Asymmetric Vinylogous Nitro-Michael Reaction of Furanones Catalyzed by Cinchona Alkaloid Derivatives

（シンコナアルカロイド誘導体を触媒とするフラノン類の
ビニロガス nitro-Michael 反応）

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Graduate School of Engineering
Osaka City University

Tohru Sekikawa

関川　徹

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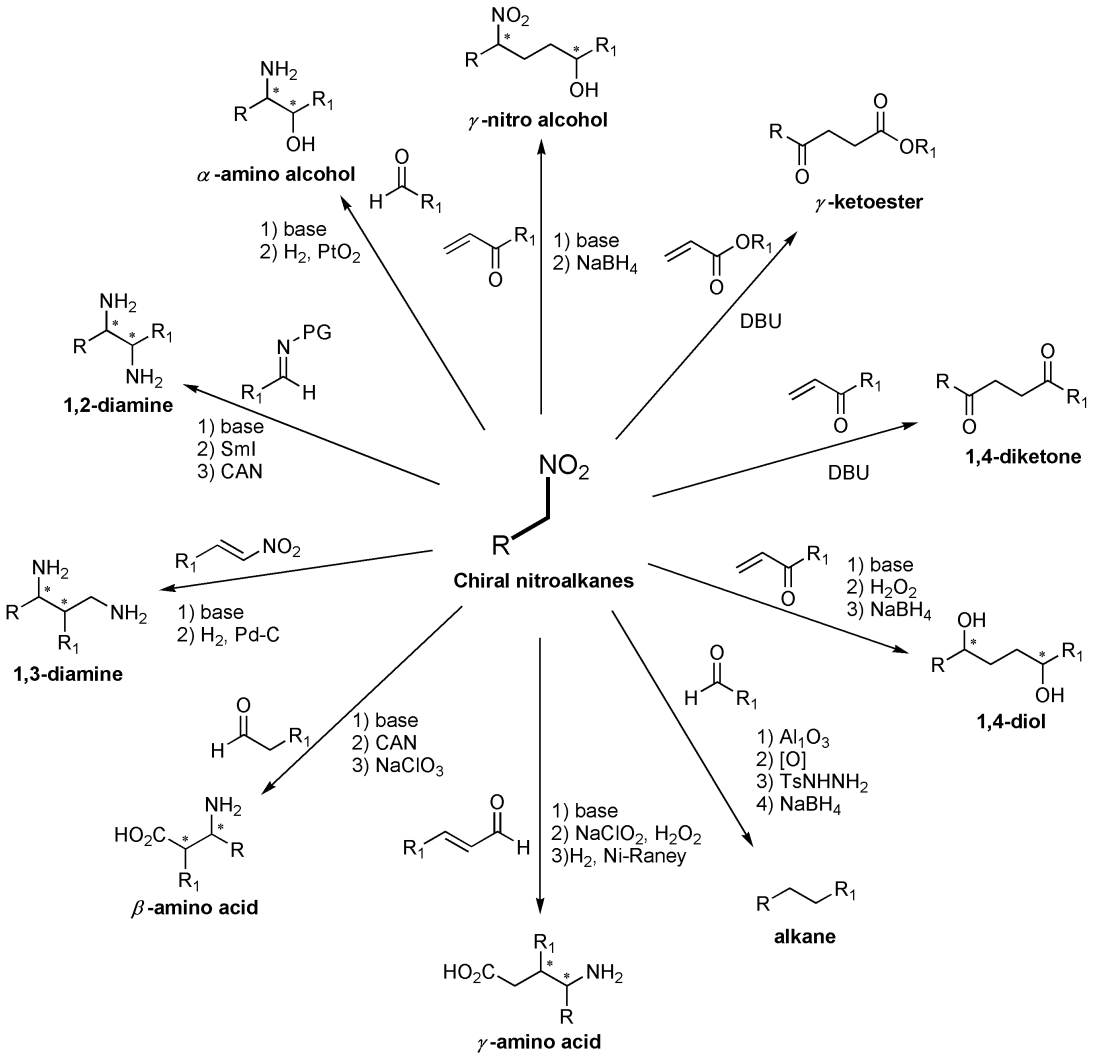
***Syn*-Selective Nitro-Michael Addition of Furanones to β,β-Disubstituted Nitroalkenes Catalyzed by *Epi*-Quinine Derivatives**

