium proton of the catalyst was expected, α-(*p*-methoxybenzoyloxy)acrolein (**9b**) was examined as a dienophile under the same conditions. Interestingly, **9b** was much more reactive than **9a**. *Endo*-**10ab** was obtained in 88% yield with 91% ee (entry 2). When the reaction was started at 0 °C, the enantioselectivity was reduced to 69% ee (entry 3). Actually, the reaction proceeded slowly even at –20 °C, and the enantioselectivity was 95% ee (entry 4). The reaction of **8a** with **9b** was scalable, and could be increased up to 2.4 mmol scale without reducing chemical yield and enantioselectivity of **10ab** (entry 5).

Scheme 2.4. Derivatation of *endo*-**10ab** to *endo*-**1**



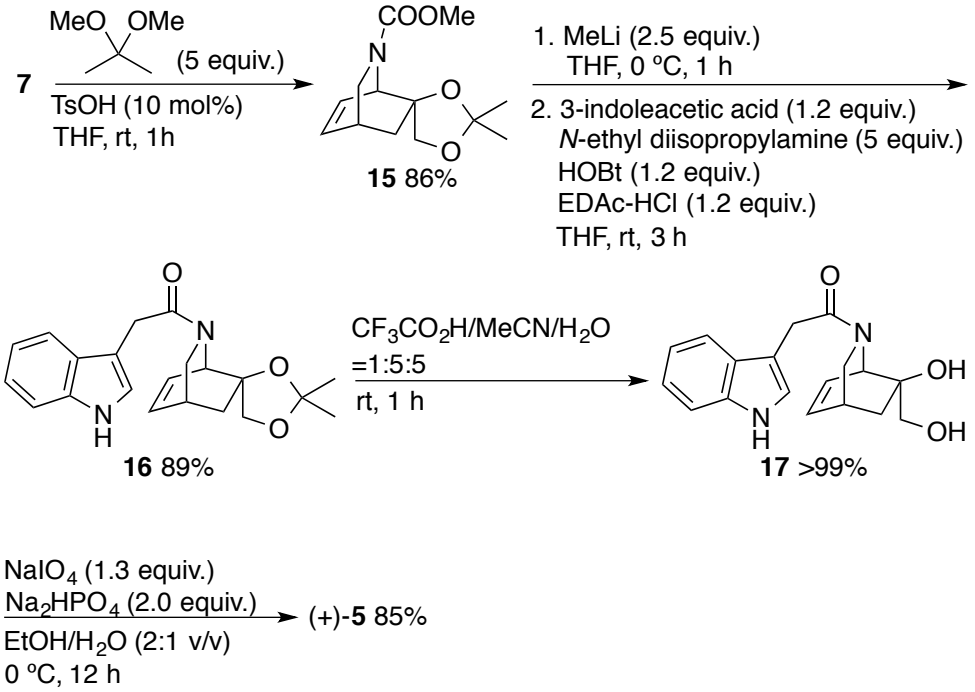
Endo-**10ab** was transformed to **12** in 56% yield under basic oxidation conditions (Scheme 2.4). This is a one-pot 4-step sequence of three different functional groups.[11] Deprotection of the *p*-methoxybenzoyl group of **10ab** was promoted by the adjacent oxyanion (Step 2 in Scheme 2.4).[12] The generation of **11** was detected by ^{1}H NMR analysis. The subsequent acetylation of **12** gave *endo*-**1** in 88% yield.

Scheme 2.5. Derivatization of *endo*-**11ab** to (–)-**4**



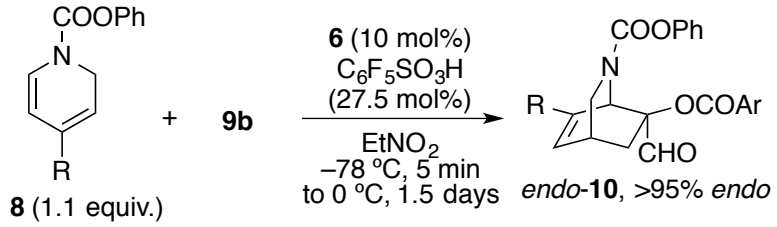
Endo-adduct **10ab** (91% ee) was converted to a key synthetic intermediate **4** of (+)-catharanthine in good yield by selective reduction of the formyl group of **10ab**, selective methanolysis of the ester moiety of **13**, oxidative cleavage of the vicinal diol moiety of **7**, and acetalization of **14** (scheme 2.5).[13] The absolute configuration of **4** was determined to be (–)-(1*R*,4*R*) by comparison of its optical rotation (91% ee, $[\alpha]_D^{26}$ = –65 (*c* = 0.4, MeOH).[4] Spiroacetal **4** can be transformed to 2-(2-(1*H*-indol-3-yl)acetyl)-2-azabicyclo[2.2.2]oct-7-en-6-one (**5**) by Doris's synthetic method (Scheme 2.2).[4] Thus, (+)-(1*R*,4*R*)-**5** can be synthesized from **7** in 49% overall yield over 5 steps. As a new and more concise synthetic route to (+)-(1*R*,4*R*)-**5**, we developed a 4-step sequence from diol **7** which included the acetalization of **7**, *N*-deprotection/acylation of **15**, the hydrolysis of **16**, and the oxidative cleavage of **17** (Scheme 6). The overall yield of (+)-**5** (91% ee, $[\alpha]_D^{24}$= +88 (*c* = 1.2, $CHCl_3$) from **7** was 65%.[4]

Scheme 2.7. Derivatization of **7** to (+)-**5**



The substrate scope of the Diels–Alder reaction of 4-substituted *N*-phenoxycarbonyl-1,2-dihydropyridines (**8b–e**) with **9b** was investigated under the optimized conditions (entry 2 in Table 2.1). The results are shown in Table 2.2. The reactions proceeded smoothly at –20 ~ 0 °C to give desired endo-adducts **10** in good to high yield with high enantioselectivity.

Table 2.2. Enantioselective Diels–Alder Reaction of **8** with **9b**



Entry	**8** (R)	**10**	
		Yield[%]	ee[%]
1[a]	**8b (Me)**	**10bb**, 95	88
2	**8c (*i*-Pr)**	**10cb**, 86	80
3	**8d (OCOC$_6$H$_4$-OMe-*p*)**	**10db**, 84	90
4[b]	**8d (OCOC$_6$H$_4$-OMe-*p*)**	**10db**, 81	95
5[b]	**8e (CH$_2$OTBS)**	**10eb**, 82	93

[a] 2.2 equiv. of **8** was used. [b] the reaction was carried out at –20 ºC, for 3 days.

To understand the reaction mechanism, the optimized geometry of iminium salt **18** prepared from **6**•3$C_6F_5SO_3H$ and **9a** was calculated using B3LYP/6-31G(d).[14,15] However, no reasonable geometries that could explain the enantioface selectivity were obtained. When a key intermediate was postulated to be an aqua complex **18**•H_2O, the desired optimized geometry was obtained as shown in Figure 2.1.

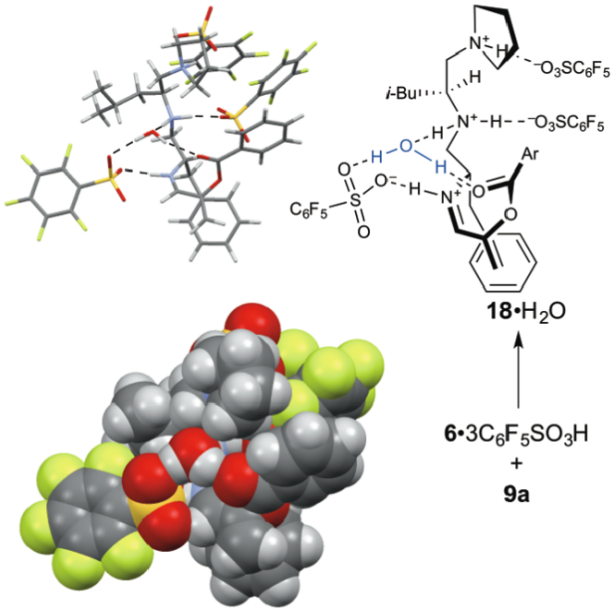


Figure 2.1. Optimized geometry (B3LYP/6-31G(d)) of iminium salt **18**•H_2O prepared from **6**•$3C_6F_5SO_3H$ and **9a** *in situ*

One water molecule stabilizes the (*Z*)-iminium geometry through three hydrogen bonds. In this geometry, the *re*-face of the dienophile is effectively shielded by the benzyl moiety of **6**•$3C_6F_5SO_3H$. Thus, 1,2-dihydropyridine can approach the *si*-face of the dienophile to give (1*R*,4*R*)-adduct enantioselectively. While this mechanism is plausible, it is not supported by any experimental evidence. Nevertheless, some water molecules may contribute to the construction of key intermediates or transition-state assemblies. Further mechanistic studies are in progress and will be reported in the near future.

3-3 Summary

In summary, we have developed the first example of a catalytic and highly enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-(acyloxy)acroleins catalyzed by **6**•$2.75C_6F_5SO_3H$, and their derivatization to some key synthetic intermediates of biologically active compounds. Furthermore, a plausible mechanism via an aqua complex such as **18**•H_2O can explain all previous results with the use of **6**•$C_6F_5SO_3H$.[10]

References and Notes

1. a) Farunk Khan, M. O.; Levi, M. S.; Clark, C. R.; Ablordeppey, S. Y.; Law, S.-J.; Wilson, N. H.; Borne, R. F. *Stud. Nat. Prod. Chem.* **2008**, *34*, 753–787; b) Silva, E. M. P.; Varandas, P. A. M. M.; Silva, A. M. S. *Synlett* **2013**, 3053–3089.
2. a) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157–6159; b) Wender, P. A.; Schaus, J. M.; White, A. W. *Heterocycles* **1987**, *25*, 263–270.
3. Baxter, E. W.; Labaree, D.; Ammon, H. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 7682–7692.
4. Moisan, L.; Thuéry, P.; Nicolas, M.; Doris, E.; Rousseau, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 5334–5336. According to this report, the specific rotations ($[a]_D^{20}$) of (+)-(1*S*,4*S*)-**4** (>99% ee) and (–)-(1*S*,4*S*)- **5** (>99% ee) are +70 (*c* = 0.4, MeOH) and –61 (*c* = 1.2, $CHCl_3$), respectively.
5. Büchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. *J. Am. Chem. Soc.* **1970**, 92, 999–1005.
6. a) Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58*, 8299–8305; b) Nakano, H.; Tsugawa, N.; Fujita, R. *Tetrahedron Lett.* **2005**, *46*, 5677–5681; c) Nakano, H.; Tsugawa, N.; Takahashi, K.; Okuyama, Y.; Fujita, R. *Tetrahedron*, **2006**, *62*, 10879–10887; d) Nishiuchi, Y.; Nakano, H.; Araki, Y.; Sato, R.; Fujita, R.; Uwai, K.; Takeshita, M. *Heterocycles* **2009**, *77*, 1323–1331; e) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y. *Chem. Commun.* **2010**, *46*, 4827–4829; f) Hirama, M.; Kato, Y.; Seki, C.; Nakano, H.; Takeshita, M.; Oshikiri, N.; Iyoda, M.; Matsuyama, H. *Tetrahedron* **2010**, *66*, 7618–7624; g) Stuttibut, C.; Kohari, Y.; Igarashi, K.; Nakano, H.; Hirama, M.; Seki, C.; Matsuyama, H.; Uwai, K.; Takano, N.; Okuyama, Y.; Osone, K.; Takeshita, M.; Kwon, E. *Tetrahedron Lett.* **2011**, *52*, 4745–4748; h) Seki, C.; Hirama, M.; Hutabarat, H. D. M. R.; Takada, J.; Stuttibut, C.; Takahashi, H.; Takaguchi, T.; Kohari, Y.; Nakano, H.; Uwai, K.; Takano, N.; Yasui, M.; Okuyama, Y.; Takeshita, M.; Matsuyama, H. *Tetrahedron* **2012**, *68*, 1774–1781; i) Okuyama, Y.; Osone, K.; Nakano, H.; Takeshita, M. *Heterocycles* **2012**, *84*, 1209–1016; j) Hutabarat, N. D. M. R.; Seki, C.; Shimizu, T.; Hirama, M.; Kohari, Y.; Nakano, H.; Uwai, K.; Takano, N.; Kwon, E.; Matsuyama, H. *Heterocycles* **2012**,

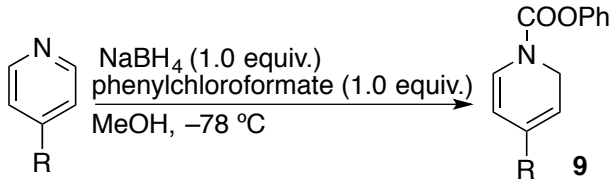
86, 203–217; k) Sakuta, Y.; Kohari, Y.; Hutabarat, N. D. M. R.; Uwai, K.; Kwon, E.; Okuyama, Y.; Seki, C.; Matsuyama, H.; Takano, N.; Tokiwa, M.; Takeshita, M.; Nakano, H. *Heterocycles* **2012**, *86*, 1379–1389.

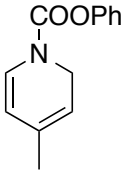
7. a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.
8. a) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama T.; *Angew. Chem. Int. Ed.* **2007**, *46*, 5734–5736; b) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron* **2009**, *65*, 3239–3245.
9. According to ref. 6a, Rawal *et al.* obtained *endo*-adduct in 89% yield with 67% ee through the enantioselective Diels–Alder reaction of *N*-phenyloxycarbonyldihydropyridine with methacrolein catalyzed by chiral Cr(III) Lewis acid.
10. a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504 (13079 correction); b) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229; c) Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457; d) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930; e) Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893; f) Sakakura, A.; Ishihara, K. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 313; g) Sakakura, A.; Yamada, H.; Ishihara, K. *Org. Lett.* **2012**, *14*, 2972; h) Sakakura, A.; Yamada, H.; Ishihara, K. *Asian J. Org. Chem.* **2012**, *1*, 133–137.
11. For the oxidation of aldehydes with I_2/KOH, see: (a) Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329–4332. (b) Jones, B. D.; Clair, J. L.; Moore, C. E.; Rheingold, A. L.; Burkart, M. D. *Org. Lett.* **2010**, *12*, 4516.
12. After the formyl group of **10ab** was oxidized to a methoxycarbonyl group, we failed to achieve selective deprotection of the *p*-methoxybenzoyl group to produce **12** under basic conditions.
13. a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358; b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899–3910.
14. Frisch, M. J. *et al.*, Gaussian 09, Revision C01, Gaussian, Inc., Wallingford, CT, 2009.
15. a) Becke, A. D. *J. Chem. Phys.* **1993**, *96*, 5648; b) Stevens, P. J.; Devlin, J. F.; Chablowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627; c) Tirado-Rives, J.; Jørgensen, W. L. *J. Chem. Theory Comput.* **2008**, *4*, 297−306.

Experimental Section

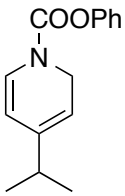
General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m =multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 spectrometer (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm × 25 cm), Daicel CHIRALCEL OZ-H (4.6 mm × 25 cm), Daicel CHIRALPAK AD-3 (4.6 mm × 25 cm), Daicel CHIRALPAK OD-3 (4.6 mm × 25 cm), Daicel CHIRALPAK IA-3 (4.6 mm × 25 cm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on JEOL JMS-700 spectrometer (for FAB) or JEOL JMS-T100GCV spectrometer (for EI). In experiments that required dry solvent, tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF) and dichloromethane (CH_2Cl_2) were purchased from Kanto, TCI or Wako as the "anhydrous." Nitroethane ($EtNO_2$), and triethylamine (Et_3N) were freshly distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially.

Synthesis of 4-substituted 1-phenoxycarbonyl-1,2-dihydropyridines (8)[1]



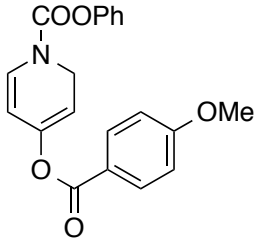


4-Methyl-1-phenoxycarbonyl-1,2-dihydropyridines (8b): To a solution of 4-methyl pyridine (4.7 g, 50 mmol) in MeOH (40 mL) was added $NaBH_4$ (1.9 g, 50 mmol) at –78ºC, the mixture was stirred for 30 min. Phenylchloroformate (7.8 g, 50 mmol) was slowly introduced to the mixture, and stirred for 3 h at the same temperature. The reaction was quenched by the successive addition of ice water and the solution was stirred until H_2 bubble stopped and then warmed up to ambient temperature. The mixture was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give 4-methyl-*N*-phenoxycarbonyl-1,2-dihydropyridines in 70% yield (7.5 g, 35 mmol). **8b**: IR ($CHCl_3$) 1726, 1359, 1204, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (3/2): δ 1.75 (s, 3H), 4.34–4.43 (m, 1.3H), 4.48–4.58 (m, 0.7H), 5.12 (d, *J*= 7.8 Hz, 0.6H), 5.16 (d, *J*= 7.8 Hz, 0.4H), 5.22–5.28 (m, 0.4H), 5.28–5.33 (m, 0.6H), 6.80 (d, *J*= 7.8 Hz, 0.4H), 6.87 (d, *J*= 7.8 Hz, 0.6H), 7.13 (d, *J*= 7.8 Hz, 2H), 7.19–7.27 (m, 1H), 7.37 (t, *J*= 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 44.0 and 44.4, 109.4 and 109.6, 113.54 and 114.1, 121.6 (2C), 124.8, 125.5 and 125.6, 129.3 and 129.4 (2C), 129.7 and 130.2, 150.9 and 151.5; HRMS (FAB) calcd for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1019, found 216.1015.

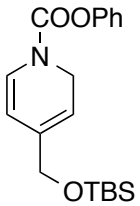


4-Isopropyl-1-phenoxycarbonyl-1,2-dihydropyridines (8c): Compound **8c** was prepared from 4-isopropylpyridine according to the procedure for the synthesis of **8b**. 56% yield. IR ($CHCl_3$) 1727, 1359, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz)

mixture of rotamers (3/2): δ 1.05 (d, *J*=6.9 Hz, 6H), 2.29 (h, *J*=6.9 Hz, 1H), 4.41 (d, *J*= 3.7 Hz, 1.3H), 4.55 (d, J= 3.7 Hz, 1.3H), 5.19–5.33 (m, 2H), 7.14 (d, J= 8.2 Hz, 1H), 7.22 (t, *J*= 7.3 Hz, 1H), 7.38 (dd, *J*= 7.8, 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1 (2C), 32.4, 44.0 and 44.3, 107.3 and 107.6, 110.8 and 111.3, 121.6 (2C), 125.1, 125.6, 125.7 and 125.9, 129.3 (2C), 139.7 and 140.1, 150.9 and 151.4; HRMS (FAB) calcd for $C_{15}H_{18}NO_2$ $[M+H]^+$ 244.1332, found 244.1333.



4-(*p*-Methoxybenzoyloxy)-1-phenoxycarbonyl-1,2-dihydropyridines (8d): Compound **8d** was prepared from 4-(*p*-methoxybenzoyloxy)pyridine[2] according to the procedure for the synthesis of **8b**. 30% yield. white solid; IR (KBr) 1732, 1718, 1602, 1510, 1333, 1283, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (3/2): δ 3.88 (s, 3H), 4.66 (d, *J*= 4.1 Hz, 1.2H), 4.81 (d, *J*= 4.1 Hz, 0.8H), 5.19 (dd, *J*= 2.3, 8.7 Hz, 0.6H), 5.21 (dd, *J*= 2.3, 8.7 Hz, 0.4H), 5.32–5.40 (m, 1H), 6.92–6.98 (m, 2.6H), 7.02 (d, *J*=8.2 Hz, 0.4H), 7.15 (d, *J*= 7.8 Hz, 2H), 7.22–7.27 (m, 1H), 7.39 (t, *J*= 7.8 Hz, 2H), 8.05 (d, *J*= 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.0 and 44.4, 55.5, 103.8 and 104.1, 104.6 and 105.0, 113.8 (2C), 112.3 and 121.5 (2C), 125.9, 127.6, 128.5, 129.4 (2C), 132.2 (2C), 144.1 and 144.5, 150.8 and 151.3, 152.0, 152.3, 163.9 and 164.3 ; HRMS (FAB) calcd for $C_{20}H_{17}NO_5$ [M] 351.1107, found 351.1111.



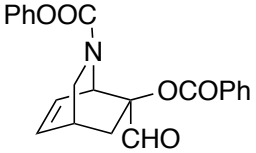
4-(*tert*-Butyldimethylsilyloxy)methyl-1-phenoxycarbonyl-1,2-dihydropyridines (8e): Compound **8e** was prepared from 4-[(*tert*-butyldimethylsilyloxy)methyl]pyridine[3] according to the procedure for the synthesis of **8b**. 47% yield. white participate; IR ($CHCl_3$) 1731, 1353, 1204 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (2/1): δ 0.10 (s, 6H), 0.93 (s, 9H),

4.12 (s, 2H), 4.30–4.62 (m, 0.4H), 4.38–4.48 (m, 0.6H), 5.19 (t, *J*= 8.3 Hz, 1H), 5.45–5.55 (m, 1H), 6.84 (d, J= 7.8 Hz, 0.3H), 6.91 (d, *J*= 7.8 Hz, 0.7H), 7.13 (d, J= 7.3 Hz, 2H), 7.28 (t, *J*= 7.3 Hz, 1H), 7.37 (dd, *J*= 7.8, 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ –5.37 (2C), 18.3, 25.9 (2C), 43.9 and 44.3, 105.3 and, 105.4, 112.5 and 113.1, 121.5 (2C), 125.4, 125.6 and 126.1, 129.3 (2C), 133.5 and 133.9, 150.7 and 150.8, 151.4 and 152.5; HRMS (FAB) calcd for $C_{19}H_{28}NO_3Si$ $[M+H]^+$ 346.1833, found 346.1834.

General procedure for the enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-(acyloxy)acroleins: α-(benzoyloxy)acrolein (**9**, 0.1 mmol) was added to a solution of chiral triamine (**6**, 3 mg, 0.01 mmol) and $C_6F_5SO_3H$ (6.8 mg) in $EtNO_2$ (0.125 mL) at –78 ºC. After the mixture was stirred at the same temperature for 5 min, 1-phenoxycarbonyl-1,2-dihydropyridine (**8**, 0.15 mmol) was added in one portion. After the reaction mixture was stirred for 1.5 days at 0 ºC or 3.0 days at –20 ºC, the reaction was quenched with Et_3N, the crude mixture was directly purified by chromatography on a silica gel column (hexane/EtOAc 10:1 to 5:2) to give Diels–Alder adducts **10**.

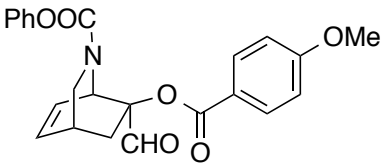
Typical Procedure for the Enantioselective Diels–Alder Reaction of 8a with 9b on Large Scale (Table 1 (entry 5).

α-(*p*-Methoxybenzoyloxy)acrolein (**9b**, 500 mg, 2.43 mmol) was added to a solution of **6** (73.6 mg, 0.24 mmol) and $C_6F_5SO_3H$ (165 mg, 0.67 mmol) in $EtNO_2$ (3.0 mL) at –20 ºC and stirred for 5 min at same temperature. After the mixture was stirred at the 0 ºC for 10 min, and cooled to –20 ºC again. The diene **8** (536 mg, 2.67 mmol) was added in one portion at same temperature. After 5 min, the reaction was stirred for 2.5 days at 0 ºC. The reaction was quenched with Et_3N, the crude product was purified directly by chromatography on a silica gel column (hexane/EtOAc 10:1 to 5:2) to give 10ab in 81% yield, 92% ee (800 mg, 1.97 mmol).



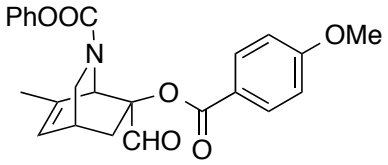
(–)-(1*R*,4*R*,7*S*)-7-Formyl-1-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-yl Benzoate (10aa, *endo* isomer, Table 2.1, entry 1): Colorless oil; $[\alpha]^{19}_D$ –27.6 (c 1.00,

$CHCl_3$) for 88% ee; HPLC (Daicel CHIRALPAK OD-3 column, hexane–*i*-PrOH = 9:1, flow rate = 1.0 mL/min) t_R = 23.7 (major) and 28.4 (minor) min; IR ($CHCl_3$) 17.16, 1404, 1290, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (1/1): δ 1.78 (dd, *J*= 14.6, 2.3 Hz, 0.5H), 1.85 (dd, *J*= 14.6, 2.3 Hz, 0.5H), 2.54 (dt, *J*= 14.6, 3.2 Hz, 0.5H), 2.62 (dt, *J*= 14.6, 3.2 Hz, 0.5H), 3.03–3.12 (m, 1H), 3.21 (dt, *J*= 10.5, 2.3 Hz, 0.5H), 3.31 (dt, *J*= 10.1, 2.3 Hz, 0.5H), 3.58 (dd, *J*= 10.6, 2.3 Hz, 0.5H), 3.69 (dd, *J*= 10.3, 2.3 Hz, 0.5H), 5.24 (d, *J*= 6.4 Hz, 0.5H), 5.34 (d, *J*= 6.4 Hz, 0.5H), 6.30 (dd, *J*= 7.1, 6.4 Hz, 0.5H), 6.39 (dd, *J*= 7.3, 7.1 Hz, 0.5H), 6.69 (dd, *J*= 14.6, 2.3 Hz, 1H), 7.02 (d, *J*= 7.3 Hz, 0.5H), 7.08 (d, *J*= 7.8 Hz, 0.5H), 7.12–7.25 (m, 1H), 7.31 (t, *J*= 8.0 Hz, 1H), 7.37 (dd, *J*= 8.0, 7.8 Hz, 1H), 7.44 (dd, *J*= 7.6, 7.3 Hz, 1H), 7.46 (dd, *J*= 7.6, 7.3 Hz, 1H), 8.05 (d, *J*= 7.4 Hz, 1H), 8.09 (d, *J*= 6.9 Hz, 1H), 9.51 (s, 0.5H), 9.55 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.5 and 30.9, 32.0 and 32.4, 46.8 and 47.0, 49.3 and 50.1, 86.1 and 86.6, 121.4 and 121.7 (2C), 125.3 and 125.5, 127.4 and 127.8, 128.6 (2C), 129.2 and 129.3 (2C), 130.0 and 130.2 (2C), 133.9 and 133.9, 137.8 and 137.8, 151.0 and 151.2, 153.3, 154.4, 166.0 and 166.1, 195.3 and 195.5; HRMS (FAB) calcd for $C_{22}H_{20}NO_5$ $[M+H]^+$ 378.1336, found 378.1340.

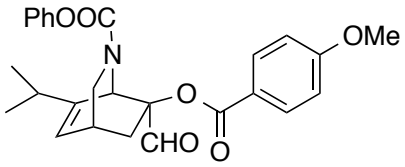


(–)-(1*R*,4*R*,7*S*)-7-Formyl-1-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-yl *p*-Methoxybenzoate (10ab, *endo* isomer, Table 2.1, entry 2–4): Colorless oil; $[\alpha]^{21}_D$ –22.4 (c 1.00, $CHCl_3$) for 95% ee; HPLC (Daicel CHIRALPAK OD-H column, hexane–*i*-PrOH = 4:1, flow rate = 1.0 mL/min) t_R = 19.3 (minor) and 22.2 (major) min; IR ($CHCl_3$) 1716, 1605, 1404, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (1/1): δ 1.76 (dd, *J*= 14.2, 1.8 Hz, 0.5H), 1.82 (dd, *J*= 14.5, 1.8 Hz, 1H), 2.52 (d, *J*= 14.2 Hz, 0.5H), 2.61 (d, *J*= 14.5 Hz, 1H), 3.02–3.10 (m, 1H), 3.20 (d, *J*= 10.6 Hz, 0.5H), 3.30 (d, *J*= 10.6 Hz, 0.5H), 3.58 (d, *J*= 9.2 Hz, 0.5H), 3.68 (d, *J*= 9.4 Hz, 0.5H), 5.26 (d, *J*= 6.0 Hz, 0.5H), 5.31 (d, *J*= 6.0 Hz, 0.5H), 6.28 (t, *J*= 6.9 Hz, 0.5H), 6.38 (dd, *J*= 6.9, 6.9 Hz, 0.5H), 6.62–6.72 (m, 1H), 6.90 (d, *J*= 7.3 Hz, 1H), 6.92 (d, *J*= 7.3 Hz, 1H), 7.03 (d, *J*= 7.8 Hz, 1H), 7.10 (d, *J*= 7.8 Hz, 1H), 7.19 (dd, *J*= 7.6, 7.3 Hz, 1H), 7.23 (t, *J*= 7.3 Hz, 1H), 7.32 (t, *J*= 7.8 Hz, 1H), 7.38 (dd, *J*= 7.8, 7.8 Hz, 1H), 7.99 (d,

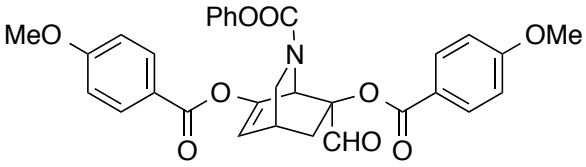
J= 8.7 Hz, 1H), 8.03 (d, *J*= 8.7 Hz, 1H), 9.50 (s, 0.5H), 9.55 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.5 and 30.9, 32.0 and 32.5, 46.8 and 47.0, 49.3 and 50.2, 55.5, 85.8 and 86.3, 113.9 and 113.9 (2C), 120.8 and 121.1, 121.5 and 121.7 (2C), 125.3 and 125.5, 127.4 and 127.9, 129.2 and 129.3 (2C), 132.2 and 132.3 (2C), 137.7, 151.0 and 151.2, 153.3 and 154.4, 164.0 and 164.1, 165.7 and 165.9, 195.5 and 195.6; HRMS (FAB) calcd for $C_{22}H_{22}NO_6$ $[M+H]^+$ 408.1442, found 408.1441.