Chapter 1

Introduction: An Overview of the Catalytic Asymmetric Nitro-Michael Reaction

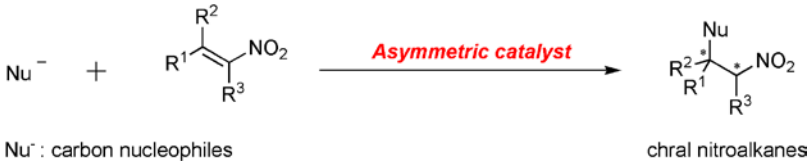
1.1 Synthetic utility of nitro-Michael reaction

Chiral nitroalkanes constitute one of the most important compounds in industry, because of the wide variety of synthetic transformations of nitro group into the important functional groups. For examples, Nef reaction,[1] nucleophilic displacement,[2] reduction to an amino group,[3] Meyer reaction,[4] and the conversion into a nitrooxide[5] are representative reactions of nitroalkanes. It must be noted that the reactions shown in Scheme 1-1 are only a part of the reactions of nitroalkanes.[6] Thus, chiral nitroalkanes are synthetically useful compounds as chiral building blocks for synthesizing 1,4-diketones,[7] 1,4-diols,[7] alkanes,[8] γ-amino acids,[9] β-amino acids,[10] 1,3-diamines,[11] 1,2-diamines,[12] α-amino alcohols,[13] γ-nitro alcohols,[7] and γ-ketoesters.[14] The syntheses of optically active polyfunctionalized compounds are often difficult by the conventional organic reactions other than those of chiral nitroalkanes.[6] In this context, the development of the synthesis of chiral nitroalkanes is continued to be an important subject in organic synthesis.



Scheme 1-1. Functional transformation of chiral nitroalkanes

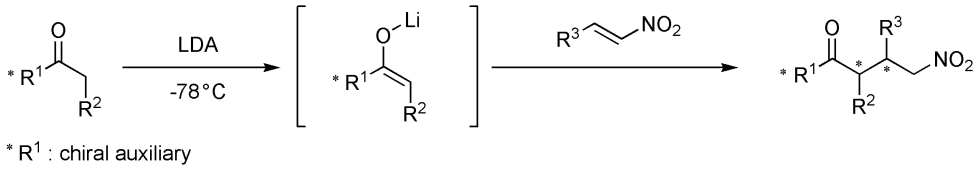
Catalytic enantioselective nitro-Michael reaction of carbon nucleophiles to nitroalkenes (*i.e.*, catalytic enantioselective conjugate addition to nitroalkenes), is a reliable and straightforward method for synthesizing the chiral nitroalkanes (Scheme 1-2).[15] The catalytic enantioselective nitro-Michael reaction can be classified into three groups according to the catalysts and the Michael donors: (1) the reactions catalyzed by metal Lewis acids; (2) asymmetric conjugate additions of organometallic compounds catalyzed by copper catalysts; (3) the reactions catalyzed by organocatalysts. In next section, the author will describe the representative examples of the catalytic asymmetric nitro-Michael reactions.