(–)-(1*R*,4*R*,7*S*)-7-Formyl-6-methyl-1-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene -7-yl *p*-Methoxybenzoate (10bb, *endo* isomer, Table 2.2, entry 1): Colorless oil; $[\alpha]^{21}_D$ –41.7(c 1.15, $CHCl_3$) for 88% ee; HPLC (Daicel CHIRALPAK OZ-H column, hexane–*i*-PrOH = 4:1, flow rate = 1.0 mL/min) t_R = 40.8 (major), 67.5 (minor) min; IR ($CHCl_3$) 1715, 1606, 1403, 1259, 1206, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (1/1): δ 1.73 (dd, *J*= 14.6, 2.3 Hz, 0.5H), 1.80 (dd, *J*= 14.2, 2.3 Hz, 0.5H), 1.96 (s, 3H), 2.56 (dt, *J*= 14.2, 2.8 Hz, 0.5H), 2.63 (dt, *J*= 14.2, 2.8 Hz, 0.5H), 2.73–2.85 (m, 1H), 3.22 (dt, *J*= 10.5, 2.3 Hz, 0.5H), 3.32 (dt, *J*= 10.5, 2.3 Hz, 0.5H), 3.54 (dd, *J*= 10.5, 1.8 Hz, 0.5H), 3.65 (dd, *J*= 10.5, 1.8 Hz, 0.5H), 3.86 (s, 1.5H), 3.87 (s, 1.5H), 5.10 (d, *J*= 6.4 Hz, 0.5H), 5.21 (d, *J*= 6.4 Hz, 0.5H), 5.86 (d, *J*= 6.4 Hz, 0.5H), 5.96 (d, *J*= 6.0 Hz, 0.5H), 6.89 (d, *J*= 8.7 Hz, 1H), 6.91 (d, *J*= 8.7 Hz, 1H), 7.19 (dd, *J*= 7.6, 7.3 Hz, 0.5H), 7.23 (dd, *J*= 7.8, 7.4 Hz, 0.5H), 7.05 (d, *J*= 7.8 Hz, 1H), 7.10 (d, *J*= 7.3 Hz, 1H), 7.33 (dd, *J*= 8.0, 7.8 Hz, 1H), 7.38 (t, *J*= 7.8 Hz, 1H), 7.99 (d, *J*= 8.7 Hz, 1H), 8.03 (d, *J*= 8.7 Hz, 1H), 9.48 (s, 0.5H), 9.53 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7 and 19.8, 31.4 and 32.0, 36.0 and 36.4, 46.4 and 46.6, 50.2 and 51.0, 55.5, 86.0 and 86.6, 113.8 (2C), 119.7 and 120.2, 121.5 and 121.8 (2C), 125.2 and 125.4, 129.2 and 129.3 (2C), 132.1 and 132.3 (2C), 147.7 and 147.9, 151.1 and 151.3, 153.2, 154.3, 164.0 and 164.1, 165.8 and 165.9, 195.5 and 195.8; HRMS (FAB) calcd for $C_{24}H_{24}NO_6$ $[M+H]^+$ 422.1598, found 422.1598.

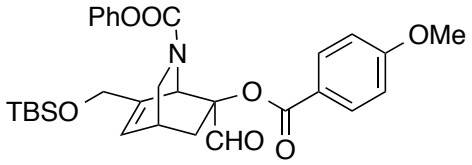


(–)-(1*R*,4*R*,7*S*)-7-Formyl-6-isopropyl-1-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-yl *p*-Methoxybenzoate (10cb, *endo* isomer, Table 2.2, entry 2): Colorless oil; $[\alpha]^{21}_{D}$ –45.6 (c 1.00, $CHCl_3$) for 80% ee; HPLC (Daicel CHIRALPAK AD-3 column, hexane–*i*-PrOH = 4:1, flow rate = 1.0 mL/min) t_R = 21.6 (minor), 38.2 (major) min; IR ($CHCl_3$) 1716, 1605, 1403, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (1/1): δ 1.11 (d, *J*= 1.8 Hz, 3H), 1.13 (d, *J*= 1.8 Hz, 3H), 1.75 (dd, *J*= 14.2, 2.3 Hz, 0.5H), 1.82 (dd, *J*= 14.2, 2.3 Hz, 0.5H), 2.44–2.64 (m, 2H), 2.90–3.12 (m, 1H), 3.15 (dt, *J*= 10.5, 2.3 Hz, 0.5H), 3.25 (dt, *J*= 10.1, 2.3 Hz, 0.5H), 3.58 (dd, *J*= 10.5, 1.8 Hz, 0.5H), 3.69 (dd, *J*= 10.1, 2.3 Hz, 0.5H), 3.86 (s, 1.5H), 3.87 (s, 1.5H), 5.15 (d, *J*= 6.4 Hz, 0.5H), 5.25 (d, *J*= 6.4 Hz, 0.5H), 5.80 (d, *J*= 6.8 Hz, 0.5H), 5.90 (d, *J*= 6.8 Hz, 0.5H), 6.89 (d, *J*= 8.7 Hz, 1H), 6.91 (d, *J*= 8.7 Hz, 1H), 7.07 (d, *J*= 7.3 Hz, 1H), 7.11 (d, *J*= 7.3 Hz, 1H), 7.19 (dd, *J*= 7.8, 7.1 Hz, 1H), 7.23 (t, *J*= 7.3 Hz, 1H), 7.34 (dd, *J*= 9.8, 8.2 Hz, 1H), 7.38 (dd, *J*= 8.0, 7.3 Hz, 1H), 7.99 (d, *J*= 8.7 Hz, 1H), 8.04 (d, *J*= 9.2 Hz, 1H), 9.47 (s, 0.5H), 9.52 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 32.1 and 32.5, 33.4 and 33.8, 47.3 and 47.4, 50.3 and 51.1, 55.5, 86.1 and 86.7, 113.8 (2C), 116.3 and 116.8, 121.0 and 121.1, 121.5 and 121.8 (2C), 125.2 and 125.4, 128.3, 129.2 and 129.3 (2C), 132.2 and 132.3 (2C), 151.1 and 151.3, 153.2 and 154.3, 156.8 and 157.1, 164.0 and 164.1, 165.8 and 165.9, 195.4 and 195.7; HRMS (FAB) calcd for $C_{26}H_{28}NO_6$ $[M+H]^+$ 450.1911, found 450.1915.



(–)-(1*R*,4*R*,7*S*)-7-Formyl-6-(*p*-methoxybenzoyl)oxy-1-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-yl *p*-Methoxybenzoate (10db, *endo* isomer, Table 2, entry 3 and 4): Colorless oil; $[\alpha]^{25}_{D}$ –47.8 (c 0.95, $CHCl_3$) for 95% ee; HPLC (Daicel CHIRALPAK IA-3 column, hexane–*i*-PrOH =1:1, flow rate = 0.5 mL/min) t_R = 44.1 (minor), 60.2 (major) min; IR ($CHCl_3$) 1718, 1605, 1511, 1402, 1259, 1162 cm^{-1}; ^1H

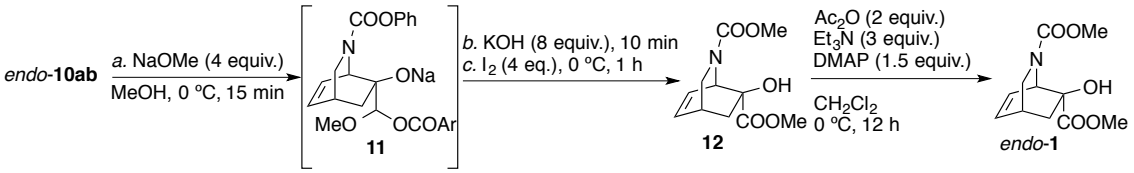
NMR ($CDCl_3$, 400 MHz) mixture of rotamers (2/1): δ 1.87 (dd, *J*= 14.4, 2.3 Hz, 0.3H), 1.94 (dd, *J*= 14.2, 2.3 Hz, 0.5H), 2.98 (dt, *J*= 10.5, 2.3 Hz, 0.3H), 3.02 (dd, *J*= 11.0, 2.8 Hz, 0.7H), 3.12–3.17 (m, 1H), 3.62–3.66 (m, 1H), 3.71 (d, *J*= 2.3 Hz, 0.3H), 3.74 (d, *J*= 1.8 Hz, 0.7H), 3.81 (dd, *J*= 2.3, 2.3 Hz, 0.7H), 3.84 (dd, *J*= 2.5, 2.3 Hz, 0.3H), 3.87 (s, 1H), 3.88 (s, 2H), 3.40 (s, 3H), 5.35 (d, *J*= 6.9 Hz, 0.7H), 5.42 (d, *J*= 6.9 Hz, 0.3H), 5.93 (dd, *J*= 7.1, 2.8 Hz, 0.7H), 6.06 (dd, *J*= 7.1, 2.8 Hz, 0.3H), 6.90 (d, *J*= 10.6 Hz, 0.7H), 6.92 (d, *J*= 6.9 Hz, 1.3H), 6.98 (d, *J*= 11.5 Hz, 2H), 7.04 (d, *J*= 7.4 Hz, 0.7H), 7.11 (d, *J*= 7.4 Hz, 1.3H), 7.19 (dd, *J*= 7.6, 7.3 Hz, 0.3H), 7.24 (t, *J*= 7.3 Hz, 0.7H), 7.34 (dd, *J*= 6.0, 6.0 Hz, 0.7H), 7.38 (dd, *J*= 7.8, 7.4 Hz, 1.3H), 9.59 (s, 0.7H), 9.65 (s, 0.3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.1 and 32.7, 35.1 and 35.4, 47.1 and 47.3, 50.9 and 51.7, 55.5 (2C), 85.9 and 86.4, 109.7 and 110.1, 113.9 and 113.9 (4C), 120.6 and 120.8, 121.5 and 121.8 (2C), 125.3 and 125.5 129.2 and 129.3 (2C), 132.2 and 132.3 (4C), 151.0 and 151.2, 153.0, 154.3, 156.6 and 156.8, 164.1 and 164.2, 165.7, 195.4 and 195.7; HRMS (FAB) calcd for $C_{31}H_{28}NO_9$ $[M+H]^+$ 558.1759, found 558.1761.



(–)-(1*R*,4*R*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)methyl-7-formyl-1-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-yl *p*-Methoxybenzoate (10eb, *endo* isomer, Table 2, entry 5): Colorless oil; $[\alpha]^{25}_D$ –28.8 (c 1.00, $CHCl_3$) for 93% ee; HPLC (Daicel CHIRALPAK OD-3 column, hexane–*i*-PrOH = 20:1, flow rate = 1.0 mL/min) t_R = 32.3 (minor), 40.7 (major) min; IR ($CHCl_3$) 1606, 1404, 1259, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (1/1): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.76 (d, *J*= 13.3 Hz, 0.5H), 1.84 (d, *J*= 14.2 Hz, 0.5H), 2.52 (d, *J*= 14.7 Hz, 0.5H), 2.60 (d, *J*= 14.2 Hz, 0.5H), 2.94 (m, 1H), 3.20 (d, *J*= 10.5 Hz, 0.5H), 3.30 (d, *J*= 10.1 Hz, 0.5H), 3.58 (d, *J*= 10.5 Hz, 0.5H), 3.68 (d, *J*= 10.1 Hz, 0.5H), 3.86 (s, 1.5H), 3.87 (s, 1.5H), 4.31 (s, 2H), 5.20 (d, *J*= 6.4 Hz, 0.5H), 5.31 (d, *J*= 6.4 Hz, 0.5H), 6.07 (d, *J*= 5.5 Hz, 0.5H), 6.17 (d, *J*= 5.0 Hz, 0.5H), 6.89 (d, *J*= 8.2 Hz, 1H), 6.91 (d, *J*= 8.2 Hz, 1H), 7.04 (d, *J*= 7.8 Hz, 1H), 7.09 (d, *J*= 7.8 Hz, 1H), 7.19 (t, *J*= 7.8 Hz, 0.5H), 7.23 (dd, *J*= 8.0, 8.7 Hz, 0.5H), 7.33 (t, *J*= 8.2 Hz, 1H), 7.38 (t, *J*= 7.8 Hz, 1H), 7.99 (d, *J*= 9.2 Hz, 1H), 8.03 (d, *J*= 8.7 Hz, 1H), 9.48 (s, 0.5H), 9.53 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ –5.5 and

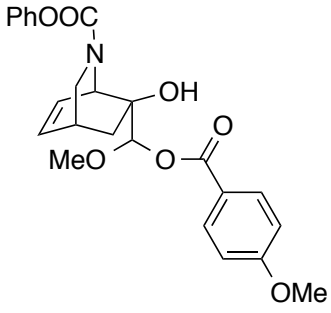
–5.4 (2C), 18.3, 25.8 (3C), 31.8 and 31.8, 32.2 and 32.4, 46.8 and 46.9, 50.1 and 50.9, 55.5, 62.6 and 62.7, 86.1 and 86.6, 113.8 (2C), 118.8 and 119.2, 120.9 and 121.1, 121.5 and 121.8 (2C), 125.2 and 125.4, 129.2 and 129.3 (2C), 132.2 and 132.3 (2C), 150.5 and 150.7, 151.1 and 151.2, 153.2 and 154.3, 164.0 and 164.1, 165.7 and 165.8, 195.3 and 195.6; HRMS (FAB) calcd for $C_{30}H_{38}NO_7Si$ $[M+H]^+$ 552.2412, found 552.2409.

Derivatation of *endo*-10ab to *endo*-1[4]

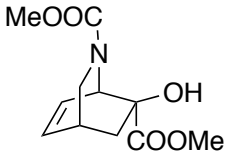


To a solution of *endo*-**11ab** (50 mg, 0.12 mmol) in MeOH (0.25 mL) was added sodium methoxide (26 mg, 0.48 mmol) at 0 ºC and the mixture was stirred for 15 min. KOH (0.25 mL of 1.9M solution in MeOH, 0.96 mmol) and I_2 (122 mg, 0.48 mmol) were added sequentially to the mixture, and stirred for 1 h at same temperature. The reaction was quenched by the successive addition of aqueous sodium thiosulfate, and then reaction mixture was warmed up to ambient temperature. The mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 1:1 to 0:1) to give **12** (14 mg, 0.057 mmol).

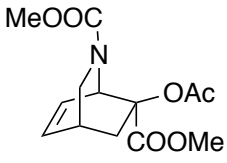
To a solution of **12** (28 mg, 0.12 mmol), DMAP (21 mg, 0.17 mmol) and triethylamine (48 μL, 0.35 mmol) in CH_2Cl_2 (0.5 mL) was added acetic anhydride (22 μL, 0.23 mmol) at 0 ºC and stirred for 12 h at same temperature. The resultant mixture was directly purified by chromatography on a silica gel column (hexane/EtOAc 1:1) to give ***endo*-1** (29 mg, 0.10 mmol) in 88% yield.



Intermediate (11): IR ($CHCl_3$) 1714, 1605, 1510, 1408, 1259, 1209, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (4/3) and stereoisomer (2/1) δ 1.48–1.71 (m, 1.3H), 1.74–1.89 (m, 0.7H), 2.76–2.93 (m, 1.3H), 2.61–2.71 (m, 0.7H), 3.11–3.16 (m, 0.4H), 3.22–3.28 (m, 0.6H), 3.44–3.51 (m, 3H), 3.51–3.60 (m, 0.5H), 3.64–3.72 (m, 0.5H), 3.82–3.90 (m, 3H), 4.71 (d, *J*= 6.0 Hz, 0.3H), 4.76 (d, *J*= 6.4 Hz, 0.1H), 4.86 (d, *J*= 6.4 Hz, 0.4H), 4.88 (d, *J*= 7.8 Hz, 0.2H), 5.71–5.78 (m, 1H), 6.38–6.62 (m, 2H), 6.87–6.98 (m, 2H), 7.08–7.23 (m, 3H), 7.29–7.42 (m, 2H), 7.98–8.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.6 and 30.9, 33.4 and 33.5 and 34.8, 46.7 and 47.1, 52.2 and 52.9 and 53.8, 55.5, 55.5, 57.0 and 57.1 and 57.8, 78.8, 99.1 and 99.7, 113.7 and 113.8 (2C), 121.7 and 121.8 (2C), 125.0 and 125.1 and 125.2, 129.1 (2C), 129.2 and 130.0 and 130.5 and 132.1, 135.6 (2C), 136.3 and 136.7, 151.3, 155.2 and 155.5, 164.1; HRMS (FAB) calcd for $C_{24}H_{26}NO_7$ $[M+H]^+$ 440.1704, found 440.1700.

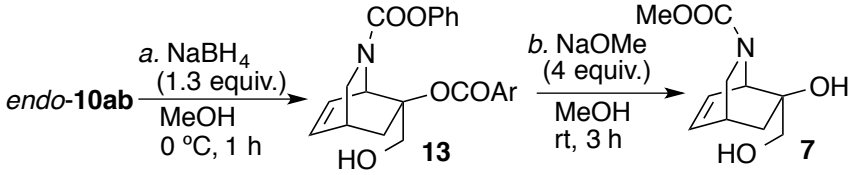


(1*R*,4*R*,7*S*)-Dimethyl 7-Hydroxy-2-azabicyclo[2.2.2]oct-5-ene-2,7- dicarboxylate (**12**): IR ($CHCl_3$) 1737, 1684, 1457, 1399, 1273, 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (2/1) δ 1.50–1.60 (m, 1H), 2.29–2.40 (m, 1H), 2.82–2.90 (m, 1H), 2.90–3.08 (m, 1H), 3.38–3.48 (m, 1H), 3.71 (s, 2.1H), 3.72 (s, 0.9H), 3.74 (s, 2.1H), 3.75 (s, 0.9 H), 4.73 (d, *J*= 6.4 Hz, 0.3H), 4.87 (d, *J*= 6.0 Hz, 0.7H), 6.27 (dd, *J*= 8.2, 7.8 Hz, 0.3H), 6.29 (dd, *J*= 7.8, 7.3 Hz, 0.7H), 6.47 (t, *J*= 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.5 and 30.7, 34.7 and 35.1, 46.4 and 46.8, 52.6 and 52.7, 52.6 and 52.7, 53.3 and 53.8, 78.1 and 78.2, 129.2 and 129.5, 136.1 and 136.2, 156.4 and 157.4, 173.2; HRMS (FAB) calcd for $C_{11}H_{16}NO_5$ $[M+H]^+$242.1023, found 242.1026.



(1*R*,4*R*,7*S*)-Dimethyl 7-Acetoxy-2-azabicyclo[2.2.2]oct-5-ene-2,7-dicarboxylate (*endo*-1): IR ($CHCl_3$) 1750, 1702, 1451, 1395, 1245, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (1/1) δ 1.60–1.70 (m, 1H), 2.06 (s, 3H), 2.33–2.43 (m, 1H), 2.87–2.94 (m, 1H), 2.99–3.07 (m, 1H), 3.33–3.43 (m, 1H), 3.69 (s, 1.5H), 3.69 (s, 1.5H), 3.71 (s, 1.5H), 3.72 (s, 1.5H), 5.03 (d, *J*= 6.4 Hz, 0.5H), 5.16 (d, *J*= 6.4 Hz, 0.5H), 6.23–6.38 (m, 1H), 6.43–6.53 (m, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 and 20.6, 30.1 and 30.4, 34.4 and 34.4, 46.1 and 46.4, 50.0 and 50.4, 52.3, 52.4, 81.8 and 81.8, 128.6 and 129.0, 135.3 and 135.7, 155.7 and 156.2, 170.2 and 170.3; HRMS (FAB) calcd for $C_{13}H_{18}NO_6$ $[M+H]^+$ 284.1129, found 284.1128.

Derivatization of *endo*-10ab to (–)-4 (Scheme 7)

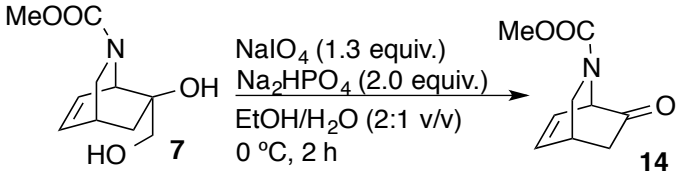


To a solution of Diels–Alder adduct (**10ab**, 615 mg, 1.51 mmol) in MeOH (10 mL) was added $NaBH_4$ (57 mg, 1.7 mmol) portion wise at 0 ºC and stirred for 1 h at same temperature. The reaction mixture was quenched with a saturated NH_4Cl aqueous solution and the solution was stirred until H_2 bubble stopped and then warmed up to ambient temperature. The mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 1:1) to give (1*R*,4*R*,7*S*)-7-Hydroxymethyl-1-phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-yl *p*-Methoxybenzoate (**13**) in 82% yield (507 mg, 1.24 mmol).

To a solution of alcohol **13** (460 mg, 1.12 mmol) in MeOH (10 mL) was added sodium methoxide (240 mg, 4.5 mmol) at ambient temperature and stirred for 1 h. The resultant mixture was concentrated and the crude product was purified by chromatography on a silica gel column (hexane/EtOAc 1:1 to 0:1) to give diol **7** in 96% yield (229 mg, 1.06 mmol).

(1*R*,4*R*,7*S*)-7-Hydroxymethyl-1-phenoxycarbonyl-2-azabicyclo-[2.2.2]-oct-5-ene-7-yl *p*-Metho- xybenzoate (13): IR ($CHCl_3$) 1710, 1606, 1409, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, a mixture of rotamers (5/1)) δ 1.49 (dt, *J* = 13.8, 2.8 Hz, 0.8H), 1.58 (d, *J* = 8.3 Hz, 0.2H), 1.66 (d, *J* = 7.4 Hz, 0.2H), 1.74 (dd, *J* = 12.2, 2.3 Hz, 0.8H), 2.67 (s, 0.2H), 2.71 (s, 0.8H), 2.87–2.96 (m, 1H), 3.18 (d, *J* = 10.5 Hz, 0.2H), 3.30 (dt, *J* = 10.5, 2.8 Hz, 0.8H), 3.57 (dd, *J* = 10.5, 1.8 Hz, 0.2H), 3.74 (dd, *J* = 10.3, 1.8 Hz, 0.8H), 3.85 (s, 3H), 4.10 (d, *J* = 11.4 Hz, 0.8 H), 4.128 (d, *J* = 11.4 Hz, 0.2H), 4.130 (d, *J* = 11.4 Hz, 0.8H), 4.19 (d, *J* = 5.7 Hz, 0.2H), 4.88 (d, *J* = 6.0 Hz, 0.2H), 4.90 (d, *J* = 6.0 Hz, 0.8H), 6.44–6.55 (m, 2H), 6.90 (d, *J* = 6.9 Hz, 2H), 7.14 (d, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.99 (d, *J* = 8.2 Hz, 0.3H), 8.01 (d, *J* = 8.7 Hz, 1.7H); ^{13}C NMR ($CDCl_3$, 100 MHz, major rotamer) δ 31.0, 34.8, 47.0, 52.8, 55.4, 69.1, 76.2, 113.7 (2C), 121.8 (2C), 125.3, 129.2 (2C), 130.7, 131.7, 131.8 (2C), 135.3, 151.3, 155.6, 163.6, 165.9; HRMS (FAB) calcd for $C_{23}H_{24}NO_6$ $[M+H]^+$ 410.1598, found 410.1596.

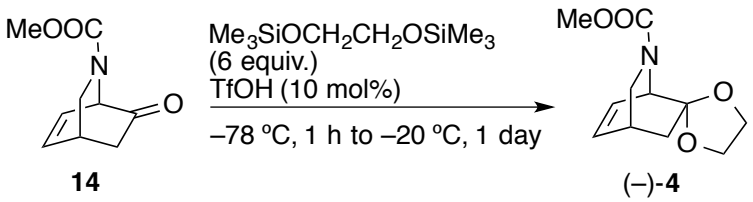
Methyl (1*R*,4*R*,7*S*)-7-Hydroxy-7-(hydroxymethyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (7): colorless oil, IR ($CHCl_3$) 1683, 1458, 1400, cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) mixture of rotamers (1/1) δ 1.33 (dt, *J*= 4.6, 2.8 Hz, 0.5H), 1.37 (dt, *J*= 4.6, 2.8 Hz, 0.5H), 1.47 (dd, *J*= 4.6, 2.8 Hz, 0.5H), 1.44 (dd, *J*= 4.8, 2.8 Hz, 0.5H), 2.79–2.88 (m, 1H), 3.04 (dt, *J*= 8.7, 2.3 Hz, 0.5H), 3.06 (dt, *J*= 8.7, 2.3 Hz, 0.5H), 3.31–3.32 (m, 2H), 3.42 (dt, *J*= 10.3, 1.8 Hz, 0.5H), 3.45 (dd, *J*= 10.3, 1.8 Hz, 0.5H), 3.71 (s, 1.5H), 3.72 (s, 1.5H), 4.66 (dd, *J*= 4.1, 3.7 Hz, 0.5H), 4.70 (dd, *J*= 5.5, 1.6 Hz, 0.5H), 6.39–6.48 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 32.2 and 32.4, 35.5 and 35.6, 47.8 and 48.2, 53.0 and 53.0, 53.7 and 54.1, 68.9, 78.0 and 78.3, 132.2 and 132.3, 135.9 and 135.9, 158.3 and 158.8; HRMS (FAB) calcd for $C_{10}H_{16}NO_4$ $[M+H]^+$ 214.1074, found 214.1071.



To a solution of diol **7** (250 mg, 1.17 mmol), Na_2HPO_4 (400 mg, 2.34 mmol) in EtOH (4 mL) and H_2O (8 mL) was added $NaIO_4$ (330 mg, 1.52 mmol) at 0 ºC and stirred for 2 h at same temperature. The reaction mixture was quenched by the successive addition of aqueous sodium thiosulfate (20 mL), and then reaction mixture was warmed up to

ambient temperature. The mixture was extracted with Et_2O (50 mL × 3). The combined organic layers were washed with brine (30 mL × 2) and dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 20:1) to give **14** in 80% yield (170 mg, 0.94 mmol).

Methyl (1*R*,4*R*)-7-oxo-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (14): IR ($CHCl_3$) 1736, 1699, 1448, 1889, 1283, 1113 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (3/2) δ 2.22 (s, 2H), 3.13–3.23 (m, 2H), 3.43–3.54 (m, 1H), 3.72 (s, 3H), 4.85 (d, *J*= 6.4 Hz, 0.6H), 5.02 (d, *J*= 5.9 Hz, 0.4H), 6.38–6.48 (m, 1H), 6.62–6.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.0 and 32.2, 36.4 and 36.5, 46.0 and 46.4, 52.8, 57.2 and 57.8, 127.7 and 128.3, 139.1 and 139.7, 155.2, 202.8 and 202.9; HRMS (FAB) calcd for $C_9H_{11}NO_3Na$ $[M+Na]^+$ 204.0631, found204.0633.



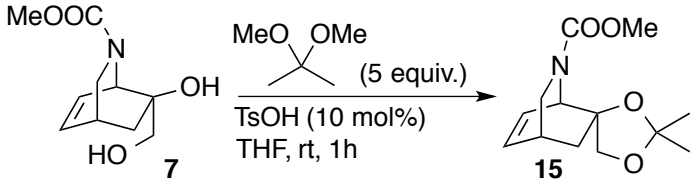
14 (–)-**4**

To a solution of ketone **14** (22 mg, 0.12 mmol) and ethylenedioxybis(trimethylsilane) (177 μL, 0.72 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of TfOH (10 μl, 0.01 mmol) in CH_2Cl_2 (0.5 mL) dropwise at –78 ºC and stirred for 1 h at same temperature.[5] The solution was warmed to –20 ºC and stirred for 1 d. The reaction mixture was quenched by a saturated $NaHCO_3$ aqueous solution (3 mL) and then warmed up to ambient temperature. The mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 1:1) to give acetal **4** in >99% yield (27 mg, 0.12 mmol).

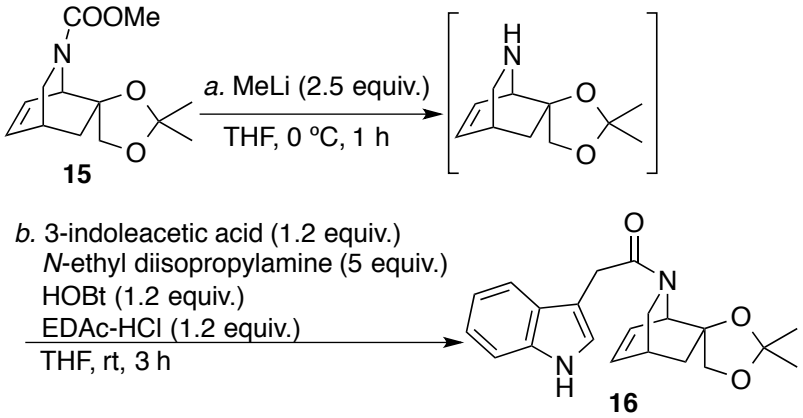
(–)-Methyl 2-azaspiro[bicyclo[2.2.2]oct[5]ene-7,2'-[1,3]dioxolane]-2-carboxylate (4):[6] Colorless oil; $[\alpha]^{26}_D$ –65 (c 0.40, $CHCl_3$) for 91% ee; IR ($CDCl_3$) 1696, 1455, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (2/1) δ 1.78–1.93 (m, 2H), 2.80–2.89 (m, 1H), 3.00 (dd, *J*= 11.8, 10.1 Hz, 1H), 3.36 (t, *J*= 9.8 Hz, 1H), 3.70 (s, 2H), 3.72 (s, 1H), 3.91–4.01 (m, 2H), 4.01–4.12 (m, 2H), 4.27 (d, *J*= 5.9 Hz, 0.3H), 4.69 (d, *J*= 5.9 Hz, 0.7H), 6.34–6.44 (m, 1H), 6.44–6.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.1 and 31.3, 37.8, 45.9 and 46.3, 49.8 and 50.5, 52.4, 64.1 and 64.3, 64.8, 111.0,

130.1 and 130.7, 135.3 and 135.8, 155.9 and 156.5; HRMS (FAB) calcd for $C_{11}H_{16}NO_4$ $[M+H]^+$ 226.1074, found 226.1077.

Derivatization of 7 to (+)-5 (Scheme 7)



To a solution of diol **7** (190 mg, 0.89 mmol) and 2,2-dimethoxy propane (560 μL, 4.45 mmol) in THF (5 mL) was added TsOH (15.2 mg, 0.09 mmol) at ambient temperature and stirred for 1 h at same temperature. The reaction mixture was quenched with a saturated $NaHCO_3$ aqueous solution (10 mL). The mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 1:1) to give **15** in 86% yield (195 mg, 0.77 mmol). **methyl(1*R*,2*S*,4*R*)-2',2'-dimethyl-6-azaspiro[bicyclo[2.2.2]octane-2,4'-[1,3] dioxolan]-7-ene-6-carboxylate (15)**: IR ($CHCl_3$) 1699, 1451, 1397 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (1/1) δ 1.33 (s, 1.5H), 1.35 (s, 1.5H), 1.46 (s, 1.5H), 1.53 (s, 1.5H), 1.57–1.66 (m, 1H), 1.81 (dd, *J*= 5.3, 2.3 Hz, 0.5H), 1.84 (dd, *J*= 5.0, 2.3 Hz, 0.5H), 2.75–2.84 (m, 1H), 3.04 (dt, *J*= 10.5, 2.8 Hz, 0.5H), 3.07 (dt, *J*= 10.5, 2.8 Hz, 0.5H), 3.44 (dd, *J*= 10.1, 1.8 Hz, 1H), 3.49 (dd, *J*= 8.7, 4.6 Hz, 1H), 3.69 (s, 3H), 3.82 (t, *J*= 9.2 Hz, 1H), 4.55 (d, *J*= 6.0 Hz, 0.5H), 4.74 (d, *J*= 6.0 Hz, 0.5H), 6.31–6.38 (m, 1H), 6.38–6.48 (m, 1H), ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.0 and 26.2, 27.1 and 27.5, 30.1 and 31.2, 36.1 and 36.3, 46.5 and 46.7, 52.0 and 52.2, 52.4 and 53.1, 73.3 and 73.3, 83.7 and 83.8, 109.4 and 109.5, 130.5 and 131.1, 136.1 and 136.7, 155.9 and 156.3; HRMS (FAB) calcd for $C_{13}H_{20}NO_4$ $[M+H]^+$ 254.1387, found 254.1385.

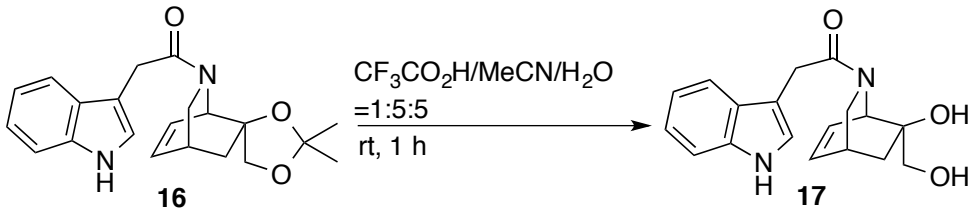


To a solution of **15** (65 mg, 0.26 mmol) in THF (1 mL) was added MeLi (0.56 mL, 1.14 M in Et_2O) at 0 ºC and stirred for 30 min at same temperature. The reaction mixture was quenched with a saturated NH_4Cl aqueous solution (2 mL) and then warmed up to ambient temperature. To the mixture was added 1 M NaOH aqueous solution untile hydrogen ion concentration reached higher than pH7. The resultant mixture was extracted with Et_2O (10 mL × 3) and CH_2Cl_2 (10 mL× 2). The combined organic layers were dried over Na_2SO_4, filtrated and concentrated.

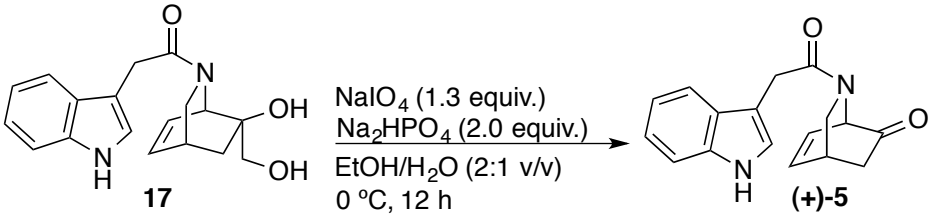
To a solution of the crude product, *N*,*N*-diisopropylethylamine (88 μL, 0.52 mmol), HOBt (35 mg, 0.26 mmol) and 3-indole acetic acid (45 mg, 0.26 mmol) in THF (2 mL) was added EDAC (49 mg, 0.26 mmol) at 0 ºC and stirred for 3 h at same temperature. The resultant mixture was poured a saturated $NaHCO_3$ aqueous solution (15 mL) and washed with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 1:1 to 0:1) to give **16** in 89% yield (81 mg, 0.23 mmol).

1-((1*R*,2*S*,4*R*)-2',2'-dimethyl-6-azaspiro[bicyclo[2.2.2]octane-2,4'-[1,3]dioxolan]-7-en-6-yl)-2-(1*H*-indol-3-yl)ethan-1-one (16): IR ($CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of rotamers (3/2) δ 1.36 (s, 1.8H), 1.38 (s, 1,2H), 1.51 (s, 1.2H), 1.54 (s, 1.8H), 1.62 (dt, *J*= 13.8, 2.8 Hz, 0.6H), 1.71 (dt, *J*= 13.3, 2.8 Hz, 0.4H), 1.82 (dd, *J*= 13.7, 2.8 Hz, 0.6H), 1.91 (dd, *J*= 13.7, 2.3 Hz, 0.4H), 2.81–2.88 (m, 0.4H), 2.74–2.81 (m, 0.6H), 3.14–3.23 (m, 1H), 3.49 (d, *J*= 9.2 Hz, 0.5H), 3.56 (d, *J*= 9.2 Hz, 0.5H), 3.58 (d, *J*= 3.2 Hz, 0.6H), 3.61 (d, *J*= 1.8 Hz, 0.6H), 3.72–3.74 (m, 1H), 3.78 (d, *J*= 9.2 Hz, 0.5H), 3.81 (d, *J*= 17.4 Hz, 0.5H), 3.85 (d, *J*= 9.2 Hz, 0.5H), 4.01 (d, *J*= 15.6 Hz, 0.5H), 4.35 (d, *J*= 6.0 Hz, 0.4H), 5.34 (dd, *J*= 6.0, 1.4 Hz, 0.6H), 6.04 (t, *J*= 6.4 Hz, 0.4H), 6.32–6.45 (m, 1.6H), 6.96 (s, 0.4H), 7.07–7.20 (m, 2.6H), 7.31 (d, *J*= 8.2 Hz, 0.6H), 7.32 (d, *J*= 7.8 Hz,

0.4H), 7.56 (d, *J*= 7.1 Hz, 0.6H), 7.58 (d, *J*= 7.6 Hz, 0.4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7 and 26.5, 27.3 and 27.6, 31.0, 31.6 and 31.8, 36.4 and 38.5, 46.9 and 47.5, 50.3, 56.3, 73.4 and 74.4, 83.5 and 83.7, 108.9 and 109.7, 109.9 and 111.1, 118.6, 119.2 and 119.4, 121.8 and 121.9, 122.6 and 122.8, 127.2 and 127.4, 129.6 and 131.3, 136.1, 136.3 and 137.7, 170.3 and 170.7; HRMS (FAB) calcd for $C_{21}H_{25}N_2O_3$ $[M+H]^+$ 353.1860, found 353.1860.



To a solution of **16** (67 mg, 0.19 mmol) in MeCN (0.5 mL) and H_2O (0.5 mL) was added trifluoroacetic acid (0.5 mL) dropwised at ambient temperature and stirred for 1 h at same temperature. The resultant mixture was quenched with a saturated $NaHCO_3$ aqueous solution. The mixture was washed with EtOAc (20 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–MeOH 1:0 to 5:1) to give **17** in >99% yield (59 mg, 0.19 mmol). **1-((1*R*,4*R*,7*S*)-7-hydroxy-7-(hydroxymethyl)-2-azabicyclo[2.2.2]oct-5-en-2-yl)-2-(1*H*-indol-3-yl)ethan-1-one (17)**: yellow participate IR (KBr) 3397, 1606, 1458 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) mixture of rotamers (3/2) δ 1.29 (t, *J*= 2.8 Hz, 0.3H), 1.33 (t, *J*= 2.7 Hz, 0.7H), 1.43 (d, *J*= 2.3 Hz, 0.7H), 1.46 (d, *J*= 2.3 Hz, 0.3H), 2.78–2.83 (m, 1H), 3.08 (dt, *J*= 11.4, 2.8 Hz, 0.5H), 3.21–3.28 (m, 2.5H), 3.47 (dd, *J*= 11.7, 1.8 Hz, 0.5H), 3.63 (dd, *J*= 10.8, 1.8 Hz, 0.5H), 3.72 (d, *J*= 15.6 Hz, 0.4H), 3.76 (d, *J*= 2.8 Hz, 1H), 4.16 (d, *J*= 15.6 Hz, 0.6H), 4.66 (d, *J*= 6.0 Hz, 0.6H), 5.21 (dd, *J*= 5.3, 1.8 Hz, 0.4H), 6.05 (ddd, *J*= 7.8, 6.4, 1.4 Hz, 0.5H), 6.33 (t, *J*= 7.4 Hz, 0.5H), 6.38 (dt, *J*= 5.5, 2.8 Hz, 1H), 6.99 (dd, *J*= 7.8, 7.4 Hz, 1H), 7.08 (dd, *J*= 8.7, 7.4 Hz, 1H), 7.06 (s, 0.4H), 7.14 (s, 0.6H), 7.32 (d, *J*= 7.8 Hz, 1H), 7.52 (d, *J*= 7.8 Hz, 0.5H), 7.58 (d, *J*= 7.8 Hz, 0.5H); ^{13}C NMR (CD_3OD, 100 MHz) δ 32.0 and 32.2, 32.7, 35.5 and 35.8, 48.1, 51.9, 56.4, 68.8 and 68.9, 77.9 and 78.1, 109.5, 112.2, 119.4 and 119.6, 119.8, 122.5 and 122.6, 124.1 and 124.2, 128.5, 131.4 and 132.0, 136.4 and 138.0, 174.0; HRMS (FAB) calcd for $C_{18}H_{21}N_2O_3$ $[M+H]^+$ 313.1547, found 313.1549.

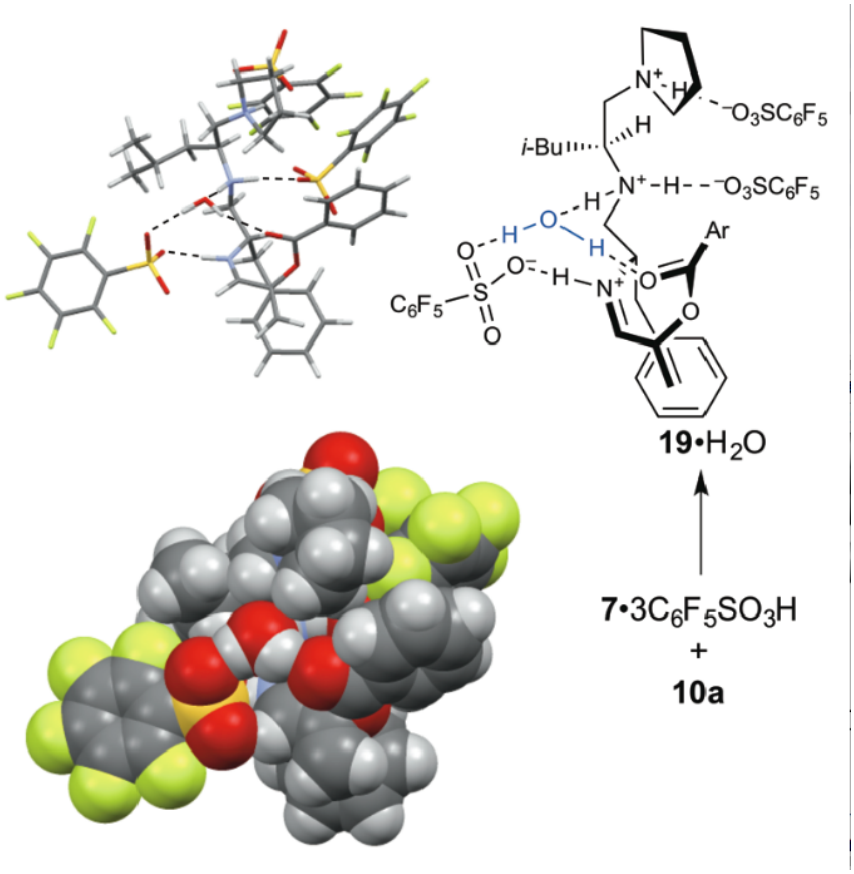


To a solution of **17** (35 mg, 0.11 mmol) and Na_2HPO_4 (32 mg, 0.22 mmol) in EtOH (0.26 mL) and H_2O (0.52 mL) was added $NaIO_4$ (31 mg, 0.15 mmol) at 0 ºC and stirred for 12 h at same temperature. The reaction mixture was quenched by the successive addition of aqueous sodium thiosulfate, and then reaction mixture was warmed up to ambient temperature. The mixture was washed with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 1:1 to 0:1) to give **5** in 85% yield (27 mg, 0.10 mmol). **(+)-(1*R*,4*R*)-2-(2-(1*H*-indol-3-yl)acetyl)-2-azabicyclo[2.2.2]oct-7-en-6-one (5)**:[6] yellow participate; $[\alpha]^{24}_{D}$ +88 (c 1.20, $CHCl_3$) for 91% ee; IR ($CHCl_3$) 3349, 1716, 1655, 1389, 1229 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) mixture of rotamers (3/2) δ 2.12–2.24 (m, 2H), 3.14–3.21 (m, 1H), 3.23 (d, *J*= 11.5 Hz, 0.4H), 3.35 (d, *J*= 9.2 Hz, 0.6H), 3.55–3.63 (m, 1H), 3.74 (s, 1H), 3.80 (d, *J*= 15.6 Hz, 0.5H), 3.87 (d, *J*= 15.6 Hz, 0.5H), 4.74 (d, *J*= 6.4 Hz, 0.4H), 5.45 (d, *J*= 6.4 Hz, 0.6H), 6.26 (dd, *J*= 7.1, 6.9 Hz, 0.4H), 6.41 (dd, *J*= 7.1, 6.9 Hz, 0.6H), 6.67 (dt, *J*= 6.9, 6.4 Hz, 1H), 7.09 (dd, *J*= 7.8, 7.6 Hz, 1H), 7.17 (dd, *J*= 7.8, 7.6 Hz, 1H), 7.05 (s, 1H), 7.36 (d, *J*= 8.2 Hz, 1H), 7.55 (d, *J*= 8.2 Hz, 0.5H), 7.58 (d, *J*= 7.8 Hz, 0.5H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 31.1 and 31.4, 31.7 and 32.3, 36.1 and 36.2, 45.9 and 46.6, 55.2, 59.8, 108.1 and 108.5, 110.8 and 110.8, 118.2 and 118.4, 119.0, 121.6 and 121.7, 122.4 and 122.5, 126.8 and 127.8, 135.8, 139.0 and 140.0, 169.8 and 169.8, 202.2 and 202.4; HRMS (FAB) calcd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$ 281.1285, found 218.1289.

Computational Methods

The quantum chemical calculations were performed using the Gaussian09[7] suites of programs. The structure in Figure 2.1 was optimized using density functional theory (DFT) methods employing three nonlocal functionals (B3LYP).[8] The standard 6-31G(d) basis set was used for geometry optimizations of the stable structures. The optimized geometries are also subjected to full frequency analyses at the same level of

theory to verify the nature of the stationary points. Equilibrium geometries are characterized by the absence of imaginary frequencies.



19•H_2O

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Imaginary frequencies: 0
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(Hartree/Particle)
 Thermal correction to Energy=                    0.976990
 Thermal correction to Enthalpy=                  0.977934
 Thermal correction to Gibbs Free Energy=         0.770864
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 Sum of electronic and thermal Energies=             -5575.299228
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                    Standard orientation:
 ---------------------------------------------------------------------
 Center     Atomic      Atomic           Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
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     2          6           0        1.570473   -2.670595   -3.956805
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123	1	0	3.919159	5.070489	-1.080505
124	1	0	1.673686	4.455433	-0.234929

References and Notes

1. (a) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321. (b) For a recent review of 1,2-dihydropyridine syntheses: Silva, E. M.; Varandas, P. A. M. M.; Silva, A. M. S. *Synthesis* **2013**, *45*, 3053. (c) Sundberg, R. J.; Amat, M.; Fernando, A. M. *J. Org. Chem.* **1987**, *52*, 3151.
2. Effenberger, F.; Mück, A. O.; Bessey, E. *Chem. Ber.* **1980**, *113*, 2086.
3. Borak, J. B.; Falvey, D. E. *J. Org. Chem.* **2009**, *74*, 3894.
4. For the oxidation of aldehydes with I_2/KOH, see: (a) Yamada, S.; Morizono, D.; Yamamoto, K. **1992**, *33*, 4329. (b) Jones, B. D.; Clair, J. L.; Moore, C. E.; Rheingold, A. L.; Burkart, M. D. *Org. Lett.* **2010**, *12*, 4516.
5. a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358; b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899–3910.
6. Moisan, L.; Thuéry, P.; Nicolas, M.; Doris, E.; Rousseau, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 5334–5336.
7. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, A˜.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *GAUSSIAN 09 Revision C01*, Gaussian, Inc., Wallingford, CT, 2009.
8. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *96*, 5648. (b) Stevens, P. J.; Devlin, J. F.; Chablowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623-11627. (c) Tirado-Rives, J.; Jorgensen, W. L. *J. Chem. Theory Comput.* **2008**, *4*, 297−306.

Chapter 3

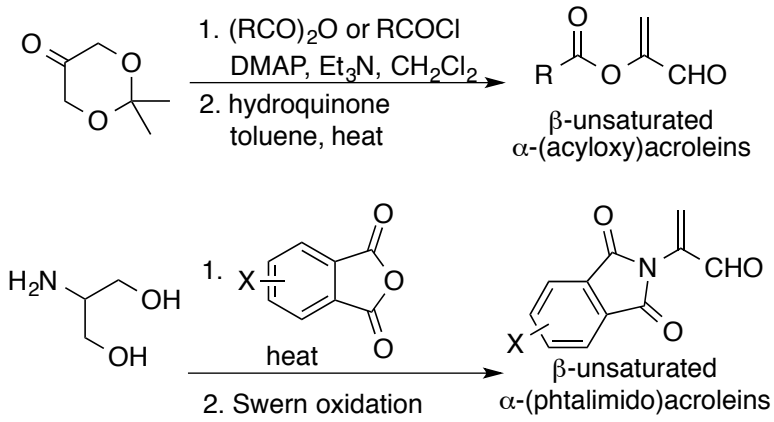
α-Heterosubstituted β-Alkylacroleins as Useful Multisubstituted Dienophiles for Enantioselective Diels–Alder Reactions

Abstract: We synthesized the dienophiles α-(*N*,*N*-diisopropylcarbamoyloxy)-β-alkylacroleins and α-(acylamino) crotonaldehydes. The enantioselective Diels–Alder reaction of these dienophiles gave the corresponding multisubstituted adducts with high enantioselectivity (up to 92%ee). The present method provides a facile route to structurally complicated chiral building blocks that contain a quaternary carbon atom substituted with an oxygen- or nitrogencontaining moiety.

3-1 Introduction

The development of efficient, short-step syntheses of highly functionalized bioactive natural compounds is currently one of the most important issues in organic synthesis. The enantioselective Diels–Alder reaction is a powerful method for the short-step synthesis of complicated organic compounds, as this reaction forms two carbon–carbon single bonds with the construction of multiple stereogenic centers.[1] We previously synthesized β-unsubstituted α-(acyloxy)acroleins[2] and α-(phthalimido)acroleins[3] according to the known procedure (Scheme 3.1). We developed an organoammonium salt catalyzed enantioselective Diels–Alder reaction and [2+2] cycloaddition reaction of these dienophiles.[4]

Scheme 3.1. Syntheses of β-Unsubstituted α-(Acyloxy)acroleins and α-(Phthalimido)acroleins



These β-unsubstituted α-heterosubstituted acroleins are useful dienophiles for the synthesis of chiral building blocks that contain quaternary carbon atoms substituted with heteroatoms. With respect to the synthesis of multisubstituted chiral cyclohexenes, α-heterosubstituted β-alkylacroleins should be useful dienophiles for the enantioselective Diels–Alder reaction, as the corresponding adducts are useful chiral building blocks for the synthesis of a variety of bioactive natural compounds.[5,6] For example, the Diels–Alder adducts would be promising candidates as chiral building blocks for the synthesis of artemisinin[7] (for Y=O) and tetrodotoxin[8] (for Y=NH) (Figure 3.1).

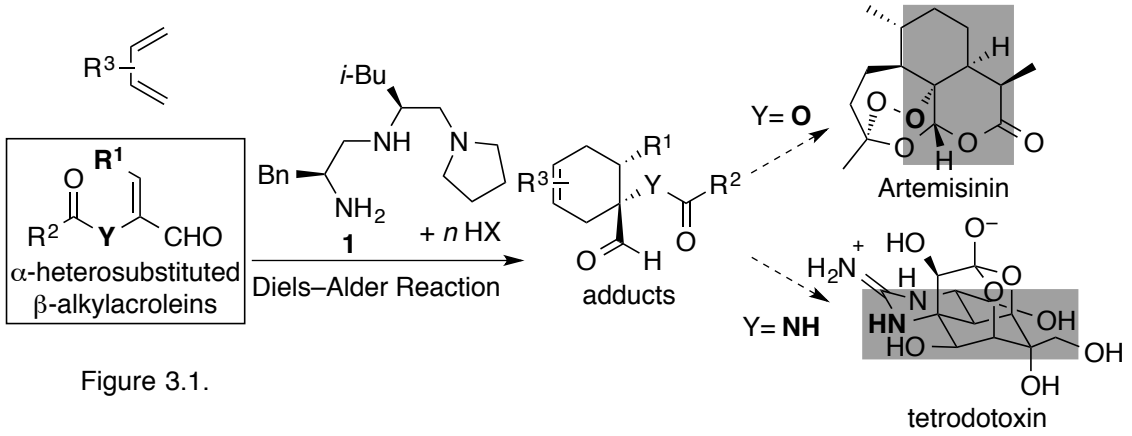


Figure 3.1.

Figure 3.1. α-Heterosubstituted β-alkylacroleins as useful multisubstituted dienophiles for enantioselective Diels–Alder reactions

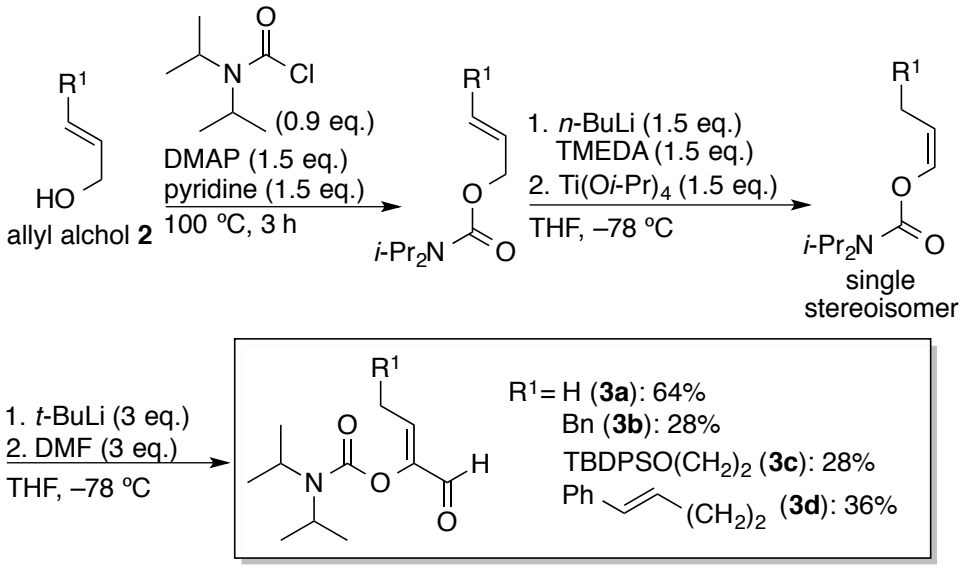
However, the Diels–Alder reaction of α-(acyloxy)- and α-(acylamino)-β-alkylacroleins has not yet been reported. Herein, we describe the synthesis of α-heterosubstituted β-alkylacroleins as highly functionalized dienophiles, and the enantioselective Diels–Alder reaction of these compounds catalyzed by the chiral triammonium salt of **1**.

3-2 Results and discussion

The present study gives new entries to multisubstituted chiral cyclohexenes, which are potential chiral building blocks for the synthesis of bioactive natural compounds. From our previous results showed that the electron-donating nature of the *O*-acyl groups is very important for obtaining high enantioselectivity in the Diels–Alder reaction of α-(acyloxy)acroleins.[4] We expected that an *N*,*N*-diisopropylcarbamoyl group should be an efficient protecting group for the α-oxygen of the substituted β-alkylacroleins. We began our study with the synthesis of α-(*N*,*N*-diisopropylcarbamoyloxy)-β-alkylacroleins **3**. As the method used to synthesize β-unsubstituted α-(acyloxy)acroleins could not be applied to the synthesis of **3**, a new route to **3** had to be developed. The most important issue in the synthesis of **3** was the selective formation of the carbon–carbon double bond. We planned to use stereoselective carbon–carbon double bond migration[9] of allylic carbamates for the synthesis of this unsaturated bond. The synthesis of **3** began with carbamoylation of

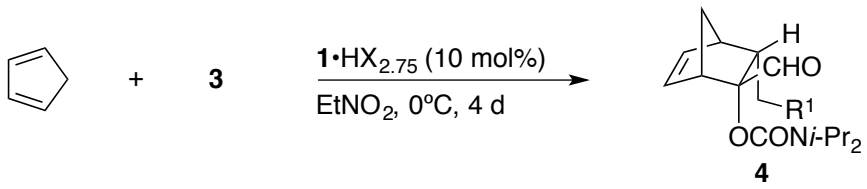
allylic alcohols **2** with diisopropylcarbamic chloride (*i*Pr_2NCOCl) in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP, Scheme 3.2).

Scheme 3.2. Synthesis of α-(*N*,*N*-Diisopropylcarbamoyloxy)-β-Alkylacroleins **3**



As expected, the carbon–carbon double bond migration of the allylic carbamates successfully gave the corresponding *Z*-vinyl carbamates as single stereoisomers. Formylation of the vinyl carbamates[10] with *t*-BuLi and *N*,*N*-dimethylformamide (DMF) gave (*Z*)-α-(*N*,*N*-diisopropylcarbamoyloxy)-β-alkylacroleins **3** as single stereoisomers in overall yields of 28–64% from **2**. With the desired α-(*N*,*N*-diisopropylcarbamoyloxy)-β-alkylacroleins **3** in hand, we investigated the chiral triammonium salt-catalyzed Diels–Alder reaction of **3** (Table 1).