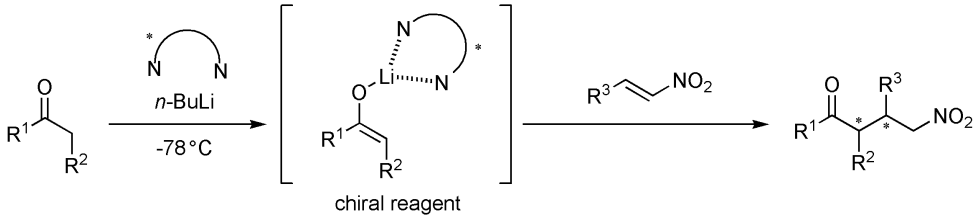
Scheme 1-2. Catalytic asymmetric nitro-Michael reaction of carbon nucleophiles

Prior to the development of catalytic asymmetric nitro-Michael reaction, the nitro-Michael reactions using chiral auxiliaries[16] as well as chiral reagents[17] were typical protocol of the asymmetric nitro-Michael reaction (Scheme 1-3). Chiral auxiliary is an organic group that is temporarily incorporated into substrates in order to induce the asymmetric induction. However, these methods have been largely replaced with catalytic asymmetric nitro-Michael reaction owing to the stoichiometric use of the expensive chiral sources.

(1) Asymmetric nitro-Michael reaction using chiral auxiliary (stoichiometric use of chiral source)



(2) Asymmetric nitro-Michael reaction by chiral reagent (stoichiometric use of chiral source)

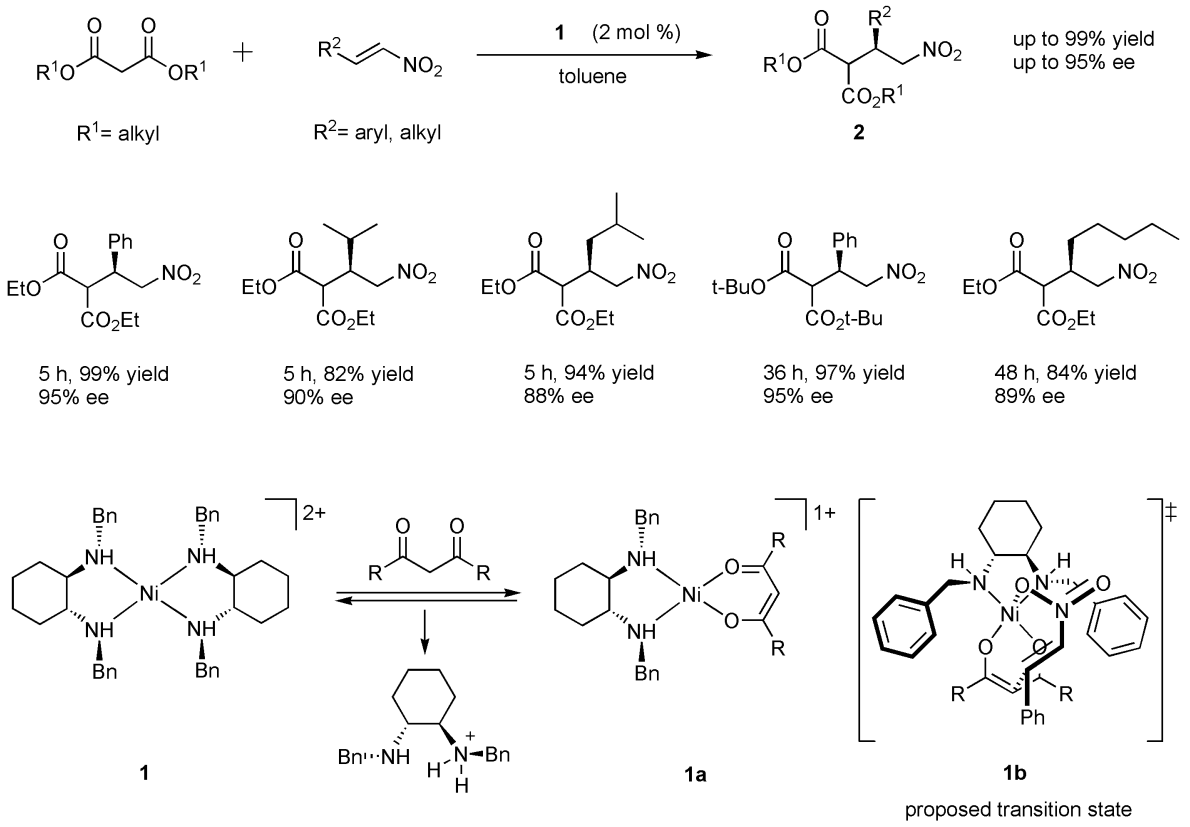


Scheme 1-3. Asymmetric nitro-Michael reactions using chiral auxiliary and chiral reagent