Table 3.1. Enantioselective Diels–Alder Reaction of α-(*N*,*N*-Diisopropylcarbamoyloxy)-β-alkylacroleins **3**[a]



Entry	**3**	HX	Yield [%]	*exo*/*endo*	ee [%][b]
1	**3a**	$C_6F_5SO_3H$	37	97:3	92
2	**3a**	TfOH	56	96:4	87
3[c]	**3a**	TfOH	85	95:5	83
4	**3b**	$C_6F_5SO_3H$	55	91:9	86
5	**3b**	TfOH	93	93:7	89
6	**3c**	TfOH	70	91:9	84
7	**3d**	TfOH	51	93:7	81

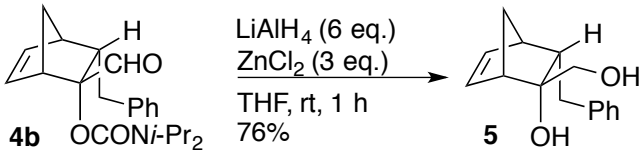
[a] The reaction of cyclopentadiene (4 equiv) with **3** (0.1 mmol) was conducted in the presence of **1**·$HX_{2.75}$ (10 mol%) in $EtNO_2$ at 0 ºC for 4 days. [b] ee Value of the major diastereomer. [c] The reaction was conducted on a 3.5 mmol

The reaction of **3** with cyclopentadiene (4 equiv) was conducted in $EtNO_2$ at 0 ºC. When the reaction of **3a** (R^1=H) was conducted in the presence of **1**•$(C_6F_5SO_3H)_{2.75}$ (10 mol%), the corresponding *exo* adduct **4a** was obtained in 92% ee, although the yield was low (37%, Table 1, entry 1). The use of trifluoromethansulfonic acid (TfOH), which is more acidic than $C_6F_5SO_3H$, improved the yield of **4a** to 56% without a significant decrease in enantioselectivity (87% ee, Table 1, entry 2). The present protocol could be conducted on a submillimole scale (Table 1, entry 3). For the reaction of **3b** (R^1=Ph), the use of TfOH again gave better results than $C_6F_5SO_3H$ (93% yield, 89% ee, Table 1, entries 4 and 5). The Diels–Alder reaction of **3c** and **3d** gave the corresponding *exo* adducts **4c** and **4d** with good enantioselectivity (Table 1, entries 6 and 7). A *tert*-butyldiphenylsilyl (TBDPS) group in **3c** was compatible under the present reaction conditions. The configuration of the carbon–carbon double bond in **3d** was retained during the reaction. Despite the good

reactivity of **3** for the reaction with cyclopentadiene, compound **3** reacted poorly with other dienes, such as cyclohexadiene and 2,3-dimethylbutadiene (<5% yield).

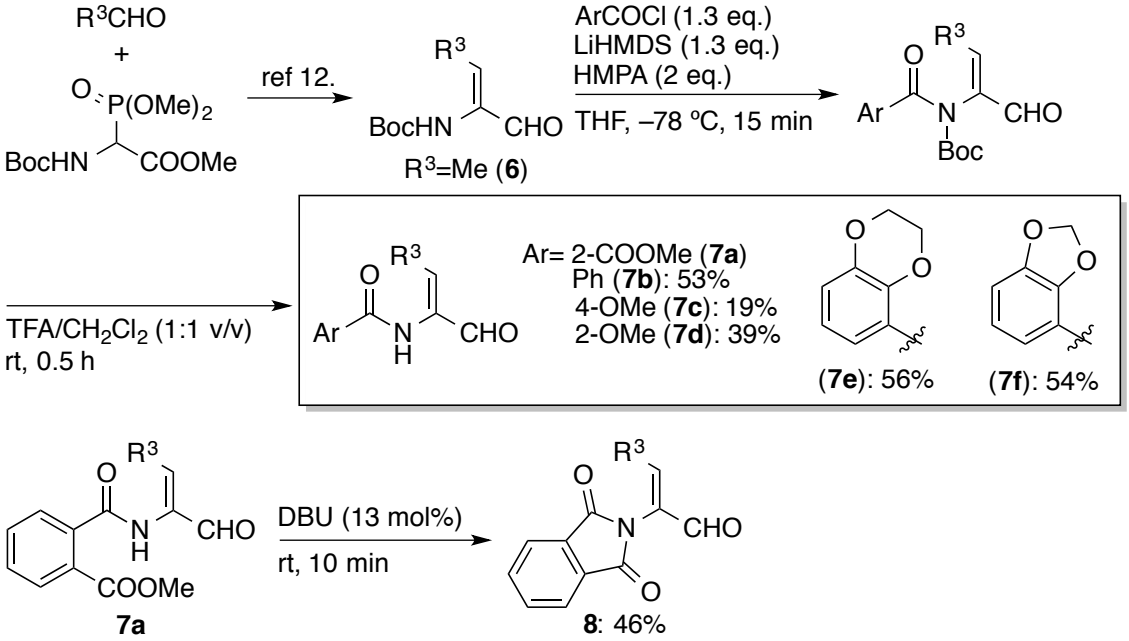
The carbamoyl group in the Diels–Alder adducts **4** can removed by reductive cleavage. For example, the treatment of **4b** with $LiAlH_4$ (6 equiv) and $ZnCl_2$ (3 equiv)[11] gave diol 5 in 76% yield (Scheme 3.3).

Scheme 3.3. Deprotection of the Carbamoyl Group of **4b**



We next focused on the synthesis of α-nitrogen-substituted β-alkylacroleins as dienophiles for the enantioselective Diels–Alder reaction. According to our previous results,[4e] we first synthesized (*Z*)-α-phthalimidocrotonaldehyde **8** starting from (*Z*)-*tert*-butyl(1-oxobut-2-en-2-yl)carbamate **6** (R^3=Me)[12] (Scheme 3.4).

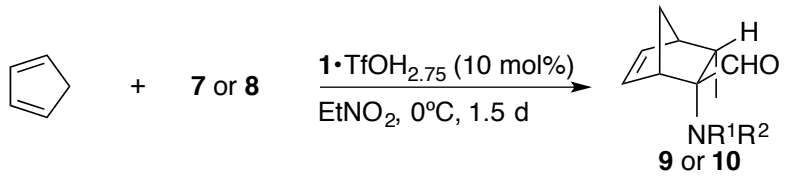
Scheme 3.4. Synthesis of (*Z*)-α-(Acylamino)crotonaldehydes **7** and (*Z*)-α-(Phthalimido)crotonaldehyde **8**.



According to the method reported by Burk *et al*, a variety of β-alkyl and β-aryl derivatives of **6** can be synthesized with complete *Z*-selectivity by changing the starting aldehyde (R^3CHO). The acylation of the carbamoyl nitrogen atom[13] of **6** with methyl 2-(chlorocarbonyl) benzoate and subsequent removal of the *tert*-butyloxycarbonyl (Boc) group gave **7a**. Treatment of **7a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 13 mol%) gave **8** in an overall yield of 46%.

When the reaction of cyclopentadiene with **8** was conducted in the presence of **1**•$TfOH_{2.75}$ (10 mol%), the corresponding adduct **9** was obtained in only 17% yield with poor distereo- and enantioselectivity (Table 3.2, entry 1).

Table 3.2. Enantioselective Diels–Alder Reaction of α-(Phthalimido)crotonaldehyde **8** and α-(Acylamino)crotonaldehydes **7**.[a]



Entry	**7** or **8**	Adduct	Yield [%]	exo/endo	ee [%]
1	**8**	**9**	17	66:34[c]	54
2[d]	**7b**	**10b**	67	84:16	72
3	**7c**	**10c**	52	84:16	72
4	**7d**	**10d**	75	98:2	70
5	**7e**	**10e**	85	97:3	77
6[e]	**7e**	**10e**	47	97:3	80
7	**7f**	**10f**	81	96:4	79

[a] The reaction of cyclopentadiene (4 equiv) with **7** or **8** (0.1 mmol) was conducted in the presence of **1**·$TfOH_{2.75}$ (10 mol%) in $EtNO_2$ at 0 ºC for 1.5 days. [b] ee Value of the major diastereomer. [c] The relative configuration of **9** was not determined. [d] The reaction was conducted for 4 days. [e] The reaction was conducted at –20 ºC for 5 days.

To improve the reactivity and enantioselectivity, we next synthesized α-(acylamino)crotonaldehydes **7** according to the method used for the synthesis of **8**. When the reaction of (*Z*)-α-(benzoylamino)crotonaldehyde **7b** was conducted under the

same conditions described above, the corresponding *exo* adduct **7b** was obtained in 67% yield, and the diastereo- and enantioselectivity were improved (Table 2, entry 2). Based on our previous results,[4] we next examined the effect of substituting the benzoyl group with an electron-donating moiety. Although the introduction of a methoxy group at the 4-position did not improve the enantioselectivity (Table 2.2, entry 3), the use of a 2-methoxybenzoyl group was associated with higher reactivity (75% yield) and excellent diastereoselectivity (dr 98:2) (Table 2, entry 4). The hydrogen bonding between the 2-methoxy group and the NH proton might have a beneficial effect and increase the diastereoselectivity. Indeed, the 1H NMR chemical shift of the NH proton of **7d** was shifted downfield by 1.88 ppm (**7d**: δ=9.59 ppm, δ=7c: 7.71 ppm). Furthermore, the use of **7e** and **7f** bearing a bicyclic benzoyl group improved both the yields and enantioselectivity (Table 2.2, entries 5 and 6). When the reaction of **7e** with cyclopentadiene was conducted at –20 ºC, the corresponding adduct **10e** was obtained in 80% ee. The reactivity of β-substituted α-(acylamino)acroleins is highly dependent on the β substituent. Thus, the β-phenyl derivative of **7f** did not react with cyclopentadiene.

3-3. Conclusion

We synthesized the dienophiles α-(*N*,*N*-diisopropylcarbamoyloxy)-β-alkylacroleins **3** and α-(acylamino)crotonaldehydes **7**. The enantioselective Diels–Alder reaction of these dienophiles gave the corresponding multisubstituted adducts with high enantioselectivity (up to 92%ee). The present method provides a facile route to structurally complicated chiral building blocks that contain a quaternary carbon atom substituted with an oxygen- or nitrogencontaining moiety. Although β-unsubstituted α-(acyloxy)acroleins, α-(phthalimido)acroleins are highly reactive with a variety of dienes, the introduction of an alkyl group on their β positions significantly decreased their reactivity. The α-heterosubstituted β-alkylacroleins react well with cyclopentadiene, but they did not react with other dienes, such as cyclohexadiene and 2,3-dimethylbutadiene.

References and Notes

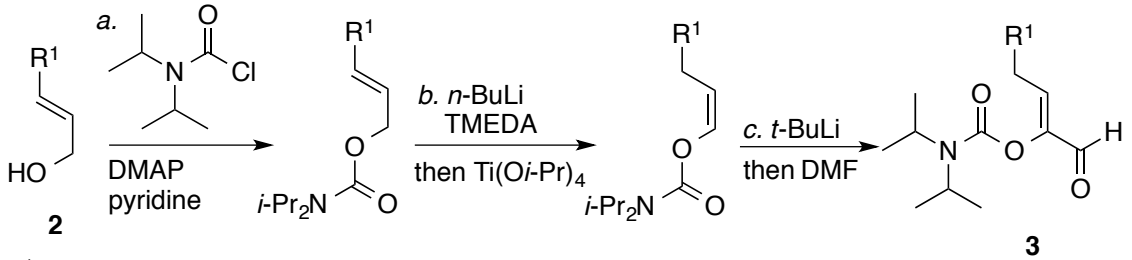
1. (a) Ishihara, K.; Sakakura, A. In *Stereoselective Synthesis*; Evans, P. A., Ed.; George Thieme Verlag KG: Stuttgart, 2011; Vol. 3, pp. 67 –123.; (b) Corey, E. J. *Angew. Chem. Int. Ed.* **2009**, 48, 2100; (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668; (d) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Ed.s.; Pergamon: Oxford, 1991; Vol. 5, pp. 315 –399.
2. Funk, R. L.; Yost, K. J. III. *J. Org. Chem.* **1996**, *61*, 2598.
3. Harada, H.; Morie, T.; Hirokawa, Y.; Kato, S.; *Chem. Pharm. Bull.* **1996**, *44*, 2205.
4. Ish**i**hara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. Additions and corrections: Ishihara, K; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 13079.; (b) Sakakura, A.; Suzuk**i**, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229.; (c) Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457.; (d) Ish**i**hara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930.; (e) Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893.
5. For recent examples of diastereoselective Diels–Alder reactions of α-heterosubstituted β-alkyldienophiles, see: (a) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331. (b) He, Y.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3689; (c) Mondal, S.; Yadav, R. N.; Ghosh, S. *Org. Lett.* **2011**, *13*, 6078. (d) Funk, R. L.; Belmar, J. *Tetrahedron Lett.* **2012**, *53*, 176.
6. For the asymmetric Diels –Alder reaction of (*Z*)-olefinic azalactones, see: H. Jiang, B. Gschwend, Ł. Albrecht, S. G. Hansen, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 9032.
7. Avery, M. A.; Fan, P.; Karle, J. M.; Bonk, J. D.; Miller, R.; Goins, D. K. *J. Med. Chem.* **1996**, *39*, 1885.
8. (a) Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537. (b) Chau, J.; Ciufolini, M. A.; *Mar. Drugs* **2011**, *9*, 2046.
9. (a) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; Hülsen, E. *Chem. Ber.* **1985**, *118*, 2822.; (b) Behrens, K.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Eur. J. Org. Chem.* **1998**, 2397.

10. Bou Chedid, R.; Brümmer, M.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 3131.
11. Marr, F.; Hoppe, D. *Org. Lett.* **2002**, *4*, 4217.
12. Burk, M. J.; Johnson, N. B.; Lee, J. R. *Tetrahedron Lett.* **1999**, *40*, 6685.
13. Hernández, J. N.; Martín, V. S. *J. Org. Chem.* **2004**, *69*, 3590.

Experimental Section

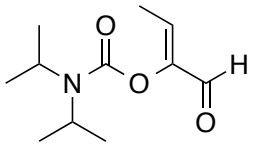
General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m =multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 spectrometer (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm × 25 cm), Daicel CHIRALCEL OZ-H (4.6 mm × 25 cm), Daicel CHIRALPAK AD-3 (4.6 mm × 25 cm), Daicel CHIRALPAK AS-3 (4.6 mm × 25 cm), Daicel CHIRALPAK IA (4.6 mm × 25 cm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on JEOL JMS-700 spectrometer (for FAB) or JEOL JMS-T100GCV spectrometer (for EI). In experiments that required dry solvent, tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF) and dichloromethane (CH_2Cl_2) were purchased from Kanto, TCI or Wako as the "anhydrous." Nitroethane ($EtNO_2$), *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) and triethylamine (Et_3N) were freshly distilled from calcium hydride. $ZnCl_2$ was dried before use by heating under reduced pressure. Other simple chemicals were analytical-grade and obtained commercially.

Synthesis of α-carbamoyl-β-alkylacroleins 3



2 **3**

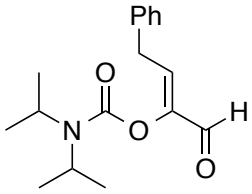
R^1 = H (**2a**)
Bn (**2b**)
TBDPSO$(CH_2)_2$ (**2c**)
Ph $(CH_2)_2$ (**2d**)



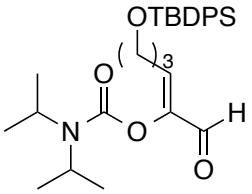
(*Z*)-1-Oxobut-2-en-2-yl Diisopropylcarbamate (3a):

To a solution of allyl alcohol (0.41 mL, 6.0 mmol) and DMAP (73.3 mg, 0.60 mmol) in pyridine (0.61 mL, 7.5 mmol) was added *N*,*N*-diisopropylcarbamic chloride (0.82 g, 5.0 mmol) at ambient temperature, and the mixture was heated at 100 ºC for 3 h. After the reaction mixture was cooled to ambient temperature, 1 M aqueous HCl (15 mL) was added, and the mixture was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with water (20 mL × 2), dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 20:1) to give allyl diisopropylcarbamate[1] in 84% yield (0.78 g, 4.2 mmol). According to the Hoppe's procedure,[2] to a solution of TMEDA (0.75 mL, 5.1 mmol) in THF (15 mL) was added a solution of *n*-BuLi in hexane (1.6 M, 3.2 mL, 5.1 mmol) at –78 ºC, and the mixture was stirred for 10 min. A solution of allyl diisopropylcarbamate (0.78 g, 4.2 mmol) in THF (3 mL) was slowly introduced to the mixture, and stirred for 1 h at the same temperature. To the resultant mixture was added a solution of Ti(O*i*-Pr)$_4$ (1.61 mL, 5.5 mmol) in THF (3 mL) dropwise, and the mixture was stirred for 1 h at –78 ºC. The reaction was quenched by the successive addition of MeOH (3 mL) and saturated aqueous Rochelle salt (5 mL), and then the reaction mixture was warmed to ambient temperature. The mixture was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with water (20 mL × 2), dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 20:1) to give (*Z*)-prop-1-en-1-yl

diisopropylcarbamate[1] in 84% yield (0.65 g, 3.5 mmol). To a solution of *t*-BuLi (1.6 M, 6.6 mL, 10.5 mmol) in THF (10 mL) was added a solution of (*Z*)-prop-1-en-1-yl diisopropylcarbamate (0.65 g, 3.5 mmol) in THF (3 mL) at –78 ºC. After stirred for 30 min, DMF (0.80 mL, 10.5 mmol) was added to the reaction mixture. After stirred for additional 30 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl aq (5 mL), and the reaction mixture was allowed to warm to ambient temperature. The mixture was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with water (20 mL × 2), dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give 3a in 91% yield (0.66 g, 3.2 mmol). **3a**: Colorless amorphous powder; IR (KBr) 1710, 1437, 1367, 1284, 1210, 1125, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.37 (m, 12H), 1.93 (d, *J* = 6.9 Hz, 3H), 3.90 (br s, 1H), 4.07 (br s, 1H), 6.40 (q, *J* = 6.9 Hz, 1H), 9.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1, 20.3 (2C), 21.4 (2C), 46.2, 47.0, 136.2, 149.1, 152.1, 186.0; HRMS (FAB) calcd for $C_{11}H_{20}NO_3$ $[M+H]^+$ 214.1443, found 214.1470.

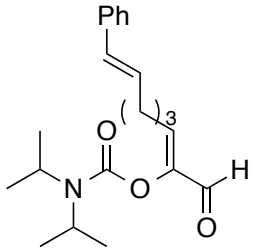


(*Z*)-1-Oxo-4-phenylbut-2-en-2-yl Diisopropylcarbamate (3b): Compound **3b** was prepared from cinnamyl alcohol according to the procedure for the synthesis of **3a**. **3b**: Colorless oil; IR ($CHCl_3$) 1700, 1438, 1370, 1281, 1211, 1148, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.43 (m, 12H), 3.66 (d, *J* = 7.4 Hz, 2H), 3.93 (br s, 1H), 4.06 (br s, 1H), 6.43 (t, *J* = 7.4 Hz, 1H), 7.21–7.30 (m, 3H), 7.33 (t, *J* = 7.3 Hz, 2H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3 (2C), 21.4 (2C), 32.5, 46.3, 47.0, 126.8, 128.6 (2C), 128.8 (2C), 137.5, 138.6, 148.0, 152.0, 186.1; HRMS (FAB) calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1756, found 290.1751.



(*Z*)-5-((tert-Butyldiphenylsilyl)oxy)-1-oxopent-2-en-2-yl Diisopropylcarbamate (3c): Compound **3c** was prepared from

(*E*)-5-[(*tert*-butyldiphenylsilyl)oxy]pent-2-en-1-ol[3] according to the procedure for the synthesis of **3a**. **3c**: Colorless oil; IR ($CHCl_3$) 1701, 1429, 1281, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H), 1.20–1.32 (m, 12H), 1.75 (tt, *J* = 6.4, 7.3 Hz, 2H), 2.45 (q, *J* = 7.3 Hz, 2H), 3.70 (t, *J* = 6.4 Hz, 2H), 3.80–3.95 (m, 1H), 3.97–4.12 (m, 1H), 6.27 (t, *J* = 7.3 Hz, 1H), 7.34–7.46 (m, 6H), 7.66 (dd, *J* = 1.4, 7.8 Hz, 4H), 9.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 20.3 (2C), 21.4 (2C), 23.1, 26.8 (3C), 31.0, 46.2, 46.9, 63.1, 127.6 (4C), 129.6 (2C), 133.6, 135.5 (4C), 140.9 (2C), 148.1, 152.1, 186.2; HRMS (FAB) calcd for $C_{29}H_{42}NO_4Si$ $[M+H]^+$ 496.2883, found 496.2880.

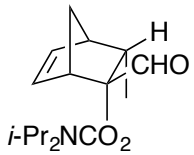


(2*Z*,7*E*)-1-Oxo-8-phenylocta-2,7-dien-2-yl Diisopropylcarbamate (3d):

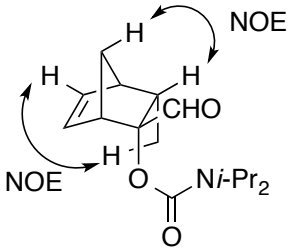
Compound **3d** was prepared from (2*E*,6*E*)-7-phenylhepta-2,6-dien-1-ol[4] according to the procedure for the synthesis of **3a**. **3d**: Colorless solid; IR (KBr) 1716, 1687, 1439, 1370, 1284, 1210, 1146, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19–1.33 (m, 12H), 1.70 (quint, *J* = 7.3 Hz, 2H), 2.28 (q, *J* = 7.3 Hz, 2H), 2.38 (q, *J* = 7.3 Hz, 2H), 3.80–3.95 (m, 1H), 3.95–4.10 (m, 1H), 6.19 (td, *J* = 7.3, 15.6 Hz, 1H), 6.32 (t, *J* = 7.3 Hz, 1H), 6.40 (d, *J* = 15.6 Hz, 1H), 7.17–7.24 (m, 1H), 7.24–7.37 (m, 4H), 9.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3 (2C), 21.3 (2C), 25.8, 27.8, 32.5, 46.2, 46.9, 125.9 (2C), 127.0, 128.4 (2C), 129.5, 130.7, 137.5, 140.4, 148.4, 152.1, 186.1; HRMS (FAB) calcd for $C_{21}H_{30}NO_3$ $[M+H]^+$ 344.2226, found 344.2203.

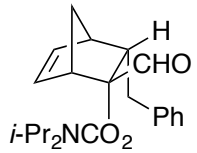
General Procedure for the Enantioselective Diels–Alder Reaction of α-Carbamoyloxy-β-Alkylacroleins 3.

To a solution of chiral triamine **1** (3.0 mg, 0.010 mmol) and TfOH (2.4 mg, 0.0275 mmol) in $EtNO_2$ (0.125 mL) was added α-carbamoyloxy-β-alkylacrolein **3** (0.10 mmol) at –78 °C. After being stirred at same temperature for 15 min, a diene (0.40 mmol) was added in one portion. The reaction mixture was stirred for several hours at 0 ºC. Upon consumption of the dienophile, the reaction was quenched with Et_3N and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using hexane–EtOAc as the eluent.

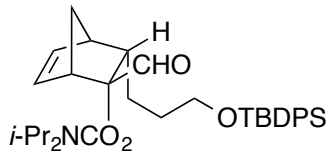


(1*S*,2*S*,3*S*,4*R*)-2-Formyl-3-methylbicyclo[2.2.1]hept-5-en-2-yl Diisopropylcarbamate (4a, *exo* isomer): Colorless oil; $[\alpha]^{25}_{D}$ –36.8 (c 1.00, $CHCl_3$) for 92% ee; HPLC (Daicel CHIRALPAK AD-3 column × 3, hexane–*i*-PrOH = 100:1, flow rate = 0.4 mL/min) t_R = 64.2 (major enantiomer of *exo* isomer), 85.3 (minor enantiomer of *exo* isomer), 81.8 (major enantiomer of *endo* isomer), 104.9 (minor enantiomer of *endo* isomer) min; IR ($CHCl_3$) 1731, 1684, 1473, 1337, 1308, 1131, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82 (d, *J* = 7.3 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.37 (td, *J* = 1.8, 9.2 Hz, 1H), 1.67 (d, *J* = 9.2 Hz, 1H), 2.76 (s, 1H), 2.88 (dq, *J* = 3.2, 7.3 Hz, 1H), 3.11 (s, 1H), 3.70–3.81 (m, 1H), 3.88–4.12 (m, 1H), 6.17 (dd, *J* = 3.2, 5.5 Hz, 1H), 6.42 (dd, *J* = 3.2, 5.5 Hz, 1H), 9.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 20.3, 20.4, 21.2 (2C), 40.7, 44.7, 45.9, 46.6, 48.3, 49.4, 91.6, 133.9, 138.6, 154.9, 197.4; HRMS (FAB) calcd for $C_{16}H_{26}NO_3$ $[M+H]^+$ 280.1913, found 280.1910. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.47 (s, 1H, CHO, *endo* isomer) and 9.61 (s, 1H, CHO, *exo* isomer). The relative configuration of major diastereomer was determined by NOE as shown below.



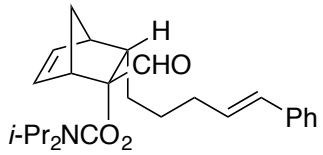


(1*S*,2*R*,3*S*,4*R*)-3-Benzyl-2-formylbicyclo[2.2.1]hept-5-en-2-ylDiisopropylcarbamate (4b, *exo* isomer): Colorless oil; $[\alpha]^{27}_{D}$ –61.0 (c 0.50, $CHCl_3$) for 89% ee; HPLC (Daicel CHIRALCEL OZ-H column × 2, hexane–*i*-PrOH = 200:1, flow rate = 0.5 mL/min) t_R = 46.9 (major enantiomer of *exo* isomer), 55.0 (major enantiomer of *endo* isomer), 61.7 (minor enantiomer of *endo* isomer), 68.8 (minor enantiomer of *exo* isomer) min; IR ($CHCl_3$) 1731, 1684, 1437, 1330, 1308, 1134 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, *J* = 6.9 Hz, 6H), 1.25 (d, *J* = 6.4 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.36 (d, *J* = 9.2 Hz, 1H), 1.61 (d, *J* = 9.2 Hz, 1H), 2.07 (t, *J* = 13.3 Hz, 1H), 2.58 (s, 1H), 2.80 (dd, *J* = 4.6, 13.3 Hz, 1H), 3.02 (td, *J* = 4.1, 11.9 Hz, 1H), 3.22 (s, 1H), 3.75–3.88 (m, 1H), 3.90–4.03 (m, 1H), 6.23 (dd, *J* = 3.2, 5.5 Hz, 1H), 6.52 (dd, *J* = 4.0, 5.5 Hz, 1H), 7.17–7.24 (m, 3H), 7.24–7.33 (m, 2H), 9.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3, 20.4, 21.2, 21.3, 35.6, 44.5, 45.1, 46.0, 46.7, 48.1, 49.7, 91.0, 126.0, 128.4 (2C), 128.8 (2C), 134.3, 138.4, 140.6, 154.8, 197.1; HRMS (FAB) calcd for $C_{22}H_{30}NO_3$ $[M+H]^+$ 356.2226, found 356.2220. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.51 (s, 1H, CHO, *endo* isomer) and 9.67 (s, 1H, CHO, *exo* isomer).



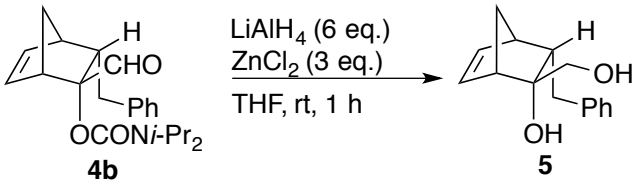
(1*S*,2*R*,3*S*,4*R*)-3-(3-(tert-Butyldiphenylsilyloxy)propyl)-2-formylbicyclo[2.2.1]hept-5-en-2-yl Diisopropylcarbamate (4c, *exo* isomer): Colorless oil; $[\alpha]^{27}_{D}$ –7.8 (c 1.00, $CHCl_3$) for 84% ee; HPLC (Daicel CHIRALCEL OZ-H column × 2, hexane–*i*-PrOH = 200:1, flow rate = 0.5 mL/min) t_R = 60.9 (major enantiomer of *exo* isomer), 66.7 (major enantiomer of *endo* isomer), 90.2 (minor enantiomer of *endo* isomer), 115.0 (minor enantiomer of *exo* isomer) min; IR ($CHCl_3$) 1732, 1681, 1429, 1329, 1308, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.02 (s, 9H), 1.13–1.20 (m, 13H), 1.32–1.42 (m, 1H), 1.40 (d, *J* = 9.2 Hz, 1H), 1.45–1.71 (m, 2H), 1.65 (d, *J* = 9.2 Hz, 1H), 2.52–2.61 (m, 1H), 2.86 (s, 1H), 3.23 (s, 1H), 3.52–3.61 (m, 1H), 3.61–3.68 (m, 1H), 3.69–3.78 (m, 1H), 3.86–3.97 (m, 1H), 6.12 (dd, J = 3.2, 5.5 Hz, 1H), 6.36 (dd, *J* = 2.7, 5.5 Hz, 1H), 7.32–7.45 (m, 6H), 7.61–7.67 (m, 4H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ

19.1, 20.3, 20.4, 21.2 (2C), 25.8, 26.8 (3C), 31.5, 44.7, 45.4, 45.9, 46.5, 46.9, 49.5, 63.9, 91.3, 127.6 (4C), 129.5 (2C), 133.9 (2C), 134.3, 135.5 (4C), 138.0, 154.8, 197.8; HRMS (FAB) calcd for $C_{34}H_{48}NO_4Si$ $[M+H]^+$ 562.3353, found 562.3361. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.45 (s, 1H, CHO, *endo* isomer) and 9.62 (s, 1H, CHO, *exo* isomer).



(1*S*,2*R*,3*S*,4*R*)-2-Formyl-3-((*E*)-6-phenylhex-5-en-1-yl)bicyclo[2.2.1]hept-5-en-2-yl Diisopropylcarbamate (4d, *exo* isomer): Colorless oil; $[\alpha]^{24}_D$–6.8 (c 1.00, $CHCl_3$) for 81% ee; HPLC (Daicel CHIRALCEL OZ-H column, hexane–*i*-PrOH =100:1, flow rate = 1.0 mL/min) t_R = 18.8 (major enantiomer of *exo* isomer), 22.6 (major enantiomerof *endo* isomer), 28.1 (minor enantiomer of *endo* isomer), 32.5 (minor enantiomer of *exo* isomer) min; IR ($CHCl_3$) 1731, 1685, 1436, 1330, 1308, 1134, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11–1.23 (m, 1H), 1.29–1.37 (m, 2H), 1.41 (d, *J* = 9.2 Hz, 1H), 1.46–1.55 (m, 2H), 1.67 (d, *J* = 9.2 Hz, 1H), 2.09–2.28 (m, 2H), 2.61–2.69 (m, 1H), 2.92 (s, 1H), 3.21 (s, 1H), 3.68–3.82 (m, 1H), 3.82–3.95 (m, 1H), 6.11–6.21 (m, 1H), 6.16 (td, *J* = 6.9, 16.0 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 6.39 (dd, *J* = 2.8, 5.5 Hz, 1H), 7.15–7.21 (m, 1H), 7.23–7.35 (m, 4H), 9.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 20.4, 21.1 (2C), 28.1, 29.0, 33.4, 44.6, 45.4, 46.0, 46.5, 46.7, 49.4, 91.4, 125.9 (2C), 126.8, 128.4 (2C), 130.0, 130.5, 134.3, 137.7, 138.0, 154.8, 197.6; HRMS (FAB) calcd for $C_{26}H_{36}NO_3$ $[M+H]^+$ 410.2695, found 410.2699. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.47 (s, 1H, CHO, *endo* isomer) and 9.63 (s, 1H, CHO, *exo* isomer).

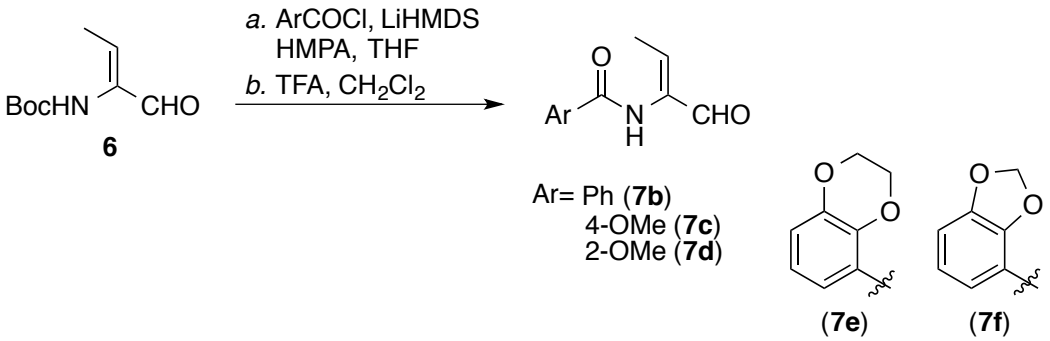
Deprotection of Diels–Alder Adduct 4b.

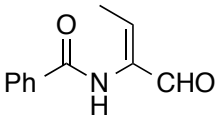


4b **5**

(1*S*,2*R*,3*S*,4*R*)-3-Benzyl-2-(hydroxymethyl)bicyclo[2.2.1]hept-5-en-2-ol (5): To a solution of **4b** (36 mg, 0.10 mmol) in THF (5 mL) were added $ZnCl_2$ (41 mg, 0.30 mmol) and $LiAlH_4$ (23 mg, 0.60 mmol) at ambient temperature, and the mixture was stirred for 1 h. The reaction was quenched by the successive addition of EtOAc (1 mL) and saturated aqueous Rochelle salt (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give **5** in 76% yield (17.5 mg, 0.076 mmol). **5**: Colorless oil; IR ($CHCl_3$) 3407, 1495, 1453, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 9.2 Hz, 1H), 1.52 (d, J = 9.2 Hz, 1H), 1.79 (s, 1H), 1.98–2.06 (m, 1H), 2.08–2.22 (m, 2H), 2.60–2.74 (m, 2H), 3.01 (s, 1H), 3.64 (d, J = 11.0 Hz, 1H), 3.71 (d, J = 11.0 Hz, 1H), 6.30 (t, J = 2.8 Hz, 1H), 6.54 (t, J = 2.8 Hz, 1H), 7.15–7.23 (m, 3H), 7.24–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.1, 45.7, 47.2, 49.9, 50.2, 69.4, 81.7, 125.9, 128.4 (2C), 128.8 (2C), 134.7, 138.9, 141.5; HRMS (FAB) calcd for $C_{15}H_{19}O_2$ [M+H+] 231.1385, found 231.1363.

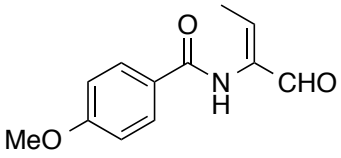
Synthesis of α-(Acylamino)crotonaldehydes 7 and 8.





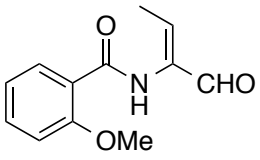
(*Z*)-N-(1-Oxobut-2-en-2-yl)benzamide (7b): To a solution of (*Z*)-*tert*-butyl (1-oxobut-2-en-2-yl)carbamate (**6**)[5] (0.28 g, 1.5 mmol) and HMPA (0.52 mL, 3.0 mmol) in THF (5 mL) was added a solution of LiHMDS in hexane (1.6 M, 1.2 mL, 2.0 mmol) at –78 ºC, and the mixture was stirred for 15 min. To the reaction mixture was added benzoyl chloride (0.23 mL, 2.0 mmol), and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL), and the mixture was allowed to warm to ambient temperature. The mixture was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with water (20 mL × 2), dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give (*Z*)-*tert*-butyl benzoyl(1-oxobut-2-en-2-yl)carbamate in 75% yield (0.33 g, 1.1 mmol). To a solution of (*Z*)-*tert*-butyl benzoyl(1-oxobut-2-en-2-yl)carbamate (0.33 g, 1.1 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL) at ambient temperature, and the mixture was stirred for 30 min. The reaction mixture was poured into saturated aqueous Na_2CO_3 (50 mL) and extracted with EtOAc (20 mL × 2). The combined organic layers were washed with saturated aqueous Na_2CO_3 (30 mL × 2), dried over Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 4:1) to give **7b** in 70% yield (0.15 g, 0.8 mmol). **7b**: Colorless oil; IR (KBr) 1698, 1656, 1515, 1485, 1292 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.08 (d, *J* = 6.9 Hz, 1H), 6.54 (q, *J* = 6.9 Hz, 1H), 7.45–7.51 (m, 2H), 7.54–7.59 (m, 1H), 7.77 (s, 1H), 7.86–7.91 (m, 2H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5, 127.5 (2C), 128.7 (2C), 132.3, 133.6,

136.6, 142.3, 165.1, 189.3; HRMS (FAB) calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$ 190.0868, found 190.0841.



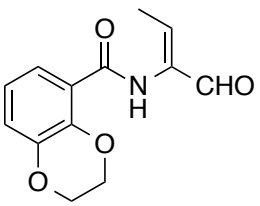
(*Z*)-4-Methoxy-N-(1-oxobut-2-en-2-yl)benzamide (7c):

Compound **7c** was prepared from **6** and 4-methoxybenzoyl chloride according to the procedure for the synthesis of **7b**. **7c**: pale brown solid; IR (KBr) 1692, 1640, 1603, 1499, 1316, 1259, 1183, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.06 (d, *J* = 6.9 Hz, 3H), 3.87 (s, 3H), 6.51 (q, *J* = 6.9 Hz, 1H), 6.96 (d, J = 8.2 Hz, 2H), 7.71 (br s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 55.4, 113.9 (2C), 125.8, 129.4 (2C), 136.7, 142.1, 162.8, 164.7, 189.5; HRMS (EI) calcd for $C_{12}H_{13}NO_3$ $[M]^+$ 219.0895, found 219.0894.



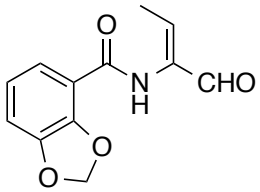
(*Z*)-2-Methoxy-N-(1-oxobut-2-en-2-yl)benzamide (7d):

Compound **7d** was prepared from **6** and 2-methoxybenzoyl chloride according to the procedure for the synthesis of **7b**. **7d**: Colorless solid; IR (KBr) 1685, 1661, 1644, 1507, 1481, 1292, 1241, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.06 (d, *J* = 7.3 Hz, 3H), 4.06 (s, 3H), 6.51 (q, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.50 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 9.36 (s, 1H), 9.59 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 56.2, 111.6, 121.0, 121.3, 132.5, 133.5, 137.3, 142.1, 157.6, 162.9, 189.5; HRMS (EI) calcd for $C_{12}H_{13}NO_3$ $[M]^+$ 219.0895, found 219.0897.

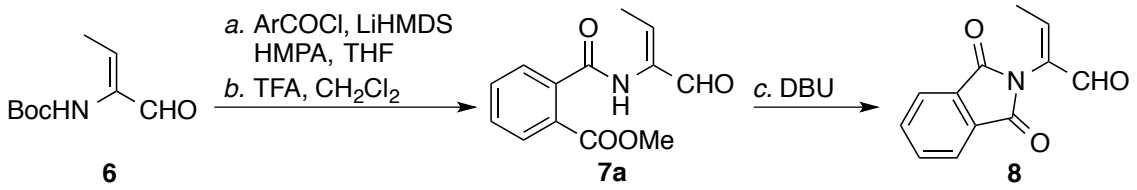


(*Z*)-N-(1-Oxobut-2-en-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-5-carboxamide (7e):

Compound **7e** was prepared from **6** and 2,3-dihydrobenzo[*b*][1,4]dioxine-5-carbonyl chloride[6] according to the procedure for the synthesis of **7b**. **7e**: Colorless solid; IR (KBr) 1671, 1652, 1526, 1472, 1287, 1255, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.06 (d, *J* = 7.3 Hz, 3H), 4.34–4.38 (m, 2H), 4.49–4.54 (m, 2H), 6.52 (q, *J* = 7.3 Hz, 1H), 6.96 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.05 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.74 (dd, *J* = 1.4, 7.8 Hz, 1H), 9.25 (br s, 1H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 63.6, 65.1, 121.3, 121.4, 121.5, 124.4, 137.2, 142.3, 142.5, 143.7, 162.3, 189.5; HRMS (EI) calcd for $C_{13}H_{13}NO_4$ $[M]^+$ 247.0845, found 247.0876.



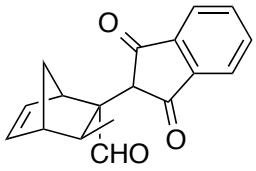
(*Z*)-N-(1-Oxobut-2-en-2-yl)benzo[*d*][1,3]dioxole-4-carboxamide (7f): Compound **7f** was prepared from **6** and benzo[*d*][1,3]dioxole-4-carbonyl chloride[6] according to the procedure for the synthesis of **7b**. **7f**: Colorless solid; IR (KBr) 1675, 1534, 1459. 1245, 1194, 1064 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07 (d, *J* = 7.3 Hz, 1H), 6.16 (s, 2H), 6.56 (q, *J* = 7.3 Hz, 1H), 6.96 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.01 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.58 (dd, *J* = 1.4, 7.8 Hz, 1H), 8.50 (br s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 101.7, 112.1, 115.2, 122.1, 122.5, 136.7, 143.0, 145.5, 147.8, 161.0, 189.2; HRMS (EI) calcd for $C_{12}H_{11}NO_4$ $[M]^+$ 233.0688, found 233.0666.



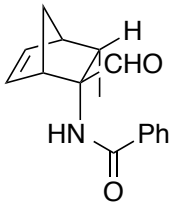
(*Z*)-2-(1,3-Dioxoisoindolin-2-yl)but-2-enal (8): Compound **7a** was prepared from **6** and methyl 2-(chlorocarbonyl)benzoate according to the procedure for the synthesis of **7b**. To a solution of **7a** (0.24 g, 0.976 mmol) in CH_2Cl_2 (5 mL) was added DBU (20 μL, 0.13 mmol) at ambient temperature, and the mixture was stirred for 10 min. The reaction was quenched by the addition of 1 M aqueous HCl (0.5 mL), and the reaction mixture was poured into water (5 mL). The solution was extracted with $CHCl_3$ (5 × 3 mL), and the combined organic layer was dried over Na_2SO_4, filtrated and concentrated.

The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give **8** in 78% yield (0.17 g 0.77 mmol). **8**: Colorless solid; IR (KBr) 1721, 1411, 1369, 1306, 1114, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.03 (d, J = 7.3 Hz, 3H), 7.21 (q, J = 7.3 Hz, 1H), 7.79 (dd, J = 3.2, 5.5 Hz, 2H), 7.93 (dd, J = 3.2, 5.5 Hz, 2H), 9.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0, 123.9 (2C), 132.0, 134.1, 134.4 (2C), 151.9 (2C), 166.3 (2C), 186.7; HRMS (FAB) calcd for $C_{12}H_{10}NO_3$ $[M+H]^+$ 216.0661, found 216.0686.

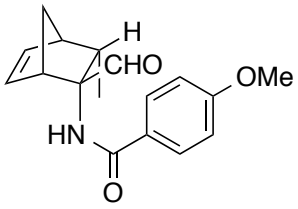
Diels–Alder Adducts 9 and 10: The enantioselective Diels–Alder reaction of cyclopentadiene with α-(acylamino)crotonaldehydes **7** and **8** was conducted according to the procedure for the reaction of α-carbamoyloxy-β-alkylacroleins **3**. The relative configuration of adduct **9** was not determined.



2-(1,3-Dioxoisoindolin-2-yl)-3-methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (9, major diastereomer): Colorless oil; $[\alpha]^{28}_D$ +29.9 (c 0.30, $CHCl_3$) for 54% ee; HPLC (Daicel CHIRALPAK IA column, hexane–*i*-PrOH = 100:1, flow rate = 1.0 mL/min) t_R = 25.2 (major isomer), 35.6 (minor isomer) min; IR ($CHCl_3$) 1712, 1644, 1367, 1119 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, *J* = 7.3 Hz, 3H), 1.58 (br s, 1H), 1.80 (br s, 1H), 2.93 (br s, 1H), 3.07 (dq, *J* = 3.1, 7.3 Hz, 1H), 6.30 (dd, *J* = 3.2, 5.5 Hz, 1H), 6.63 (dd, *J* = 3.2, 5.5 Hz, 1H), 7.68–7.76 (m, 2H), 7.76–7.87 (m, 2H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 47.8, 48.8, 49.6, 50.1, 77.2, 123.1 (2C), 131.8, 131.9 (2C), 134.1 (2C), 140.5, 169.5 (2C), 200.8; HRMS (FAB) calcd for $C_{17}H_{15}NO_3$ $[M]^+$ 281.1052, found 281.1053. The diastereo ratio was determined by ^1H NMR analysis: δ 9.18 (s, 1H, CHO, major diastereomer) and 9.68 (s, 1H, CHO, minor diastereomer).

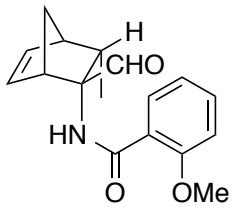


***N*-((1*S*,2*S*,3*S*,4*R*)-2-Formyl-3-methylbicyclo[2.2.1]hept-5-en-2-yl)benzamide (10b, *exo* isomer)**: Colorless solid; $[\alpha]^{27}_{D}$ –3.8 (c 1.00, $CHCl_3$) for 72% ee; HPLC (Daicel CHIRALPAK AD-3 column × 2, hexane–*i*-PrOH = 20:1, flow rate = 0.5 mL/min) t_R = 108.4 (major enantiomer of *exo* isomer), 113.5 (minor enantiomer of *exo* isomer), 130.0 (major enantiomer of *endo* isomer), 145.9 (minor enantiomer of *endo* isomer) min; IR ($CHCl_3$) 1725, 1638, 1514, 1482, 1134 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.82 (d, J = 7.3 Hz, 3H), 1.46 (d, J = 9.2 Hz, 3H), 1.74 (d, *J* = 9.2 Hz, 3H), 2.87 (s, 1H), 3.08–3.18 (m, 2H), 6.10 (s, 1H), 6.32 (dd, *J* = 2.8, 5.3 Hz, 1H), 6.61 (dd, *J* = 2.8, 5.3 Hz, 1H), 7.45 (t, *J* = 6.9 Hz, 2H), 7.54 (t, *J* = 6.9, 1H), 7.72 (d, *J* = 6.9 Hz, 2H), 9.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 39.9, 45.5, 49.0, 49.2, 71.8, 126.9 (2C), 128.7 (2C), 131.8, 132.0, 143.0, 167.8, 197.9; HRMS (FAB) calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1338, found 256.1340. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.69 (s, 1H, CHO, exo isomer) and 9.77 (s, 1H, CHO, *endo* isomer).

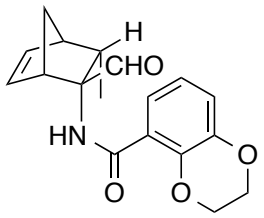


***N*-((1*S*,2*S*,3*S*,4*R*)-2-Formyl-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-4-methoxybenza mide (10c, *exo* isomer):** Colorless oil; $[\alpha]^{26}_{D}$ –13.7 (c 0.60, $CHCl_3$) for 72% ee; HPLC (Daicel CHIRALCEL AS-3 column, hexane–*i*-PrOH = 20:1, flow rate = 1.0 mL/min) t_R = 26.1 (major enantiomer of *exo* isomer), 29.2 (minor enantiomer of *exo* isomer), 31.4 (major enantiomer of *endo* isomer), 34.0 (minor enantiomer of *endo* isomer) min; IR ($CHCl_3$) 1725, 1640, 1606, 1489, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80 (d, *J* = 7.3 Hz, 3H), 1.45 (d, *J* = 9.2 Hz, 1H), 1.74 (d, *J* = 9.2 Hz, 1H), 2.86 (s, 1H), 3.09–3.17 (m, 2H), 3.86 (s, 3H), 6.00 (s, 1H), 6.31 (dd, *J* = 3.2, 4.9 Hz, 1H), 6.61 (dd, *J* = 3.2, 5.7 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 9.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 39.9, 45.5, 49.0, 49.2, 55.5, 71.7, 113.9 (2C), 125.2, 128.8 (2C), 131.8, 143.0, 162.6, 167.3, 197.9; HRMS (EI) calcd for $C_{17}H_{19}NO_3$ $[M]^+$

285.1365, found 285.1369. The *exo*/*endo* ratio was determined by ^{1}H NMR analysis: δ 9.67 (s, 1H, CHO, *exo* isomer) and 9.76 (s, 1H, CHO, *endo* isomer).

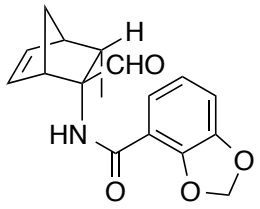


***N*-((1*S*,2*S*,3*S*,4*R*)-2-Formyl-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-2-methoxybenzamide (10d, *exo* isomer):** Colorless oil; $[\alpha]^{28}_{D}$ –14.3 (c 1.00, $CHCl_3$) for 70% ee; HPLC (Daicel CHIRALCEL OD-H column, hexane–*i*-PrOH = 20:1, flow rate = 1.0 mL/min) t_R = 37.0 (major enantiomer of *exo* isomer), 70.5 (minor enantiomer of *exo* isomer) min; IR ($CHCl_3$) 1726, 1648, 1600, 1518, 1482, 1305, 1240, 1129 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (d, *J* = 7.3 Hz, 3H), 1.43 (d, *J* = 9.2 Hz, 1H), 1.73 (d, *J* = 9.2 Hz, 1H), 2.85 (s, 1H), 3.03–3.12 (m, 1H), 3.14 (s, 1H), 4.00 (s, 3H), 6.25 (dd, *J* = 2.8, 5.5 Hz, 1H), 6.56 (dd, *J* = 2.8, 5.5 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 7.08 (dd, *J* = 7.3, 7.8 Hz, 1H), 7.48 (dd, *J* = 7.3, 8.2 Hz, 1H), 8.10 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 9.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.9, 39.7, 45.3, 48.9, 49.2, 56.1, 71.7, 111.3, 120.1, 121.5, 132.3, 132.5, 133.3, 141.8, 157.6, 165.5, 198.3; HRMS (EI) calcd for $C_{17}H_{19}NO_3$ $[M]^+$ 285.1365, found 285.1379. The *exo*/*endo* ratio was determined by ^{1}H NMR analysis: δ 9.69 (s, 1H, CHO, *exo* isomer) and 9.77 (s, 1H, CHO, *endo* isomer).



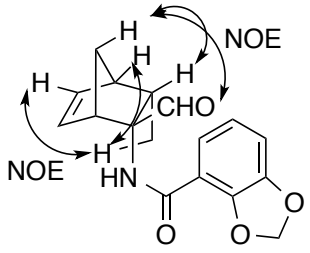
***N*-((1*S*,2*S*,3*S*,4*R*)-2-formyl-3-methylbicyclo[2.2.1]hept-5-en-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-5-carboxamide (10e, *exo* isomer): Colorless oil:** $[\alpha]^{27}_{D}$ –21.1 (c 1.00, $CHCl_3$) for 77% ee; HPLC (Daicel CHIRALCEL OD-H column, hexane–*i*-PrOH = 10:1, flow rate = 0.5 mL/min) t_R = 52.9 (major enantiomer of *exo* isomer), 74.3 (minor enantiomer of *exo* isomer) min; IR ($CHCl_3$) 1720, 1645, 1585, 1517, 1464, 1285, 1254, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (d, *J* = 6.9 Hz, 3H), 1.43 (d, *J* = 9.2 Hz,

1H), 1.73 (d, *J* = 9.2 Hz, 1H), 2.85 (s, 1H), 3.07 (dq, *J* = 3.2, 6.9 Hz, 1H), 3.14 (s, 1H), 4.35 (t, *J* = 4.1 Hz, 2H), 4.42–4.46 (m, 2H), 6.22 (dd, *J* = 2.8, 5.5 Hz, 1H), 6.55 (dd, *J* = 2.8, 5.5 Hz, 1H), 6.94 (t, *J* = 7.8 Hz, 1H), 7.03 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.69 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.81 (s, 1H), 9.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.9, 39.7, 45.3, 48.8, 49.2, 63.5, 65.1, 71.8, 120.6, 121.3, 121.5, 124.2, 132.4, 141.9, 142.2, 143.5, 165.0, 198.2; HRMS (EI) calcd for $C_{18}H_{19}NO_4$ $[M]^+$ 313.1341, found 313.1349. The *exo*/*endo* ratio was determined by ^{1}H NMR analysis: δ 9.67 (s, 1H, CHO, *exo* isomer) and 9.77 (s, 1H, CHO, *endo* isomer).



***N*-((1*S*,2*S*,3*S*,4*R*)-2-formyl-3-methylbicyclo[2.2.1]hept-5-en-2-yl)benzo[*d*][1,3]dioxole-4-carboxamide (10f, *exo* isomer):** Colorless oil; $[\alpha]^{26}_D$ –25.8 (c 1.00, $CHCl_3$) for 79% ee; HPLC (Daicel CHIRALCEL OD-H column, hexane–*i*-PrOH = 20:1, flow rate = 1.0 mL/min) t_R = 27.8 (major enantiomer of *exo* isomer), 40.9 (minor enantiomer of *exo* isomer) min; IR (KBr) 1720, 1649, 1593, 1523, 1456, 1248, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (d, *J* = 7.1 Hz, 3H), 1.44 (d, *J* = 9.2 Hz, 1H), 1.73 (d, *J* = 9.2 Hz, 1H), 2.84 (s, 1H), 3.07 (dq, *J* = 3.2, 7.1 Hz, 1H), 3.14 (s, 1H), 6.12 (s, 2H), 6.24 (dd, *J* = 3.2, 5.7 Hz, 1H), 6.56 (dd, *J* = 3.2, 5.7 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.98 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.05 (s, 1H), 7.50 (dd, J = 1.4, 7.8 Hz, 1H), 9.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 39.8, 45.3, 48.8, 49.3, 71.8, 101.5, 112.0, 114.6, 122.2, 122.4, 132.3, 142.2, 145.3, 147.4, 163.7, 198.1; HRMS (EI) calcd for $C_{17}H_{17}NO_4$ $[M]^+$ 299.1158, found 299.1150.

The *exo*/*endo* ratio was determined by ^{1}H NMR analysis: δ 9.67 (s, 1H, CHO, *exo* isomer) and 9.77 (s, 1H, CHO, *endo* isomer). The relative configuration of major diastereomer was determined by NOE as shown below.



References and Note

1. D. Hoppe, R. Hanko, A. Brönneke, F. Lichtenberg, E. Hülsen, *Chem. Ber.* **1985**, *118*, 2822.
2. K. Behrens, R. Fröhlich, O. Meyer, D. Hoppe, *Eur. J. Org. Chem.* **1998**, 2397.
3. R. K. Boeckman, Jr., M. R. del Rosario Ferreira, L. H. Mitchell, P. Shao, M. J. Neeb, Y. Fang, *Tetrahedron* **2011**, *67*, 9787.
4. A. Johns, J. A. Murphy, M. S. Sherburn, *Tetrahedron* **1989**, *45*, 7835.
5. M. J. Burk, N. B. Johnson, J. R. Lee, *Tetrahedron Lett.* **1999**, *40*, 6685.
6. Z. Huang, Y. Liu, Y. Li, L. Xiong, Z. Cui, H. Song, H. Liu, Q. Zhao, Q. Wang, J. *Agric. Food Chem.* **2011**, *59*, 635.

Chapter 4

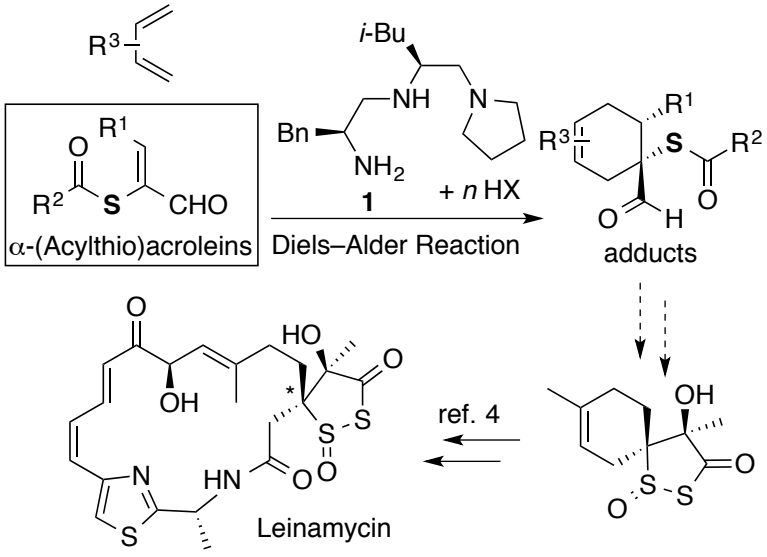
Enantioselective Diels–Alder Reaction with β-Substituted/Unsubstituted α-(Acylthio)acroleins

Abstract: A catalytic and enantioselective Diels–Alder reaction of α-(carbamoylthio)acroleins induced by an organoammonium salt of chiral triamine is described. α-(Carbamoylthio)acroleins are designed and synthesized as new sulfur-containing dienophiles for the first time. The Diels–Alder reaction affords chiral tertiary thiol precursors with up to 91% ee.

4-1 Introduction

α-(Acylthio)acroleins would also be useful dienophiles for the construction of sulfur-containing quaternary carbons. The corresponding adducts are potential chiral intermediates for the synthesis of sulfur-containing bioactive natural products.[1] For example, the Diels–Alder adduct of an α-(acylthio)acrolein with isoprene would be readily converted to a key synthetic intermediate of leinamycin[2] (Scheme 4.1).

Scheme 4.1. Diels–Alder Reaction of α-(Acylthio)acroleins for the Synthesis of Sulfur-Containing Quaternary Carbons



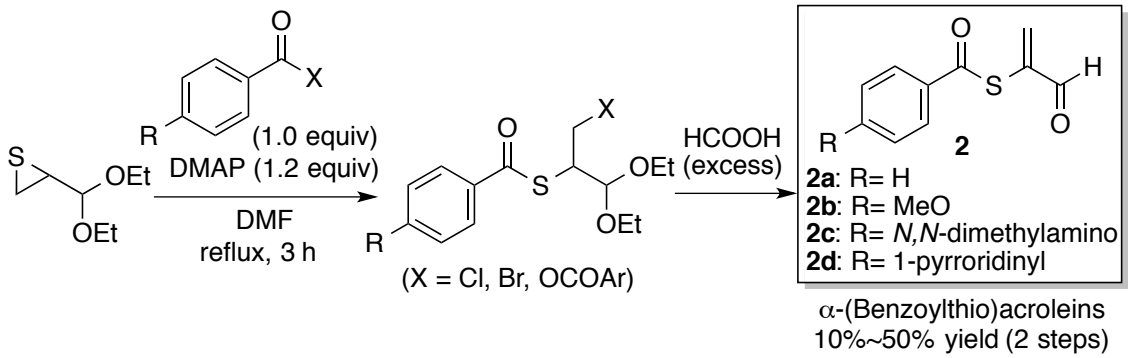
Although some methods for the synthesis of sulfur-containing quaternary stereogenic centers have been reported,[3] most of these methods produce chiral thioethers and only a few can give tertiary thiols.[3b,e] We report here the catalytic and enantioselective Diels–Alder reaction of α-(acylthio)acroleins to give optically active tertiary thiol precursors.