1.2 Asymmetric nitro-Michael reaction catalyzed by chiral Lewis acids

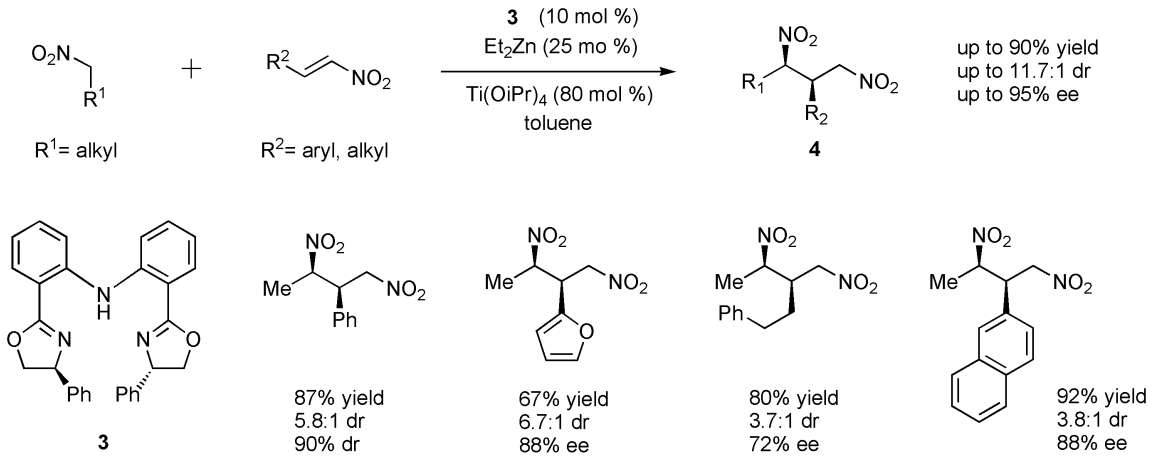
Lewis acid/organic base combination catalysts are widely used for the asymmetric nitro-Michael reaction.[18] Deprotonation of carbonyl compounds by organic bases affords enolate anions, which are effectively stabilized by chiral Lewis acids to give chiral metal enolates. Subsequent conjugate addition of chiral enolates to nitroalkenes activated by chiral Lewis acids affords the chiral nitroalkanes.

Typical example of the asymmetric nitro-Michael reaction promoted by Lewis acid/organic base combination catalysts is shown in Scheme 1-4. With a 2 mol % of chiral nickel (II) Lewis acid **1**, the nitro-Michael products **2** were obtained in high yields with excellent enantioselectivities (up to 95% ee), whereas the diastereoselectivities are low. In this reaction, chiral diamine ligand acts as organic base, which deprotonate the 1,3-dicarbonyl compounds to afford chiral nickel enolate **1a**. Nucleophilic attack of **1a** to nitroalkenes activated nickel Lewis acid would take place through the plausible transition state **1b**, where the steric repulsion between the chiral nickel enolate and incoming nitroalkene as well as the electrostatic interaction between the nickel Lewis acid and the nitro group moiety may lead to high asymmetric induction.[19]



Scheme 1-4. Represenatative chiral Lewis acid/organic base catalyzed asymmetric nitro-Michael reaction.