4-2 Results and discussion

On the basis of our previous results, benzoyl groups were considered to be promising candidates as protecting groups for the α-mercapto group. We first

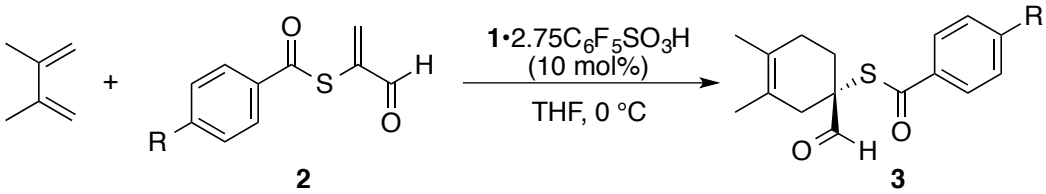
synthesized β-unsubstituted α-(benzoylthio)acroleins **2** based on the acylation[4] of 2-(diethoxymethyl)thiirane (Scheme 4.2).[5]

Scheme 4.2. Synthesis of α-(Acylthio)acroleins



The Diels–Alder reaction of 2,3-dimethylbutadiene (4 equiv) with **2a–d** was conducted in the presence of **1**•2.75$C_6F_5SO_3H$ (10 mol%) in $EtNO_2$ at 0 ºC (Table 4.1). As a result, the enantioselectivities of the corresponding adducts **3** highly depended on the benzoyl groups. The introduction of an electron-donating dialkylamino group at the 4-position increased the enantioselectivity, and dienophile **2d** bearing a pyrrolidinyl group gave the highest enantioselectivity (entry 4). However, the enantioselectivity of **2d** (72%ee) was still lower than those of α-(4-methoxybenzoyloxy)acrolein (92% yield, 92% ee)[6a] and α-(phthalimido)acrolein (82% yield, 96% ee)[6b] in the **1**•2.75$C_6F_5SO_3H$-catalyzed Diels–Alder reaction of 2,3-dimethylbutadiene.

Table 4.1. Enantioselective Diels–Alder Reaction of α-(Benzoylthio)acroleins **2**[a]



entry	**2** [Ar]	**3**, yield[%]	ee[b][%]
1	**2a**,	**3a**, 58	43
2	**2b**	**3b**, 53	44
3	**2c**	**3c**, 28	68
4	**2d**	**3d**, 30	72

[a] Reaction of **2** (0.1 mmol) with 2,3-dimethylbutadiene (4 equiv) was conducted in the presence of **1**•2.75$C_6F_5SO_3H$ (10 mol%) in $EtNO_2$ at 0 ºC for 36 h. [b] Determined by HPLC analysis.

It is conceivable that the formation of stronger hydrogen bonding between the acyl group and an ammonium proton of the catalyst might stabilize the conformation of the transition state to increase the enantioselectivity.

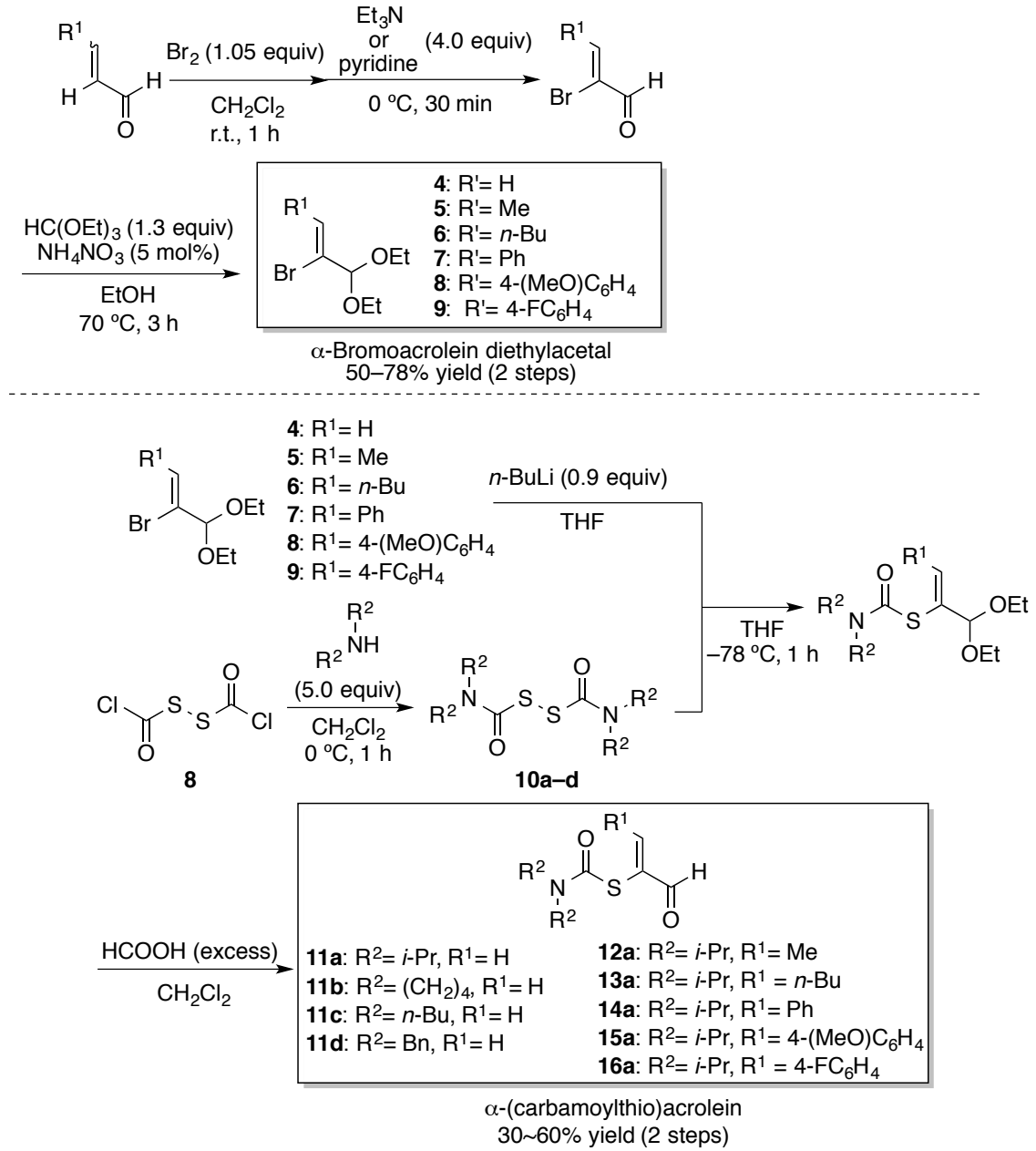
The lower basicity of thioesters compared to esters and imides resulted in the lower enantioselectivity of α-(benzoylthio)acroleins **2a**–**d** than α-(4-methoxybenzoyloxy)acrolein and α-(phthalimido)acrolein. In addition, although the α-benzoylacroleins **2c** and **2d** gave good enantioselectivities, the yields of the corresponding adducts **3c** and **3d** were low (entries 3 and 4). The low yields were mainly attributed to the low solubilities of **2c** and **2d** in $EtNO_2$. Therefore, both the solubility and the basicity of the acyl group of **2** had to be improved to achieve high yield and enantioselectivity.

Thus, we next designed α-(carbamoylthio)acroleins **11a–d** (R^1 = H, Scheme 4.3) as new α-sulfur-substituted acroleins to overcome the above problems. The carbamoyl groups were expected to have a stronger electron-donating ability than the benzoyl groups. However, it would be very difficult to promote the carbamoylation of 2-(diethoxymethyl) thiirane with dialkylcarbamoyl chlorides, since the dialkylcarbamoyl chlorides were much less electrophilic than the carboxylic chlorides.

Thus, we developed a new synthetic route for **11** based on the umpolung strategy: C–S bond formation between a "carbamoylthio cation R_2NCOS^+" and a "vinyl anion RCH=C^-CHO".

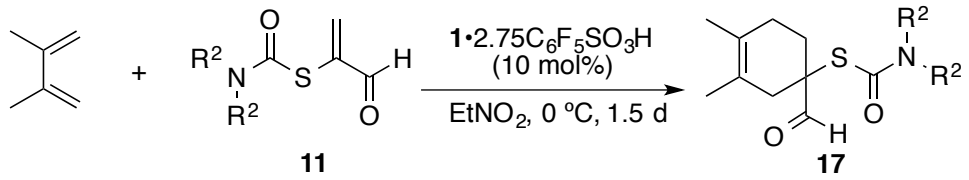
According to this strategy, bis(carbamoyl)disulfides **10**, synthetic equivalents of a carbamoylthio cation, were prepared from bis(chlorocarbonyl)disulfide[7] and secondary amines. Lithiation[8] of α-bromoacrolein diethylacetals **4**[9] generated the corresponding vinyl anion. The reaction of the vinyl anion with **10** followed by acid hydrolysis of the acetal moiety gave **11a–d** in yields of 30–50%.

Scheme 4.3. Synthesis of α-(Carbamoylthio)acroleins



As expected, α-(carbamoylthio)acroleins **11a–d** were readily soluble in $EtNO_2$ under the reaction conditions, and showed high reactivities and enantioselectivity in the **1**•2.75$C_6F_5SO_3H$-catalyzed Diels–Alder reaction with 2,3-dimethylbutadiene (entries 1–4, Table 4.2).

Table 4.2. Enantioselective Diels–Alder Reaction of 2,3-Dimethylbutadiene with β-Unsubstituted α-(Carbamoylthio)acroleins[a]



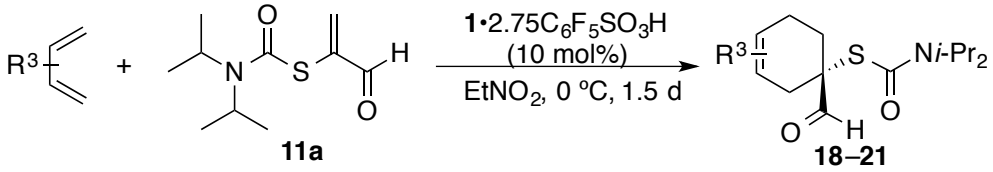
entry	Dienophile	R^2	Adduct	Yield[%]	ee[%][b]
1	**11a**	*i*-Pr	**17a**	65	74
2	**11b**	$(C_2H_2)_4$	**17b**	20	76
3	**11c**	*n*-Bu	**17c**	67	48
4	**11d**	Bn	**17d**	66	66

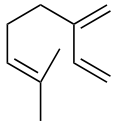
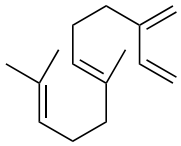
[a] Reactions of 2,3-dimethylbutadiene (4 equiv) with **11a**–**11d** (0.1 mmol) were conducted in the presence of **1**•2.75$C_6F_5SO_3H$(10 mol %) in EtNO2 at 0 ºC for 1.5 days. [b] Determined by HPLC analysis.

Although **11b** bearing a pyrrolidinecarbonylthio group gave the highest enantioselectivity (76% ee), the yield of the corresponding adduct **17b** was low (20%) because **11b** was labile under the reaction conditions (entry 2). Dienophile **11a** bearing an *N*,*N*-diisopropylaminocarbonylthio group was stable and gave the adduct **17a** in 65% yield with 74% ee (entry 1).

With the optimized dienophile **11a** in hand, we next examined the enantioselective Diels–Alder reaction with representative dienes (Table 4.3).

Table 4.3. Enantioselective Diels–Alder Reaction of Various Dienes with β-Unsubstituted α-(Carbamoylthio)acroleins[a]



entry	diene	Adduct	Yield[%]	ee[%][b]
1		**18**	68	81
2		**19**	67	73
3		**20**	74	67
4		**21**	79	0 (*exo*/*endo*=56:44)

[a]Reactions of diene(4 equiv) with **11a** (0.1 mmol) were conducted in the presence of **1**•2.75$C_6F_5SO_3H$(10 mol %) in EtNO2 at 0 ºC for 1.5 days. [b]Determined by HPLC analysis.

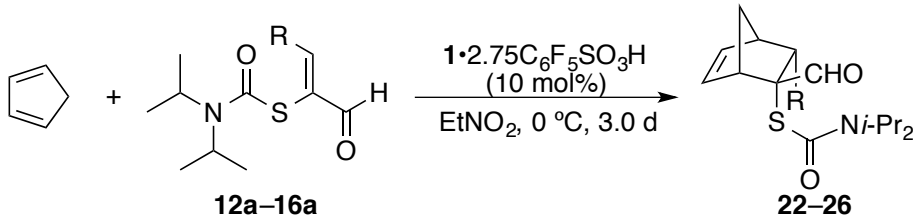
2-Alkyl-substituted dienes such as isoprene, myrcene, and (*E*)-β-farnesene smoothly reacted with **11a** to give the corresponding 4-alkyl-substituted adducts **18–20** with >99% regioselectivity and 67–81%ee (entries 1–4). In contrast, the reaction of **11a** with cyclopentadiene gave the corresponding adduct **21** in racemic form (entry 4).

According to the synthetic method for **11** desribed in Scheme 4.3, β-substituted α-(carbamoylthio)acroleins **12a**–**16a** ($R^1 \neq$ H) were synthesized in 41–60% yields. In this reaction sequence, the bromination of β-substituted acroleins followed by acetalization selectively afforded *cis*-β-substituted α-bromoacrolein diethylacetals **5–9** despite the fact that the starting β-substituted acroleins were isomeric mixtures.[10] The Diels–Alder reactions of β-substituted α-(carbamoylthio)acroleins **12a–16a** with

cyclopentadiene were also catalyzed by 1•2.75$C_6F_5SO_3H$ (10 mol %) and gave the corresponding adducts **22–26** with high enantioselectiv enantioselectivities (Table 4.4).

In particular, β-aryl-substituted dienophiles **14a–16a** showed more than 90% ee (entries 3–5). The absolute configuration of the major diastereomer of the adduct **26** was determined to be (2*R*,3*R*) by X-ray crystallographic analysis (Figure 4.1.).

Table 4.4. Enantioselective Diels–Alder Reaction of cyclopentadiene with β-Substituted α-(Carbamoylthio)acroleins[a]



12a–16a **22–26**

Entry	dienophile	R	Adduct	Yield[%]	*exo*/*endo*[b]	ee[%][c]
1	**12a**	Me	**22**	88	87:13	88
2	**13a**	*n*-Bu	**23**	83	91:9	84
3	**14a**	Ph	**24**	68	75:25	91
4	**15a**	4-(OMe)C_6H_4	**25**	42	78:22	90
5	**16a**	4-FC_6H_4	**26**	67	75:25	90

[a]Reactions of cyclopentadiene (4 equiv) with **12a**–**16a** were conducted in the presence of **1**•2.75$C_6F_5SO_3H$ (10 mol %) in $EtNO_2$ at 0 ºC for 3 days. [b]Determined by ^1H NMR analysis. [c]Determined by HPLC analysis.

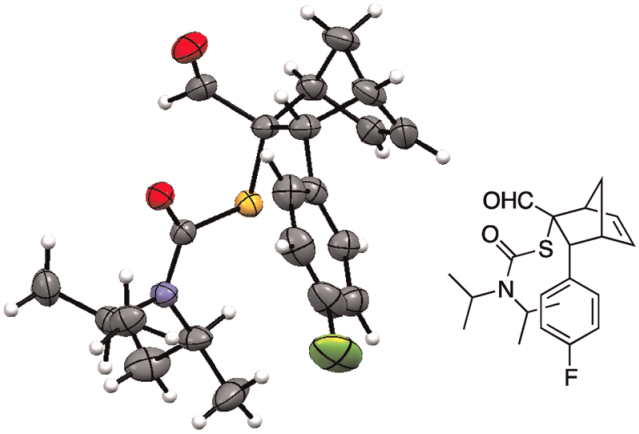
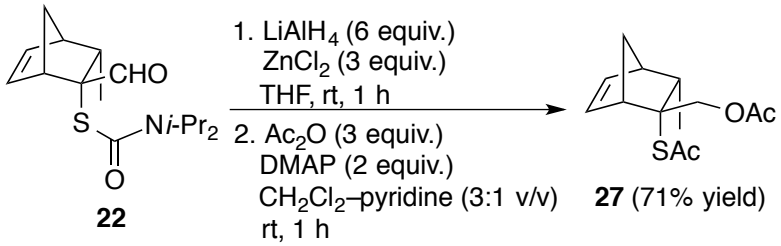


Figure 4.1. X-ray single-crystal structure of *exo*-**26** with thermal ellipsoids drawn at a 50% probability level.

The stereochemical outcome of *exo*-**26** was consistent with those of the Diels–Alder adducts of α-(acyloxy)acroleins and α-(phthalimido)acroleins. The carbamoyl group in the Diels–Alder adducts could be removed by reductive cleavage. For example, the treatment of **22** with $LiAlH_4$ (6 equiv) and $ZnCl_2$ (3 equiv.)[11] followed by acetylation of the resultant hydroxyl group and mercapto group gave **27** in 71% yield (Scheme 4.4).



Scheme 4.4. Derivatization of **22**

4-3 Conclusion

We have developed an organocatalytic and enantioselective Diels–Alder reaction of α-(carbamoylthio)acroleins to provide chiral tertiary thiol precursors for the first time. β-Unsubstituted or β-substituted α-(carbamoylthio)acroleins **11–16** were designed and synthesized as new sulfur-containing dienophiles.

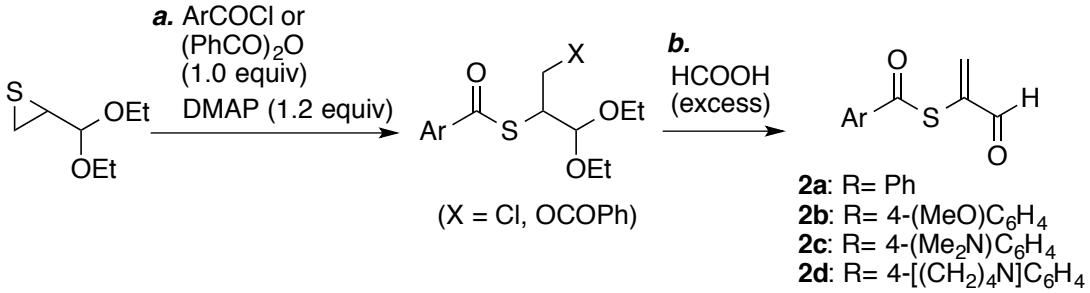
References and Notes

1. For representative examples of bioactive compounds bearing sulfur-containing quaternary carbons, see: (a) Hofmeister, H.; Hoyer, G.-A.; Cleve, G.; Laurent, H.; Wiechert, R. *Chem. Ber.* **1976**, *109*, 185. (b) Costa, M. d. C.; Teixeira, S. G.; Rodrigues, C. B.; RybergFigueiredo, P.; Marcelo Curto, M. J. *Tetrahedron* **2005**, *61*, 4403. (c) Asthana, R. K.; Srivastava, A.; Singh, A. P.; Deepali; Singh, S. P.;Nath, G.; Srivastava,R.; Srivastave, B. S. *J. Appl. Phycol.* **2006**, *18*, 33. (d) Sawant, S.; Youssef, D.; Mayer,A.; Sylvester, P.; Wali,V.; Arant, M.; El Sayed, K. A. *Chem. Pharm. Bull.* **2006**, *54*, 1119. (e) Dormann, K. L.; Brückner, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1160.
2. Pattenden, G.; Shuker, A. J. *Tetrahedron Lett.* **1991**, *32*, 6625.
3. (a) Aggarwal, V. K.; Jones, D. E.; Martin-Castro, A. M. *Eur. J. Org. Chem.* **2000**, 2939. (b) Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jørgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 5689. (c) Jereb, M.; Togni, A. *Org. Lett.* **2005**, *7*, 4041. (d) Lu, H.; Zhang, F.; Meng, X.; Duan, S.; Xiao,W. *Org. Lett.* **2009**, *11*, 3946. (e) Fujiwara, Y. Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293.
4. (a) Sander, M. *Chem. Rev.* **1966**, *66*, 297. (b) Silvestri, M. G.; Wong, C.-H. *J. Org. Chem.* **2001**, *66*, 910.
5. Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897.
6. (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504; correction **2005**, *127*, 13079. (b) Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893.
7. Barany, G.; Schroll, A. L.; Mott, A. W.; Halsrud, D. A. *J. Org. Chem.* **1983**, *48*, 4750.
8. Takahashi, T.; Yokoyama, H.; Haino, T.; Yamada, H. *J. Org. Chem.* **1992**, *57*, 3521.
9. Barlow, A. j.; Compton, B. J.; Weavers, R. T. *J. Org. Chem.* **2005**, *70*, 2470.
10. (a) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088. (b) Gilly, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631.
11. Marr, F.; Hoppe, D. *Org. Lett.* **2002**, *4*, 4217.

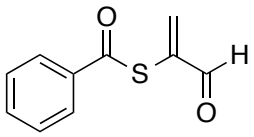
Experimental Section

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 spectrometer (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm × 25 cm), Daicel CHIRALPAK AD-H (4.6 mm × 25 cm), Daicel CHIRALCEL AS-H (4.6 mm × 25 cm), Daicel CHIRALPAK OZ-H (4.6 mm × 25 cm), Daicel CHIRALPAK AS-3 (4.6 mm × 25 cm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. GC analysis was performed with Shimadzu 17A instruments with a flame-ionization detector and a capillary column of PEG-HT Bonded (25 m × 0.25 mm) using nitrogen as carrier gas. The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385 or Fuji Silysia Chemical Ltd. Cromatorex® NH-DM1020 or Fuji Silysia Chemical Ltd. Cromatorex® DIOL-MB100). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on JEOL JMS-700 spectrometer. In experiments that required dry solvent, ether, *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from TCI or Wako as the “anhydrous” and stored over MS 4Å. Carbon tetrachloride, Chloroform, and dichloromethane were freshly distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially.

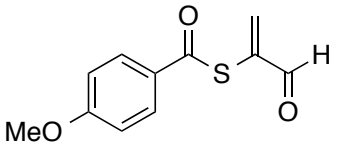
Synthesis of α-(Benzoylthio)acroleins 10a–d.



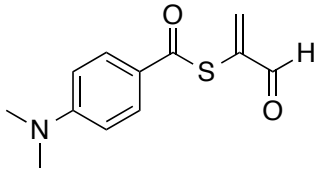
The acylation[1] of 2-(diethoxymethyl)thiirane[2] with benzoic anhydride or a carboxylic chloride followed by hydrolysis with formic acid gave the corresponding α-(benzoylthio)acroleins **2**. The rather low yields of **2** were mainly attributed to the low reactivity in the acylation of the thiirane.



***S*-3-Oxoprop-1-en-2-yl Benzothioate (2a):** A solution of benzoic anhydride (0.68 g, 3.0 mmol), DMAP (73 mg, 0.60 mmol), 2-(diethoxymethyl)thiirane[2] (0.49 g, 3.0 mmol) and activated MS 4A (powder, 1.0 g) in toluene (10 mL) was refluxed for 12 h. After being cooled to ambient temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc (3 mL × 2). The combined organic layer was dried over anhydrous $MgSO_4$, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane). The product was dissolved in formic acid (1 mL), and stirred for 1.5 h at ambient temperature. The reaction mixture was diluted with EtOAc (20 mL) and quenched with saturated aqueous $NaHCO_3$ (20 mL). The layers were separated, and the organic layer was washed with H_2O (10 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 4:1) to give **10a** in 30% yield. Colorless solid; IR (KBr) 1700, 1671, 1579, 1448, 1211, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.86 (s, 1H), 6.92 (s, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.63 (t, J = 7.8 Hz, 1H), 7.98 (d, J = 7.8 Hz, 2H), 9.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.7, 128.8, 134.1 (2C), 135.9, 138.7, 142.2 (2C), 188.2, 188.4; HRMS (FAB) calcd for $C_{10}H_9O_2S$ $[M+H]^+$ 193.0323, found 193.0325.

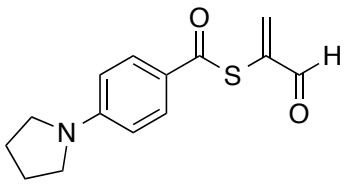


***S*-3-Oxoprop-1-en-2-yl 4-Methoxybenzothioate (2b):** A solution of *p*-anisic acid (0.46 g, 3.0 mmol), dimethylformamide (2 drops) in CH_2Cl_2 was added oxalyl chloride (0.52 mL, 6.0 mmol) at 0 ºC. The mixture was stirred for 12 h at ambient temperature. The reaction mixture was concentrated in *vacuo* to give a crude 4-methoxybenzoyl chloride. A solution of the 4-methoxybenzoyl chloride, DMAP (0.44 g, 4.2 mmol), 2-(diethoxymethyl)thiirane (0.49 g, 3.0 mmol) in DMF (15 mL) was refluxed for 12 h. After being cooled to ambient temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL), and extracted with EtOAc (3 mL × 2). The combined organic layer was dried over anhydrous $MgSO_4$, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane). The product was dissolved in formic acid (1 mL), and stirred for 1.5 h at ambient temperature. The reaction mixture was diluted with EtOAc (20 mL) and quenched with saturated $NaHCO_3$ (20 mL). The layers were separated, and the organic phase was washed with H_2O (10 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 4:1) to give **10b** in 30% yield. Colorless solid; IR (KBr) 1703, 1654, 1600, 1508, 1314, 1268, 1215, 1169, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.89 (s, 3H), 6.02 (d, *J* = 1.8 Hz, 1H), 6.19 (d, *J* = 1.8 Hz, 1H), 6.96 (d, *J* = 9.2 Hz, 2H), 8.08 (d, *J* = 9.2 Hz, 2H), 9.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.6, 114.0 (2C), 128.6, 130.0 (2C), 138.8, 141.8, 164.3, 186.6, 188.6; HRMS (EI) calcd for $C_{11}H_{10}O_3S$ $[M+H]^+$ 222.0347, found 222.0351.



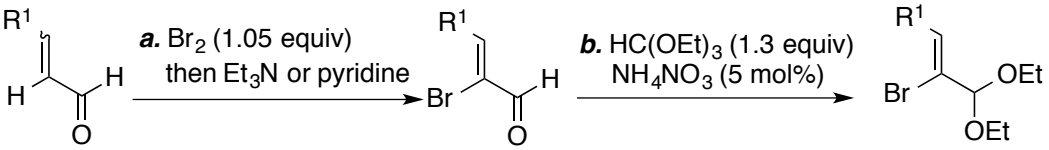
***S*-3-Oxoprop-1-en-2-yl 4-(Dimethylamino)benzothioate (2c):** **10c** was synthesized from 4-(*N*,*N*-dimethylamino)benzoic acid according to the same manner with **10b**. 15% yield. Yellow solid; IR (KBr) 1707, 1638, 1604, 1381, 1316, 1247, 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 6H), 6.51 (d, J = 8.7 Hz, 2H), 6.75 (s, 1H), 6.84 (s, 1H), 7.87 (d, *J* = 8.7 Hz, 2H), 9.61 (s, 1H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 40.0 (2C), 110.6 (2C), 123.1, 130.0 (2C), 139.2, 140.7, 154.1, 185.6, 189.1; HRMS (EI) calcd for $C_{12}H_{14}NO_2S$ $[M+H]^+$ 236.0745, found 236.0717.

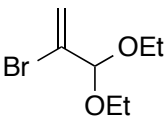


***S*-3-Oxoprop-1-en-2-yl 4-(Pyrrolidin-1-yl)benzothioate (2d):** Compound **3d** was synthesized from 4-(Pyrrolidin-1-yl)benzoic acid according to the same manner with **1c** 10% yield. Yellow solid; IR (KBr) 1708, 1640, 1601, 1527, 1402, 1243, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.00–2.10 (m, 4H), 3.32–3.42 (m, 4H), 6.50 (d, J = 8.7 Hz, 2H), 6.74 (s, 1H), 6.83 (s, 1H), 7.85 (d, *J* = 8.7 Hz 1H), 9.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4 (2C), 47.6 (2C), 110.8 (2C), 122.6 (2C), 130.2 (2C), 139.3, 140.6, 151.7, 185.4, 189.2; HRMS (EI) calcd for $C_{14}H_{15}NO_2S$ $[M^+]$ 261.0824, found 262.0827.

Synthesis of α-Bromoacrolein Diethylacetals 4–9.

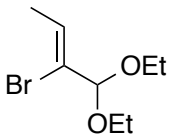


4: R'= H
5: R'= Me
6: R'= *n*-Bu
7: R'= Ph
8: R'= 4-$(MeO)C_6H_4$
9: R'= 4-FC_6H_4

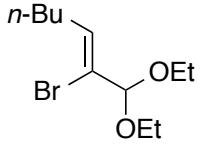


2-Bromo-3,3-diethoxyprop-1-ene (4):[3] To a solution of acrolein (R^1 = H, 7.42 mL, 100 mmol) in CH_2Cl_2 (100 mL) was added Br_2 (5.4 mL, 105 mmol) at –78 ºC, and the mixture was stirred at ambient temperature for 1 h. To the reaction mixture was added Et_3N (16.7 mL, 120 mmol) at 0 ºC, and the mixture was stirred at ambient temperature for 0.5 h. To the resulting reaction mixture was added saturated aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), and the mixture was extracted with Et_2O (20 mL × 2). The organic layers were dried over anhydrous

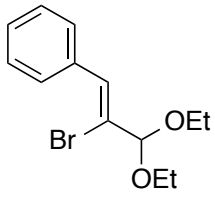
$MgSO_4$, filtrated and concentrated to give a crude α-bromoacrolein. A solution of the crude product, $(EtO)_3CH$ (16.6 mL, 100 mmol) and NH_4NO_3 (0.40 g, 5 mmol) in EtOH (5 mL) was refluxed for 2 h. The reaction mixture was poured into H_2O (30 mL), and extracted with EtOAc (15 mL × 2). The organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane) to give **4** (10.4 g, 50% yield). Yellow oil; IR ($CHCl_3$) 1444, 1374, 1108, 1063 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, J = 6.9 Hz, 6H), 3.54 (qd, J = 6.9, 9.2 Hz, 2H), 3.64 (qd, J = 2.3, 9.2 Hz, 2H), 4.83 (br s, 1H), 5.74 (d, J = 1.1 Hz, 1H), 6.12 (dd, J = 1.1, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0 (2C), 61.8 (2C), 101.5, 119.5, 129.9; HRMS (EI) calcd for $C_7H_{14}BrO_2^+$ [M+H$^+$] 209.0177, found 209.0151.



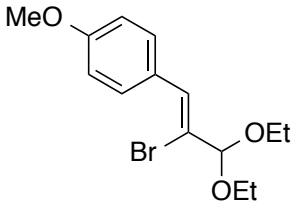
(*Z*)-2-Bromo-1,1-diethoxybut-2-ene (5):[4] To a solution of crotonaldehyde (R^1 = Me, 4.14 ml, 50 mmol) in CH_2Cl_2 (100 mL) was added Br_2 (2.7 mL, 53 mmol) at –78 ºC, and the mixture was stirred at ambient temperature for 1 h. To the reaction mixture was added pyridine (16.2 mL, 200 mmol) and stirred at ambient temperature for 0.5 h. To the resulting reaction mixture was added saturated aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), and the mixture was extracted with Et_2O (20 mL × 2). The organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated to give α-bromocrotonaldehyde. A solution of the crude product, $(EtO)_3CH$ (8.3 mL, 50 mmol) and NH_4NO_3 (0.20 g, 2.5 mmol) in EtOH (5 mL) was refluxed for 10 h. The reaction mixture poured into H_2O (30 mL), and extracted with EtOAc (15 mL × 2). The organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane) to give **5** (7.8 g, 70% yield) as a single diastereomer. Yellow oil; IR ($CHCl_3$) 1660, 1444, 1373, 1335, 1269, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) **δ** 1.24 (t, J = 6.9 Hz, 6H), 1.81 (d, J = 6.9 Hz, 3H), 3.51 (qd, J = 6.9, 9.2 Hz, 2H), 3.63 (qd, J = 6.9, 9.2 Hz, 2H), 4.80 (br s, 1H), 6.32 (qd, J = 6.9, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0 (2C), 16.2, 61.8 (2C), 102.5, 125.2, 127.2; HRMS (EI) calcd for $C_8H_{16}BrO_2^+$ [M+H$^+$] 223.0334, found 223.0315.



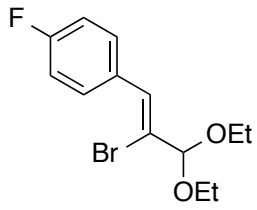
(*Z*)-2-Bromo-1,1-diethoxyhept-2-ene (6): Compound **6** was synthesized from trans-2-heptenal (R^1 = *n*-Bu) according to the same manner with **5**. Yellow oil; IR ($CHCl_3$) 1654, 1457, 1371, 1329, 1270, 1119, 1057, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.25 (t, *J* = 6.9 Hz, 6H), 1.30–1.47 (m, 4H), 2.24 (q, *J* = 7.3 Hz, 2H), 3.51 (qd, *J* = 6.9, 9.2 Hz, 2H), 3.62 (qd, *J* = 6.9, 9.2 Hz, 2H), 4.80 (s, 1H), 6.23 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 15.0 (2C), 22.3, 30.3 (2C), 61.8 (2C), 102.4, 123.9, 132.6; HRMS (FAB) calcd for $C_{11}H_{21}BrNa$ $[M+Na]^+$ 287.0623, found 287.0620.



(*Z*)-(2-Bromo-3,3-diethoxyprop-1-enyl)benzene (7):[5] Compound **7** was synthesized from cinnamaldehyde **7c** (R^1 = Ph) according to the same manner with **5**.

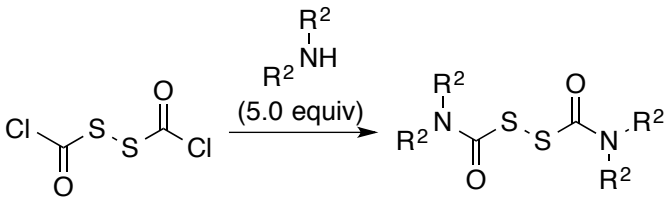


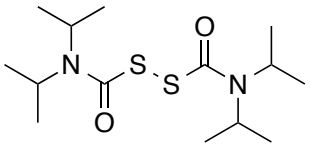
(*Z*)-1-(2-bromo-3,3-diethoxyprop-1-enyl)-4-methoxybenzene (8): Compound **8** was synthesized from (*E*)-3-(4-methoxyphenyl)acrylaldehyde (R^1 = 4-(MeO)C_6H_4) according to the same manner with **5**. Yellow oil; IR ($CHCl_3$) 1607, 1501, 1251, 1178, 1123, 1112, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* = 6.9 Hz, 6H), 3.59 (qd, *J* = 6.9, 9.2 Hz, 2H), 3.69 (qd, *J* = 7.3, 9.2 Hz, 2H), 3.84 (s, 3H), 4.95 (s, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.1 (2C), 55.2, 61.9 (2C), 103.3, 113.5 (2C), 120.5, 127.0, 129.3, 130.8 (2C), 159.6; HRMS (EI) calcd for $C_{14}H_{19}BrO_3$ $[M]^+$ 314.0518, found 314.0522.



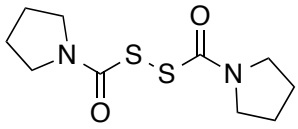
(*Z*)-1-(2-Bromo-3,3-diethoxyprop-1-enyl)-4-fluorobenzene (9): Compound **9** was synthesized from (*E*)-3-(4-fluorophenyl)acrylaldehyde **7e** (R^1 = 4-FC_6H_4) according to the same manner with **5**. Yellow oil; IR ($CHCl_3$) 1603, 1508, 1232, 1160, 1123, 1099, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 6.9 Hz, 6H), 3.59 (qd, *J* = 6.9, 9.2 Hz, 2 H), 3.70 (qd, *J* = 6.9, 9.2 Hz, 2H), 4.97 (s, 1H), 7.06 (dd, *J* = 8.7, 8.7 Hz, 2H), 7.68 (dd, *J* = 5.5, 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0 (2C), 61.9 (2C), 103.0, 115.1 (d, J_{C-F} = 21.9 Hz, 2C), 122.5, 128.7, 130.7, 131.1 (d, J_{C-F} = 7.6 Hz, 2C), 162.3 (d, J_{C-F} = 247 Hz); HRMS (EI) calcd for $C_{13}H_{16}BrFO_2$ $[M]^+$ 302.0318, found 314.0320.

Synthesis of Bis(carbamoyl)disulfides 10.

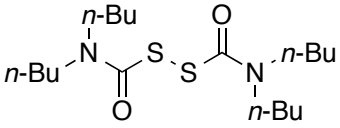




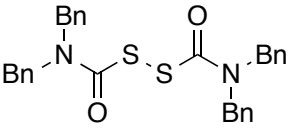
Bis(*N*,*N*-diisppropylcarbamoyl)disulfide (10a): To a solution of *N*,*N*-diisopropylamine (7.0 mL, 50 mmol) in CH_2Cl_2 (25 mL) was added bis(chlorocarbonyl)disulfide[6] (1.9 g, 10 mmol) slowly at 0 ºC, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was poured into 1 M aqueous HCl (10 mL), and extracted with chloroform (10 mL × 2). The combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated. The residue was purified by recrystallization from a mixture of hexane and acetone to give **10a** (2.2 g, 68% yield). Colorless solid; IR (KBr) 1678, 1460, 1418, 1370, 1268, 1209, 1152, 1110 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (br s, 24 H), 3.52 (br s, 2H), 4.33 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7 (8C), 48.0 (br, 2C), 50.5 (br, 2C), 160.8 (2C); HRMS (FAB) calcd for $C_{14}H_{29}N_2O_2S_2$ $[M+H]^+$ 321.1670, found 321.1673.



Bis(pyrrolidinylcarbonyl)disulfide (10b):[7] Compound **10b** was synthesized from pyrrolidine according to the same manner with **10a**. Colorless solid; IR (KBr) 1678, 1459, 1361, 1293, 1250, 1222, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.84–2.09 (m, 8H), 3.56 (t, J = 6.9 Hz, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.4 (2C), 25.8 (2C), 46.0 (2C), 48.3 (2C), 161.2 (2C); HRMS (FAB) calcd for $C_{10}H_{17}N_2O_2S_2$ $[M+H]^+$ 261.0731, found 261.0734.

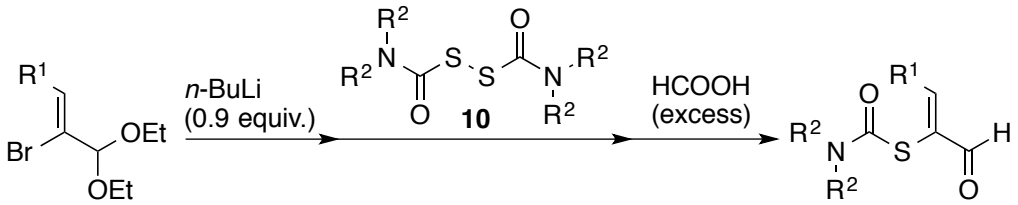


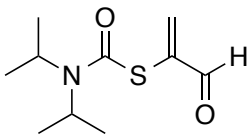
Bis(*N*,*N*-dibutylcarbamoyl)disulfide (10c): Compound **10c** was synthesized from dibutylamine according to the same manner with 10c. The crude product was purified by flash column chromatography on silica gel (hexane–EtOAc 10:1). Yellow oil; R_f= 0.45 (hexane–EtOAc 5:1); IR ($CHCl_3$) 1683, 1466, 1406, 1374, 1253, 1202, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84–1.02 (m, 12H), 1.24–1.43 (m, 8H), 1.48–1.74 (m, 8H), 3.39 (br s, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (4C), 20.1 (4C), 29.8 (2C), 30.8 (2C), 48.4 (2C), 48.8 (2C), 163.2 (2C); HRMS (FAB) calcd for $C_{18}H_{37}N_2O_2S_2$ $[M+H]^+$ 377.2296, found 377.2301.



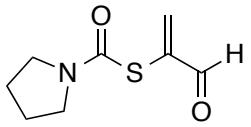
Bis(*N*,*N*-dibenzylcabamoyl)disulfide (10d): Compound **10d** was synthesized from dibenzylamine according to the same manner with **10a**. Colorless solid; IR (KBr) 1673, 1496, 1455, 1405, 1362, 1264, 1174, 1078 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.62 (s, 8H), 7.22–7.30 (br s, 4H), 7.26–7.43 (br s, 16H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.4 (2C), 50.6 (2C), 127.6 (4C), 127.7 (2C), 128.0(2C), 128.4 (4C), 128.7 (4C), 128.9 (4C), 135.0 (2C), 135.8 (2C), 164.6 (2C); HRMS (FAB) calcd for $C_{30}H_{29}N_2O_2S_2$ $[M+H]^+$ 513.1670, found 513.1668.

Synthesis of α-(Carbamoylthio)acroleins 11–16.

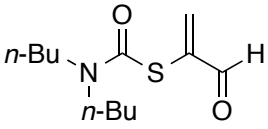




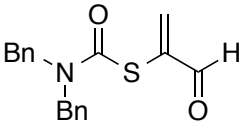
***S*-3-Oxoprop-1-en-2-yl Diisopropylcarbamothioate (11a):** To a solution of **4** (0.25 g, 1.2 mmol) in THF (3 mL) was added 1.6 M solution of *n*-BuLi in hexane (0.68 mL, 1.1 mmol) at –78 ºC, and the mixture was stirred at –78 °C for 0.5 h. The reaction mixture was added to a solution of **10a** (0.32 g, 1 mmol) in THF (3 mL) via cannula at –78 °C, and the mixture was stirred at –78 ºC for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was allowed to warm to ambient temperature. The layers were separated, and the organic layer was washed with H_2O (10 mL × 2). The organic layer was dried over anhydrous Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1). To a solution of the crude product in CH_2Cl_2 (5 mL) was added formic acid (1 mL), and the mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was diluted with $CHCl_3$ (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The layers were separated, and the organic layer was washed with H_2O (5 mL × 2). The organic phase was dried over anhydrous Na_2SO_4, filtrated and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 5:1) to give **11a** (0.11 g, 50% yield). Colorless solid; R_f = 0.29 (hexane–EtOAc 5:1); IR (KBr) 1696, 1661, 1419, 1367, 1279, 1209, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (br s, 6H), 1.35 (br s, 6H), 3.52 (br s, 1H), 4.07 (br s, 1H), 6.52 (s, 1H), 6.68 (s, 1H), 9.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4 (4C), 47.4 (br), 50.6 (br), 138.0, 139.4, 161.6, 189.0; HRMS (FAB) calcd for $C_{10}H_{18}NO_2S$ $[M+H]^+$ 216.1058, found 216.1081.



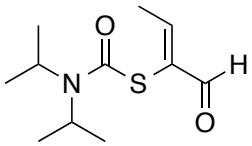
***S*-3-Oxoprop-1-en-2-yl Pyrrolidine-1-carbothioate (11b):** Compound **11b** was synthesized from **4** and **10b** according to the same manner with **11a**. Colorless solid; R_f = 0.32 (hexane–EtOAc 1:1); IR (KBr) 1707, 1663, 1458, 1372, 1337, 1224, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92 (q, *J* = 6.9 Hz, 2H), 1.99 (q, *J* = 6.9 Hz, 2H), 3.47 (t, *J* = 6.9 Hz, 2H), 3.51 (q, *J*= 6.9 Hz, 2H), 6.70 (s, 1H), 6.72 (s, 1H), 9.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 25.5, 46.3, 47.3, 139.3, 139.8, 161.8, 189.1; HRMS (FAB) calcd for $C_8H_{12}NO_2S$ $[M+H]^+$ 186.0589, found 186.0592.



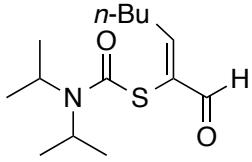
***S*-3-Oxoprop-1-en-2-yl Dibutylcarbamothioate (11c):** Compound **11c** was synthesized from **4** and **10c** according to the same manner with **11a**. Pale yellow oil; R_f = 0.31 (hexane–EtOAc 5:1); IR ($CDCl_3$) 1733, 1650, 1458, 1409, 1375, 1206, 1125, 1063 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 7.3 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H), 1.19–1.44 (m, 4H), 1.46–1.77 (m 4H), 3.32 (t, *J* = 6.9 Hz, 4H), 6.59 (s, 1H), 6.68 (s, 1H), 9.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (2C), 20.0 (2C), 29.9, 30.5, 47.6, 48.5, 138.7, 139.4, 163.9, 189.0; HRMS (FAB) calcd for $C_{12}H_{22}NO_2S$ $[M+H]^+$ 244.1371, found 244.1362.



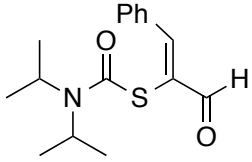
***S*-3-Oxoprop-1-en-2-yl Dibenzylcarbamothioate (11d):** Compound **11d** was synthesized from **4** and **10d** according to the same manner with **11a**. Colorless solid; IR (KBr) 1708, 1661, 1496, 1454, 1404, 1362, 1185, 1078 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.51 (s, 4H), 6.73 (s, 1H), 6.77 (s, 1H), 7.18–7.24 (m, 2H), 7.26–7.43 (m, 8H), 9.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 49.3, 50.9, 127.4 (2C), 127.7, 128.0, 128.3 (2C), 128.7 (2C), 128.9 (2C), 135.2, 135.9, 139.5, 139.8, 165.3, 188.6; HRMS (FAB) calcd for $C_{18}H_{18}NO_2S$ $[M+H]^+$ 312.1058, found 312.1052.



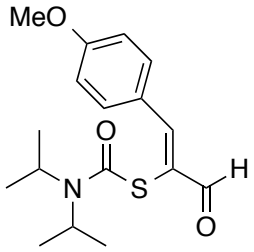
(Z)-S-1-Oxobut-2-en-2-yl Diisopropylcarbamothioate (12a): Compound **12a** was synthesized from **5** and **10a** according to the same manner with **11a**. Pale yellow solid; IR (KBr) 1692, 1657, 1616, 1423, 1371, 1282, 1214, 1177, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (br s, 12H), 2.14 (d, J = 6.9 Hz, 3H), 3.47 (s, 1H), 3.47 (br s, 1H), 4.21 (br s, 1H), 7.34 (q, J = 6.9 Hz, 1H), 9.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.9, 20.5 (4C), 47.4 (br), 50.5 (br), 134.9, 156.4, 160.9, 189.9; HRMS (FAB) calcd for $C_{11}H_{20}NO_2S$ $[M+H]^+$ 230,1215, found 230.1214.



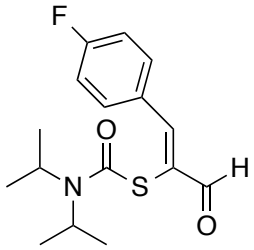
(*Z*)-S-1-Oxohept-2-en-2-yl Diisopropylcarbamothioate (13a): Compound **13a** was synthesized from **6** and **10a** according to the same manner with **11a**. Pale yellow oil; R_f = 0.36 (hexane–EtOAc 4:1); IR ($CHCl_3$) 1701, 1668, 1609, 1457, 1420, 1372, 1276, 1209, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.20–1.45 (m, 14H), 1.51 (quint, *J* = 7.4 Hz, 2H), 2.55 (q, *J* = 7.4 Hz, 2H), 3.47 (br s, 1H), 4.21 (br s, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 20.6 (4C), 22.4, 30.2, 30.6, 47.5 (br), 50.6 (br), 133.8, 161.1, 161.2, 190.1; HRMS (FAB) calcd for $C_{14}H_{26}NO_2S$ $[M+H]^+$ 272.1684, found 272.1690.



(*Z*)-S-3-Oxo-1-phenylprop-1-en-2-yl Diisopropylcarbamothioate (14a): Compound **14a** was synthesized from **7** and **10a** according to the same manner with **11a**. Pale yellow solid; IR (KBr) 1695, 1657, 1596, 1378, 1280, 1208, 1122, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (br s, 12H), 3.49 (br s, 1H), 4.25 (br s, 1H), 7.40–7.49 (m, 3H), 7.79–7.88 (m, 2H), 7.91 (s, 1H), 9.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6 (4C), 47.6, 50.8, 128.4 (2C), 130.7, 130.9, 131.1 (2C), 133.9, 151.4, 161.0, 190.5; HRMS (FAB) calcd for $C_{16}H_{22}NO_2S$ $[M+H]^+$ 292.1371, found 292.1370.



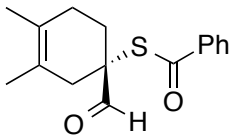
(*Z*)-S-1-(4-Methoxyphenyl)-3-oxoprop-1-en-2-yl Diisopropylcarbamothioate (15a): Compound **15a** was synthesized from **8** and **10a** according to the same manner with **11a**. Pale yellow solid; IR (KBr) 1686, 1655, 1596, 1508, 1421, 1307, 1278, 1261, 1175, 1131, 1108, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (br s, 6H), 1.33 (br s, 6H), 3.49 (br s, 1H), 3.86 (s, 3H), 4.30 (br s, 1H), 6.94 (d, J = 8.7 Hz, 2H), 7.85 (s, 1H), 7.89 (d, J = 8.7 Hz, 2H), 9.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7 (4C), 47.7 (br), 50.8 (br), 55.5, 114.1 (2C), 126.7, 128.0, 133.6 (2C), 152.7, 161.1, 161.9, 190.9; HRMS (FAB) calcd for $C_{17}H_{24}NO_3S$ $[M+H]^+$ 322.1477, found 322.1469.



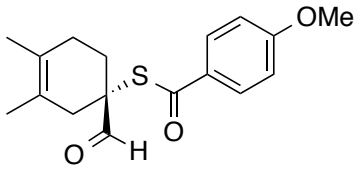
(*Z*)-S-1-(4-Fluorophenyl)-3-oxoprop-1-en-2-yl Diisopropylcarbamothioate (16a): Compound **16a** was synthesized from **9** and **10a** according to the same manner with **11a**. Pale yellow solid; IR (KBr) 1699, 1651, 1591, 1506, 1420, 1373, 1281, 1227, 1206, 1192, 1121, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (br s, 6H), 1.33 (br s, 6H), 3.50 (br s, 1H), 4.24 (br s, 1H), 7.12 (dd, J = 8.7, 8.7 Hz, 2H), 7.855 (dd, J = 6.0, 8.7 Hz, 2H), 7.863 (s, 1H), 9.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7 (4C), 47.8 (br), 50.9 (br), 115.8 (d, J_{C-F} = 21.9 Hz, 2C), 130.2, 130.5, 133.4 (d, J_{C-F} = 8.6 Hz, 2C), 150.2, 160.8, 164.0 (d, J_{C-F} = 250 Hz),190.5; HRMS (FAB) calcd for $C_{16}H_{21}NO_2SF$ $[M+H]^+$ 310.1277, found 310.1267.

General Procedure for the Enantioselective Diels–Alder Reaction of α-(Acylthio)acroleins.

To a solution of chiral triamine **1** (3.0 mg, 0.010 mmol) and pentafluorobenzenesulfonic acid (6.8 mg, 0.0275 mmol) in $EtNO_2$ (0.125 mL) was added α-(acylthio)acrolein (0.10 mmol) at –78ºC. After being stirred at same temperature for 15 min, a diene (0.40 mmol) was added in one portion. The reaction mixture was stirred for several hours at 0 ºC. Upon consumption of α-(acylthio)acrolein, the reaction was quenched with Et_3N and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using hexane–EtOAc as the eluent. The corresponding physical and spectroscopic data for adducts **3**, **17**–**26** are as follows.

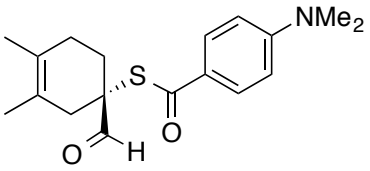


(*S*)-*S*-1-Formyl-3,4-dimethylcyclohex-3-enyl Benzothioate (3a): Colorless oil; $[\alpha]^{24}_D$ –33.9 (c 1.0, $CHCl_3$) for 43% ee; HPLC (Daicel Chiralcel OD-H column, hexane–*i*-PrOH 200:1, flow rate 1.0 mL/min) t_R = 14.6 (minor enantiomer), 17.2 (major enantiomer) min; IR ($CHCl_3$) 1726, 1656, 1447, 1209, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 3H), 1.66 (s, 3H), 1.98–2.21 (m, 4H), 2.26 (d, *J* = 17.9 Hz, 1H), 2.80 (d, *J* = 17.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.93 (d, *J* = 7.4 Hz, 2H), 9.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 19.1, 27.3, 28.7, 36.4, 58.9, 122.4, 125.2, 127.4 (2C), 128.7 (2C), 133.8, 136.2, 191.3, 199.2; HRMS (FAB) calcd for $C_{16}H_{19}O_2S$ [M+H+] 275.1106, found 275.1100.

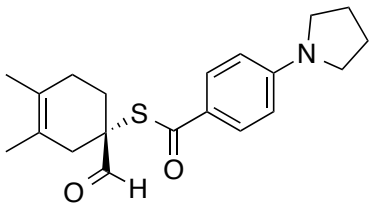


(*S*)-S-1-Formyl-3,4-dimethylcyclohex-3-enyl 4-Methoxybenzothioate(3b): Colorless oil; $[\alpha]^{24}_D$ –17.2 (c 1.8, $CHCl_3$) for 44% ee; HPLC (Daicel Chiralcel OD-H column, hexane–*i*-PrOH 40:1, flow rate 1.0 mL/min) t_R = 14.9 (minor enantiomer), 19.2 (major enantiomer) min; IR ($CHCl_3$) 1725, 1650, 1600, 1508, 1262, 1217, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64 (s, 3H), 1.66 (s, 3H), 1.97–2.23 (m, 4H), 2.25 (br d, *J* = 17.9 Hz, 1H), 2.79 (br d, *J* = 17.9 Hz, 1H), 3.86 (s,

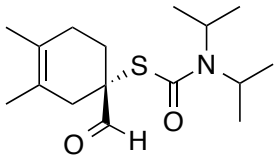
3H), 6.91 (d, J = 9.2 Hz, 2H), 7.89 (d, J = 9.2 Hz 2H), 9.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 19.1, 27.3, 28.7, 36.5, 55.5, 58.7, 113.8 (2C), 122.5, 125.1, 129.1, 129.7 (2C), 164.1, 189.7, 199.4; HRMS (FAB) calcd for $C_{17}H_{21}O_3S$ $[M+H]^+$ 305.1211, found 305.1224.



(S)-S-1-Formyl-3,4-dimethylcyclohex-3-enyl 4-(Dimethylamino)benzothioate (3c): Pale yellow solid; $[\alpha]^{22}_D$ –33.2 (c 1.0, $CHCl_3$) for 68% ee; HPLC (Daicel Chiralcel AD-H column, hexane–*i*-PrOH 20:1, flow rate 1.0 mL/min) t_R = 35.8 (major enantiomer), 42.5 (minor enantiomer) min; IR (KBr) 1721, 1638, 1596, 1525, 1372, 1242, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63–1.70 (br s, 6H), 1.96–2.22 (m, 4H), 2.25 (d, J = 17.9 Hz, 1H), 2.79 (d, J = 17.0 Hz, 1H), 3.06 (s, 6H), 6.60 (d, J = 9.2 Hz, 2H), 7.81 (d, J = 9.2 Hz, 2H), 9.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 19.1, 27.4, 28.8, 36.7, 40.0 (2C), 58.3, 110.5 (2C), 122.6, 123.6, 125.0, 129.6 (2C), 153.9, 188.8, 199.9; HRMS (FAB) calcd for $C_{18}H_{24}NO_2S$ $[M+H]^+$ 318.1528, found 318.1543.

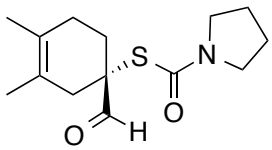


(*S*)-*S*-1-Formyl-3,4-dimethylcyclohex-3-enyl 4-(Pyrrolidin-1-yl)benzothioate (3d): Pale yellow solid; $[\alpha]^{22}_D$ –34.8 (c 1.4, $CHCl_3$) for 72% ee; HPLC (Daicel Chiralcel AD-H column, hexane–*i*-PrOH 40:1, flow rate 1.0 mL/min) t_R = 57.9 (major enantiomer), 71.1 (minor enantiomer) min; IR (KBr) 1719, 1638, 1592, 1525, 1395, 1216, 1174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55–1.64 (m, 6H), 1.94–2.22 (m, 8H), 2.25 (d, J = 17.4 Hz, 1H), 2.53 (d, J = 17.4 Hz, 1H), 3.32–3.41 (m, 4H), 6.46 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.7 Hz, 2H), 9.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 19.2, 25.5 (2C), 27.5, 28.9, 36.8, 47.6 (2C), 58.3, 110.7, 122.7, 123.2, 125.1, 129.9 (2C), 151.6, 188.7, 200.0; HRMS (FAB) calcd for $[M+H]^+$ 344.1684, found 344.1674.



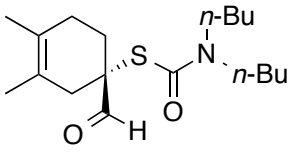
(*S*)-*S*-1-Formyl-3,4-dimethylcyclohex-3-enyl

Diisopropylcarbamothioate (17a): $[\alpha]^{23}_{D}$ –13.7 (c 1.6, $CHCl_3$) for 74% ee; HPLC (Daicel Chiralcel AS-3 and AS-H × 2, hexane–*i*-PrOH = 100:1, flow rate = 0.4 mL/min) t_R = 64.5 (major, (–)-enantiomer), 67.1 (minor, (+)-enantiomer) min; IR ($CHCl_3$) 1723, 1648, 1422, 1371, 1285, 1211, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10–1.44 (m, 12H), 1.63 (s, 3H), 1.65 (s, 3H), 1.91–1.99 (m, 2H), 1.98–2.19 (m, 2H), 2.19 (d, *J* = 18.3 Hz, 1H), 2.70 (d, *J* = 17.0 Hz, 1H), 3.43 (br s, 1H), 3.99 (br s,1H), 9.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 19.2, 20.7 (4C), 27.7, 29.0, 37.1, 47.4 (br), 50.7 (br), 58.2, 122.8, 125.1, 164.1, 200.3; HRMS (FAB) calcd for $C_{16}H_{28}O_2NS^+$ $[M+H^+]$ 298.1841, found 298.1865.