Nitroalkanes are also widely used as a Michael donor. For example, it has been reported that the catalytic asymmetric nitro-Michael reaction of nitroalkanes to nitroalkenes catalyzed by chiral zinc complex (Scheme 1-5).[20] With a 10 mol % of C_2-symmetric tridentate bisoxazoline ligand **3**, 25 mol % of diethyl zinc and sub-stoichiometric amount of tetraisopropoxy titanium, the corresponding nitro-Michael products **4** were obtained in moderate to high yields with excellent enantioselectivities (up to 95% ee), while the diastereoselctivities are moderate.

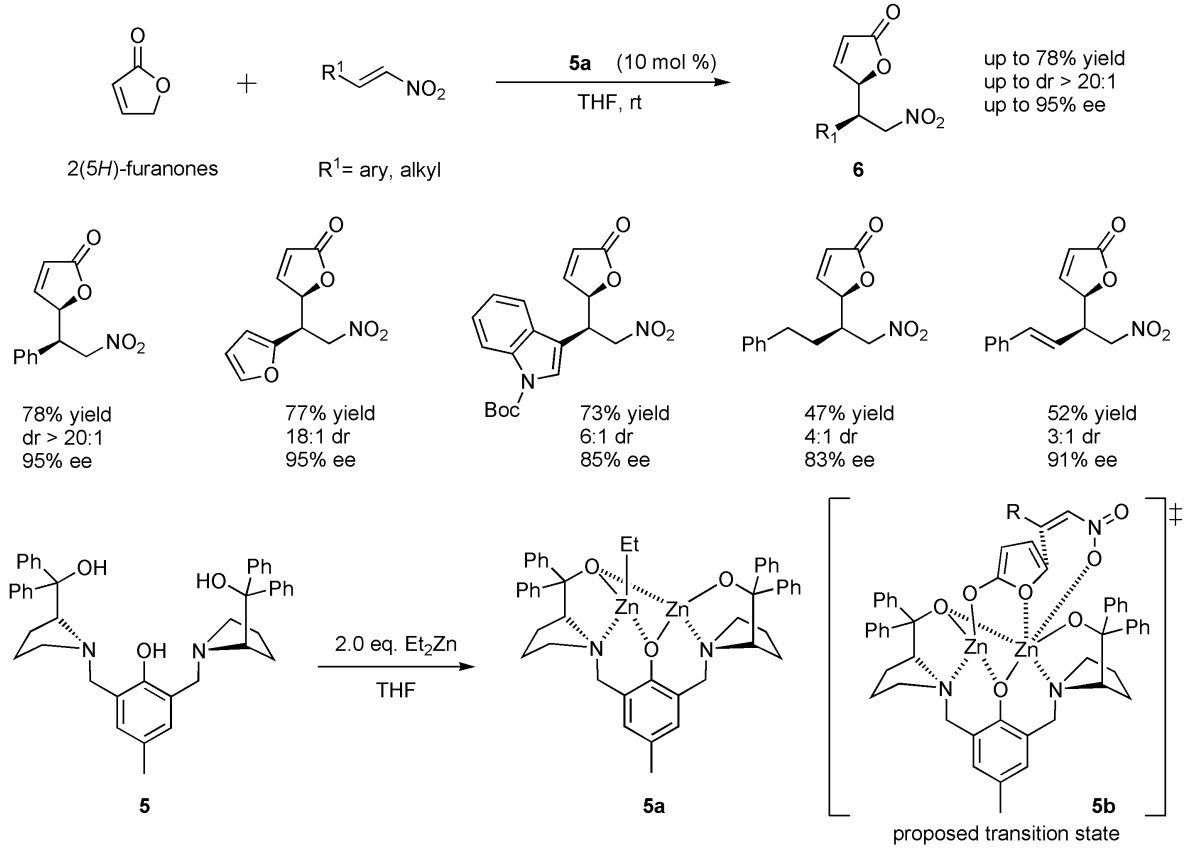


Scheme 1-5. Asymmetric nitro-Michael reaction of nitroalkanes catalyzed by chiral **3** / zinc complex