(S)-S-1-Formyl-3,4-dimethylcyclohex-3-enyl

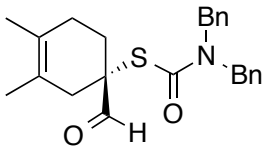
Pyrrolidine-1-carbothioate (17b): Colorless oil; $[\alpha]^{24}_{D}$ –29.5 (c 0.50, $CHCl_3$) for 76% ee; HPLC (Daicel Chiralcel AS-H column, hexane–*i*-PrOH = 20:1, flow rate = 1.0 mL/min) t_R = 18.5 (major enantiomer), 24.1 (minor enantiomer) min; IR ($CHCl_3$) 1718, 1647, 1373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.65 (s, 3H), 1.88 (q, *J* = 6.4 Hz, 2H), 1.91–2.02 (m, 2H), 2.02–2.21 (m, 2H), 2.24 (d, *J* = 17.9 Hz, 1H), 2.76 (d, *J* = 17.4 Hz, 1H), 3.34 (t, J = 6,4 Hz 2H), 3.46 (t, J = 6.4 Hz, 2H), 9.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 19.0, 24.5, 25.7, 27.7, 28.7, 37.1, 46.5, 46.9, 58.3, 122.7, 125.0, 164.3, 200.0; HRMS (FAB) calcd for $C_{14}H_{22}NO_2S$ $[M+H]^+$ 268.1371, found 268.1368.



(S)-S-1-Formyl-3,4-dimethylcyclohex-3-enyl

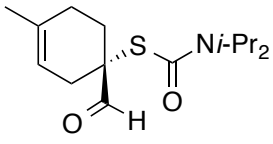
Dibutylcarbamothioat (17c): Colorless oil; $[\alpha]^{24}_{D}$ –30.0 (c 1.16, $CHCl_3$) for 66% ee; HPLC (Daicel Chiralcel AS-3 and AS-H column, hexane–*i*-PrOH = 100:1, flow rate =

0.5 mL/min) t_R = 40.3 (major enantiomer) min, 42.8 (minor enantiomer) min; IR ($CHCl_3$) 1724, 1643, 1409, 1206, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H), 1.18–1.38 (m, 4H), 1.47 (tt, *J* = 7.8, 7.8 Hz, 2H), 1.55 (tt, *J* = 7.8, 7.8 Hz, 2H), 1.61 (s, 3H), 1.63 (s, 3H), 1.89–1.97 (m, 2H), 1.96–2.15 (m, 2H), 2.18 (d, *J* = 18.3 Hz, 1H), 2.71 (d, *J* = 17.4 Hz, 1H), 3.13–3.34 (m, 4H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (2C), 18.7, 19.0, 20.1 (2C), 27.6, 28.8, 29.8, 30.4, 37.0, 46.9, 48.5, 58.3, 122.7, 124.9, 165.9, 200.0; HRMS (FAB) calcd for $C_{18}H_{32}NO_2S$ $[M+H]^+$ 326.2154, found 326.2170.



(*S*)-*S*-1-Formyl-3,4-dimethylcyclohex-3-enyl

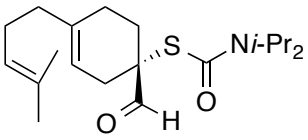
Dibenzylcarbamothioate (17d): Colorless oil; $[\alpha]^{23}_D$ –2.56 (c 0.72, $CHCl_3$) for 48% ee; HPLC (Daicel Chiralcel OZ-H column, hexane–*i*-PrOH = 20:1, flow rate = 1.0 mL/min) t_R = 14.5 (major enantiomer), 11.1 (minor enantiomer) min; IR ($CHCl_3$) 1724, 1643, 1495, 1454, 1406, 1186, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.67 (s, 3H), 1.96–2.23 (m, 4H), 2.28 (d, *J* = 17.9 Hz, 1H), 2.80 (d, *J* = 17.9 Hz, 1H), 4.35–4.65 (m, 4H), 7.11–7.51 (m, 10H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 19.1, 27.5, 28.8, 36.9, 48.5, 50.8, 59.0, 122.5, 125.1, 127.4, 127.7 (2C), 127.9, 128.3 (2C), 128.7 (2C), 128.8 (2C), 135.4, 136.2, 167.4, 199.7; HRMS (FAB) calcd for $C_{24}H_{28}NO_2S$ $[M+H]^+$ 394.1841, found 394.1843.



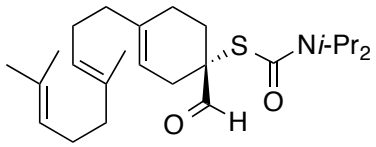
(*S*)-*S*-1-Formyl-4-methylcyclohex-3-enyl

Diisopropylcarbamothioate (18): Colorless oil; $[\alpha]^{24}_D$ –32.5 (c 1.48, $CHCl_3$) for 81% ee; HPLC (Daicel Chiralcel OZ-H column, hexane–i-PrOH = 100:1, flow rate = 0.5 mL/min) t_R = 22.1 (major enantiomer), 24.6 (minor enantiomer) min; IR ($CHCl_3$) 1721, 1647, 1422, 1371, 1285, 1210, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12–1.43 (m, 12H), 1.68 (s, 3H), 1.96–2.04 (m, 2H), 2.04–2.16 (m, 2H), 2.29 (d, *J* = 17.9 Hz, 1H), 2.73 (d, *J* = 18.3 Hz, 1H), 3.44 (br s, 1H), 3.99 (br s, 1H), 5.38 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.50 (2C), 20.53 (2C), 23.3, 27.35, 27.40, 31.1, 47.3 (br),

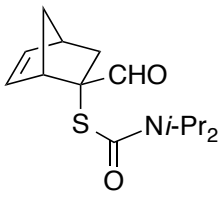
50.6 (br), 57.2, 117.8, 133.4, 163.8, 200.2; HRMS (FAB) calcd for $C_{15}H_{26}NO_2S$ $[M+H]^+$ 284.1684, found 284.1692.



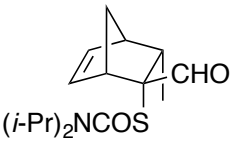
(*S*)-*S*-1-Formyl-4-(4-methylpent-3-enyl)cyclohex-3-enyl Diisopropylcarbamothioate (19): Colorless oil; $[\alpha]^{24}_D$ –5.6 (c 1.00, $CHCl_3$) for 81% ee; HPLC (Daicel Chiralcel OZ-H column, hexane–i-PrOH = 500:1, flow rate = 0.5 mL/min) t_R = 97.6 (major enantiomer), 117.1 (minor enantiomer) min; IR ($CHCl_3$) 1722, 1647, 1422, 1373, 1285, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13–1.44 (m, 12H), 1.61 (s, 3H), 1.69 (s, 3H), 1.90–2.04 (m, 4H), 2.04–2.23 (m, 4H), 2.31 (d, J = 17.9 Hz, 1H), 2.77 (d, J = 17.9 Hz, 1H), 3.44 (br s, 1H), 3.99 (br s, 1H), 5.05–5.13 (m, 1H), 5.39 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 20.5 (4C), 25.7, 26.2, 27.4, 31.1, 37.2, 47.2 (br), 50.6 (br), 57.4, 117.5, 123.9, 131.6, 137.0, 163.9, 200.3; HRMS (FAB) calcd for $C_{20}H_{34}NO_2S$ $[M+H]_+$ 352.2310, found 352.2328.



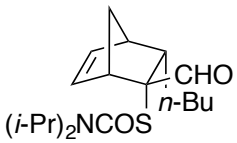
(*S*,*E*)-*S*-4-(4,8-Dimethylnona-3,7-dienyl)-1-formylcyclohex-3-enyl Diisopropylcarbamothioate (20): Colorless oil; $[\alpha]^{22}_D$ –9.2 (c 1.04, $CHCl_3$) for 67% ee; HPLC (Daicel Chiralcel OZ-H column, hexane–*i*-PrOH = 500:1, flow rate = 0.5 mL/min) t_R = 76.0 (major enantiomer) min, 93.1 (minor enantiomer) min; IR ($CHCl_3$) 1723, 1648, 1422, 1372, 1285, 1036 cm_{-1}; $_1H$ NMR (400 MHz, $CDCl_3$) δ 1.04–1.44 (m, 12H), 1.60 (s, 6H), 1.68 (s, 3H), 1.89–2.02 (m, 6H), 2.02–2.20(m, 6H), 2.30 (d, J = 18.3 Hz, 1H), 2.75 (d, J = 17.8 Hz, 1H), 3.43 (br s, 1H), 3.98 (br s, 1H), 5.09 (s, 3H), 5.10 (s, 3H), 5.39 (s, 1H), 9.58 (s, 1H); $_{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.0, 17.7, 20.5 (4C), 25.7 (2C), 26.1, 26.7, 27.4, 31.1, 37.2, 39.7, 47.2 (br), 50.5 (br), 57.4, 117.5, 123.9, 124.3, 131.3, 135.2, 137.0, 163.9, 200.3; HRMS (FAB) calcd for $C_{25}H_{42}NO_2S$ $[M+H]^+$ 420.2936, found 420.2925.



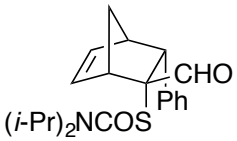
2-Formylbicyclo[2.2.1]hept-5-en-2-yl Diisopropylcarbamothioate (21, ca. 1:1 diastereomer mixture): Colorless oil; HPLC (Daicel Chiralcel OD-H × 3 column, hexane–*i*-PrOH = 100:1, flow rate = 0.5 mL/min) t_R = 59.2, 62.3 min; IR ($CHCl_3$) 1718, 1651, 1636, 1284 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10–1.46 (m, 13H), 1.54–1.62 (m, 1H), 1.90–1.96 (s, 0.5H), 1.99 (dd, J = 3.6, 12.8 Hz, 0.5H), 2.14 (dd, J = 2.8, 12.8 Hz, 0.5H), 2.75 (dd, J = 3.6, 12.8 Hz, 0.5H), 2.98 (s, 1H), 3.13 (s, 0.5H), 3.27 (s, 0.5H), 3.42 (br s, 1H), 3.92 (br s, 1H), 6.04–6.11 (m, 1H), 6.30 (dd, J = 3.2, 5.5 Hz, 0.5H), 6.36 (dd, J = 3.2, 5.5 Hz, 0.5H), 9.60 (s, 0.5H), 9.64 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (4C), 36.6 (0.5C), 38.6 (0.5C), 42.4 (0.5C), 43.1 (0.5C), 46.2 (0.5C), 47.2 (br), 48.2 (0.5C), 48.5 (0.5C), 49.3 (0.5C), 50.9 (br), 63.5 (0.5C), 65.3 (0.5C), 132.6 (0.5C), 133.5 (0.5C), 139.9 (0.5C), 140.2 (0.5C), 164.4 (0.5C), 164.5 (0.5C), 199.0 (0.5C), 200.5 (0.5C); HRMS (FAB) calcd for $C_{15}H_{24}NO_2S$ $[M+H]^+$ 282.1526, found 282.1531.



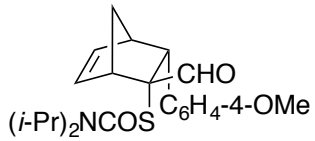
***S*-(1*S*,2*S*,3*S*,4*R*)-2-Formyl-3-methylbicyclo[2.2.1]hept-5-en-2-yl Diisopropylcarbamothioate (22, *exo* isomer):** Colorless oil; $[\alpha]^{24}_D$ 105.5 (c 0.95, $CHCl_3$) for 88% ee; HPLC (Daicel Chiralcel AS-H column × 2, hexane–*i*-PrOH = 100:1, flow rate = 0.5 mL/min) t_R = 30.3 (major enantiomer of *exo* isomer), 33.3 (minor enantiomer of *exo* isomer), 36.3 (major enantiomer of *endo* isomer), 44.0 (minor enantiomer of *endo* isomer) min; IR ($CHCl_3$) 1726, 1647, 1452, 1425, 1373, 1287, 1211, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 7.3 Hz, 3H), 1.05–1.46 (m, 13H), 1.68 (d, J = 8.7 Hz, 1H), 2.82 (s, 1H), 2.98 (s, 1H), 3.17 (ddd, J = 3.2, 6.9, 14.2 Hz, 1H), 3.41 (br s, 1H), 4.00 (br s, 1H), 6.12 (dd, J = 2.8, 5.5 Hz, 1H), 6.35 (dd, J = 2.8, 5.5 Hz, 1H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 16.5, 20.5 (4C), 38.0, 45.4, 47.0 (br), 48.7, 50.0, 50.8 (br), 70.8, 133.8, 139.2, 165.9, 198.7; HRMS (FAB) calcd for $C_{16}H_{26}NO_2S$ $[M+H]^+$ 296.1684, found 296.1688. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.50 (s,1H, CHO, *endo* isomer) and 9.54 (s, 1H, CHO, *exo* isomer).



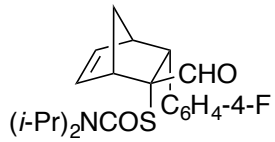
***S*-(1*S*,2*R*,3*S*,4*R*)-3-Butyl-2-formylbicyclo[2.2.1]hept-5-en-2-yl Diisopropylcarbamothioate (23, *exo* isomer):** Colorless oil; $[\alpha]^{24}_{D}$ 151.0 (c 1.20, $CHCl_3$) for 88% ee; HPLC (Daicel Chiralcel AD-H column × 2, hexane–*i*-PrOH = 500:1, flow rate = 0.5 mL/min) t_R = 34.3 (major enantiomer of *exo* isomer), 52.9 (minor enantiomer of *exo* isomer), 57.6 (major enantiomer of *endo* isomer), 87.0 (minor enantiomer of *endo* isomer) min; IR ($CHCl_3$) 1718, 1636, 1457, 1422, 1371, 1285, 1211, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9 Hz, 3H), 0.98–1.48 (m, 18H), 1.63 (d, *J* = 9.2 Hz, 1H), 2.90–3.06 (m, 3H), 3.42 (br s, 1H), 4.01 (br s, 1H), 6.11 (dd, *J* = 2.8, 5.6 Hz, 1H), 6.32 (dd, *J* = 2.8, 5.6 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 13.9, 20.5 (4C), 22.9, 30.7, 30.9, 43.4, 44.9, 45.4, 47.1 (br), 49.6, 50.7, 70.6, 134.0, 138.7, 165.0, 198.5; HRMS (FAB) calcd for $C_{19}H_{32}NO_2S$ $[M+H]^+$ 338.2154, found 338.2159. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.51 (s, 1H, CHO, *endo* isomer) and 9.53 (s, 1H, CHO, *exo* isomer).



***S*-(1*S*,2*R*,3*R*,4*R*)-2-Formyl-3-phenylbicyclo[2.2.1]hept-5-en-2-yl Diisopropylcarbamothioate (24, *exo* isomer):** Colorless oil; $[\alpha]^{24}_{D}$ 155.9 (c 1.55, $CHCl_3$) for 91% ee; HPLC (Daicel Chiralcel AD-H column × 2, hexane–*i*-PrOH = 100:1, flow rate = 0.5 mL/min) t_R = 30.5 (major enantiomer of *exo* isomer), 34.8 (minor enantiomer of *exo* isomer), 44.2 (major enantiomer of *endo* isomer), 59.4 (minor enantiomer of *endo* isomer) min; IR ($CHCl_3$) 1718, 1647, 1452, 1422, 1370, 1285, 1210, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.71 (s, 3H), 0.88 (s, 3H), 1.07 (s, 3H), 1.12 (s, 3H), 1.45 (d, *J* = 8.7 Hz, 1H), 1.88 (d, *J* = 9.2 Hz, 1H), 3.07 (br s, 1H), 3.10 (s, 1H), 3.16 (s, 1H), 3.75 (br s, 1H), 4.47 (d, *J* = 3.2 Hz, 1H), 6.33 (dd, *J* = 3.2, 5.5 Hz, 1H), 6.61 (dd, *J* = 3.2, 5.5 Hz, 1H), 7.10–7.19 (m, 2H), 7.19–7.26 (m, 1H), 7.28–7.35 (m, 2H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (4C), 46.9, 47.1, 49.5, 49.8, 49.9, 50.5, 73.1, 126.1, 127.0 (2C), 130.9 (2C), 134.5, 139.5, 140.5, 162.9, 197.6; HRMS (FAB) calcd for $C_{21}H_{28}NO_2S$ $[M+H]^+$ 358.1841, found 358.1830. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.58 (s, 1H, CHO, *exo* isomer) and 9.66 (s, 1H, CHO, *endo* isomer).



***S*-(1*S*,2*R*,3*R*,4*R*)-2-Formyl-3-(4-methoxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl Diisopropylcarbamothioate (25, *exo* isomer):** Colorless oil; $[\alpha]^{23}_{D}$ 133.6 (c 1.60, $CHCl_3$) for 90% ee; HPLC (Daicel Chiralcel AD-H column × 2, hexane–*i*-PrOH = 100:1, flow rate = 0.5 mL/min) t_R = 31.7 (major enantiomer of exo isomer), 33.2 (minor enantiomer of exo isomer), 46.8 (major enantiomer of endo isomer), 92.2 (minor enantiomer of endo isomer) min; IR ($CHCl_3$) 1715, 1646, 1513, 1458, 1422, 1370, 1284, 1249, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (s, 3H), 0.91 (s, 3H), 1.07 (s, 3H), 1.14 (s, 3H), 1.44 (d, *J* = 9.2 Hz, 1H), 1.87 (d, *J* = 8.7 Hz, 1H), 3.05 (br s, 1H), 3.09 (s, 1H), 3.13 (s, 1H), 3.73 (s, 3H), 3.78 (br s, 1H), 4.39–4.43 (m, 1H), 6.32 (dd, *J* = 3.2, 5.5 Hz, 1H), 6.60 (dd, *J* = 3.2, 5.5 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0 (4C), 46.8, 47.1, 48.8, 49.76, 49.79, 50.5, 55.1, 73.2, 112.4 (2C), 131.9 (2C), 132.6, 134.6, 139.4, 157.9, 163.0, 197.8; HRMS (FAB) calcd for $C_{22}H_{30}NO_3S$ $[M+H]^+$ 388.1946, found 388.1942. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.58 (s, 1H, CHO, *exo* isomer) and 9.67 (s, 1H, CHO, *endo* isomer).

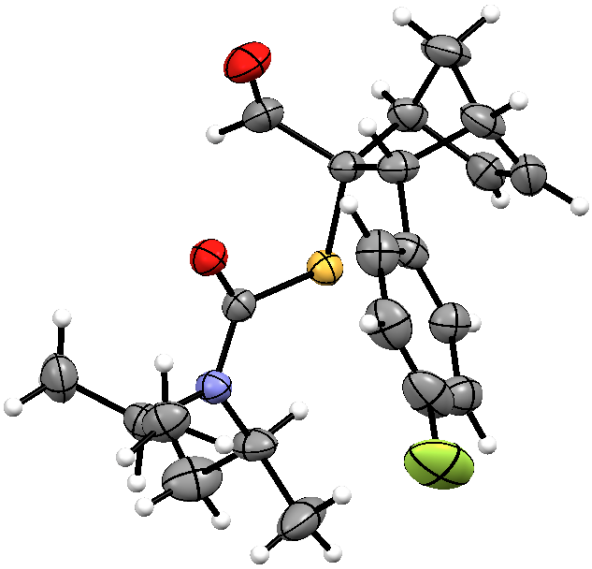


***S*-(1*S*,2*R*,3*R*,4*R*)-2-Formyl-3-(4-fluorophenyl)bicyclo[2.2.1]hept-5-en-2-yl Diisopropylcarbamothioate (26, *exo* isomer):** Colorless solid; $[\alpha]^{24}_{D}$ 170.8 (c 1.00, $CHCl_3$) for 90% ee; HPLC (Daicel Chiralcel AD-H column × 2, hexane–*i*-PrOH = 100:1, flow rate = 0.5 mL/min) t_R = 31.6 (major enantiomer of exo isomer), 34.3 (minor enantiomer of exo isomer), 48.2 (major enantiomer of endo isomer), 61.1 (minor enantiomer of endo isomer) min; IR ($CHCl_3$) 1716, 1646, 1509, 1423, 1371, 1285, 1225, 1211, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (s, 3H), 0.91 (s, 3H), 1.08 (s, 3H), 1.13 (s, 3H), 1.46 (d, *J* = 9.2 Hz, 1H), 1.87 (d, *J* = 8.7 Hz, 1H), 3.05 (br s, 1H), 3.09 (s, 1H), 3.13 (s, 1H), 3.75 (s, 1H), 4.48 (d, *J* = 3.2 Hz, 1H), 6.34 (dd, *J* = 3.2, 5.5 Hz, 1H), 6.58 (dd, *J* = 3.2, 5.5 Hz, 1H), 6.83 (t, *J* = 8.7 Hz, 1H), 7.29 (dd, *J* = 5.5, 8.7 Hz, 2H), 9.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0 (4C), 46.9, 47.0, 48.6, 49.8 (2C), 50.6,

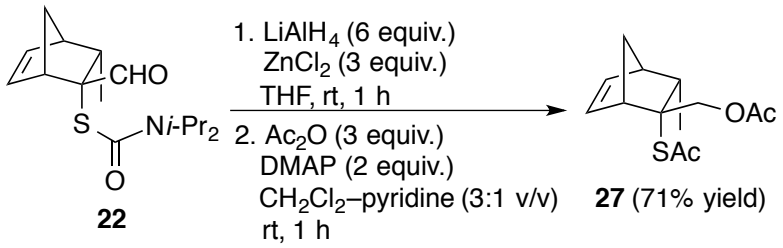
73.1, 113.5 (d, J_{C-F} = 20.0 Hz, 2C), 132.3 (d, J_{C-F} = 7.6 Hz, 2C), 136.2, 139.2, 161.5 (d, J_{C-F} = 246 Hz), 162.7, 197.3; HRMS (FAB) calcd for $C_{21}H_{27}FNO_2S$ $[M+H]^+$ 376.1747, found 376.1750. The *exo*/*endo* ratio was determined by ^1H NMR analysis: δ 9.55 (s, 1H, CHO, *exo* isomer) and 9.63 (s, 1H, CHO, *endo* isomer).

X-ray Crystallographic Analysis of exo-26.

Bruker SMART APEX diffractometer with CCD detector (graphite monochromator, MoKa radiation, l = 0.71073 Å). The structure was solved by direct methods and expanded using Fourier techniques. Formula $C_{21}H_{26}FNO_2S$, colorless, crystal dimensions 0.20 Å~ 0.20 Å~ 0.15 mm_3, monoclinic, space group $P2_1$ (#4), a = 8.1417(17) Å, b = 14.590(3) Å, c = 17.092(4) Å, β = 102.781(4)°, V = 1980.0(7) $Å_3$, Z = 4, and D_{calc} = 1.260 g cm_{-3}, F(000) = 800, μ = 0.187 mm_{-1}, T = 173(2) K. 9250 reflections collected, 8067 independent reflections with I > 2σ(I) ($2\theta_{max}$ = 28.35°), and 493 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0711 and wR2 = 0.1946, GOF = 0.922. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk]. Supplementary publication no. CCDC-874912.



Derivatization of 22.



To a solution of **22** (29.5 mg, 0.10 mmol) in Et_2O (3 mL) was added $ZnCl_2$ (41 mg, 0.30 mmol), $LiAlH_4$ (23 mg, 0.60 mmol)[8] at ambient temperature, and the mixture was stirred for 1 h. The reaction was quenched by the successive addition of EtOAc (1 mL) and saturated aqueous solution of Rochelle salt (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL × 2). The organic layers were combined and dried over anhydrous Na_2SO_4. The solvents were removed in vacuo, and CH_2Cl_2 (3 mL) was added immediately under an atmosphere of nitrogen. To this solution were added pyridine (1 mL), DMAP (24.4 mg, 0.2 mmol) and Ac_2O (28.4 μL, 0.3 mmol) at ambient temperature, and the mixture was stirred for 1 h. The reaction was quenched with 6 M aqueous HCl (2.5 mL) and the mixture was extracted with EtOAc (15 mL × 2). The organic layers were combined and dried over anhydrous Na_2SO_4. The solvents were removed in vacuo, and the residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give 27 (17.9 mg, 71% yield).

((1*S*,2*S*,3*S*,4*R*)-2-(Acetylthio)-3-methylbicyclo[2.2.1]hept-5-en-2-yl)methyl Acetate (27): IR ($CHCl_3$) 1743, 1685, 1377, 1232, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, J = 7.3 Hz, 3H), 1.22–1.33 (m, 1H), 1.58–1.67 (m, 2H), 2.09 (s, 3H), 2.24 (s, 3H), 2.74 (s, 1H), 3.54 (s, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 5.97–6.17 (m, 1H), 6.17–6.35 (m, 1H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 21.0, 31.1, 42.7, 46.3, 48.2, 49.3, 63.1, 69.4, 135.5, 137.1, 170.9, 196.2; HRMS (FAB) calcd for $C_{13}H_{19}O_3S$ $[M+H]^+$ 255.1055, found 255.1037.

References and Notes

1. (a) Sander, M. *Chem. Rev.* **1966**, *66*, 297. (b) Silvestri, M. G.; Wong, C.-H. *J. Org. Chem.* **2001**, *66*, 910.
2. Pederson, R. L.; Liu, K. K.-C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.*, **1990**, *55*, 4897.
3. (a) Barlow, A. J.; Compton, B. J.; Weavers, R. T. *J. Org. Chem.* **2005**, *70*, 2470; (b) Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.
4. Takahashi, T.; Yokoyama, H.; Haino, T.; Yamada, H. *J. Org. Chem.* **1992**, *57*, 3521.
5. Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631.
6. (a) Barany, G.; Schroll, A. L.; Mott, A. W.; Halsrud, D. A. *J. Org. Chem.* **1983**, *48*, 4750; (b) Pattenden. G,; Shuker. A. J. *Tetrahedron Lett.* **1991**, *32*, 6625.
7. Kobayashi, N.; Osawa, A.; Fujisawa, T. *Chem. Lett.* **1973**, *2*, 1315.
8. Marr, F.; Hoppe, D. *Org. Lett.* **2002**, *4*, 4217.

Publication List

1) Sakakura, A.; Yamada, H.; Ishihara, K.
"Enantioselective Diels–Alder Reaction of α-(Acylthio)acroleins: a New Entry to Sulfur-containing Chiral Quaternary Carbons"
Organic Letters **2012**, *14*, 2972–2975.

2) Sakakura, A.; Yamada, H.; Ishihara, K.
"α-Heterosubstituted β-Alkylacroleins as Useful Multi-substituted Dienophiles for the Enantioselective Diels–Alder Reaction"
Asian Journal of Organic Chemistry **2012**, 1, 133–137.
(Inside cover article)

3) Ishihara, K.; Yamada, H.; Akakura, M.
"The First Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines with α-Acyloxyacrolein Catalyzed by Chiral Primary Ammonium Salt"
In preparation.

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Finally, I would like to thank my friends and especially my parents for their true regard and unwavering support during my Ph.D study. Thank you.

January 2014

Hiroki Yamada

＜発表論文＞

1) Sakakura, A.; Yamada, H.; Ishihara, K.

“Enantioselective Diels–Alder Reaction of α-(Acylthio)acroleins: a New Entry to Sulfur-containing Chiral Quaternary Carbons”

Organic Letters **2012**, *14*, 2972–2975.

2) Sakakura, A.; Yamada, H.; Ishihara, K.

“α-Heterosubstituted β-Alkylacroleins as Useful Multi-substituted Dienophiles for the Enantioselective Diels–Alder Reaction”

Asian Journal of Organic Chemistry **2012**, 1, 133–137.

(Inside cover article)

3) Ishihara, K.; Yamada, H.; Akakura, M.

“The First Enantioselective Diels–Alder Reaction of 1,2-Dihydropyridines with α-Acyloxyacrolein Catalyzed by Chiral Primary Ammonium Salt”

In preparation.

＜国内学会発表＞

(1) ○山田浩貴、坂倉　彰、石原一彰

「キラル有機アンモニウム塩触媒を用いたα-(アシルチオ)アクロレインのエナンチオ選択的 Diels–Alder 反応」

日本化学会第 90 回春季年会、4F6–37、大阪（平成 22 年 3 月）、口頭 A 講演

(2) ○山田浩貴、坂倉　彰、石原一彰

「キラル有機アンモニウム塩触媒を用いたα-(カルバモイルチオ)アクロレインのエナンチオ選択的 Diels–Alder 反応」

日本化学会第 91 回春季年会、2C2-06、神奈川（平成 23 年 3 月）、口頭 A 講演

(3) ○山田浩貴、坂倉　彰、石原一彰

「キラル有機アンモニウム塩触媒を用いたβ-アルキル-α-ヘテロ置換型アクロレインのエナンチオ選択的 Diels–Alder 反応」

日本化学会第 92 回春季年会、3K3-35、神奈川（平成 24 年 3 月）、口頭 B 講演

(4) ○山田浩貴、石原一彰
「キラル有機アンモニウム塩触媒を用いる 1,2-ジヒドロピリジンとα-ヘテロ置換アクロレインによるエナンチオ選択的 Diels-Alder 反応」
日本化学会第 93 回春季年会、3E5-08、滋賀（平成 25 年 3 月）、口頭 A 講演

(5) ○山田浩貴、石原一彰
「キラル有機アンモニウム塩触媒を用いる 1,2-ジヒドロピリジンとα-ヘテロ置換アクロレインによるエナンチオ選択的 Diels-Alder 反応とその合成的応用」
日本化学会第 94 回春季年会、名古屋（平成 26 年 3 月）、口頭 B 講演

<受賞>
日本化学会第 92 回春季年会　学生講演賞（平成 24 年 3 月）

<研究留学>
平成 25 年 6 月 1 日 ～ 8 月 31 日
Prof. Michael J. Krische
The department of Chemistry and Biochemistry,
The University of Texas at Austin