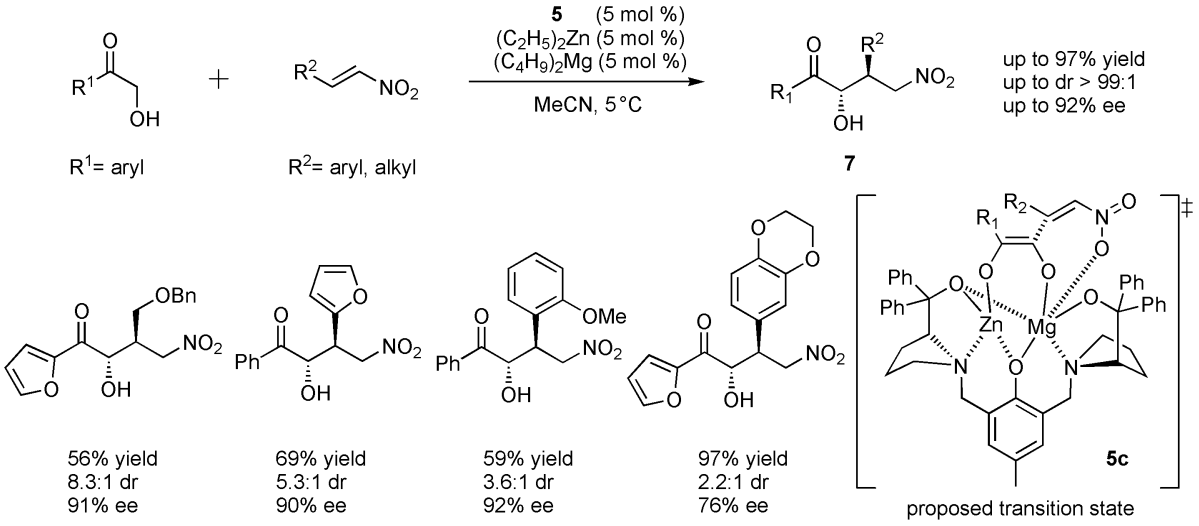
Trost and his co-workers reported the catalytic asymmetric vinylogous nitro-Michael reaction of 2(5*H*)-furanones to nitroalkenes catalyzed by chiral dinuclear zinc complex (Scheme 1-6).[21] The dinuclear zinc complex **5a** is generated in situ by reacting the chiral ligand **5** with two equivalent diethyl zinc in THF. In the presence of 10 mol % of chiral zinc complex **5a**, dienolates derived from 2(5*H*)-furanones undergo the asymmetric conjugate addition to β-aryl substituted nitroalkenes activated by **5a**, giving the corresponding Michael adducts **6** in high yields with excellent diastereo- and enantioselectivities (up to 95% ee). This reaction has a wide substrate scope: both β-aryl substituted nitroalkenes as well as low reactive β-alkyl substituted nitroalkenes can participate into the reaction. However, the reaction of β-alkyl substituted nitroalkenes leads to low to moderate diastereoselectivities. Furthermore, 5-substituted furanones fail to undergo the chiral zinc catalyzed nitro-Michael reaction. The significant steric repulsion between the β-substituted nitroalkenes and the 5-substituted dienolates derived from 5-substituted furanones seems to be the reason for the difficulty of the nitro-Michael reaction of 5-substituted furanones.

Trost and his co-workers also reported the catalytic asymmetric nitro-Michael reaction of α-hydroxyketones to nitroalkenes catalyzed by chiral dinulear zinc-magnesium complex (Scheme 1-7).[22] In the presence of a 5 mol % of chiral ligand **5** and organometallic reagents

such as diethyl zinc and dibuthyl magnesium, the corresponding nitro-Michael products **7** were obtained in moderate to good yields with high enantioselectivities (up to 92% ee). However, the diastereoselectivities of this reaction are low to moderate.



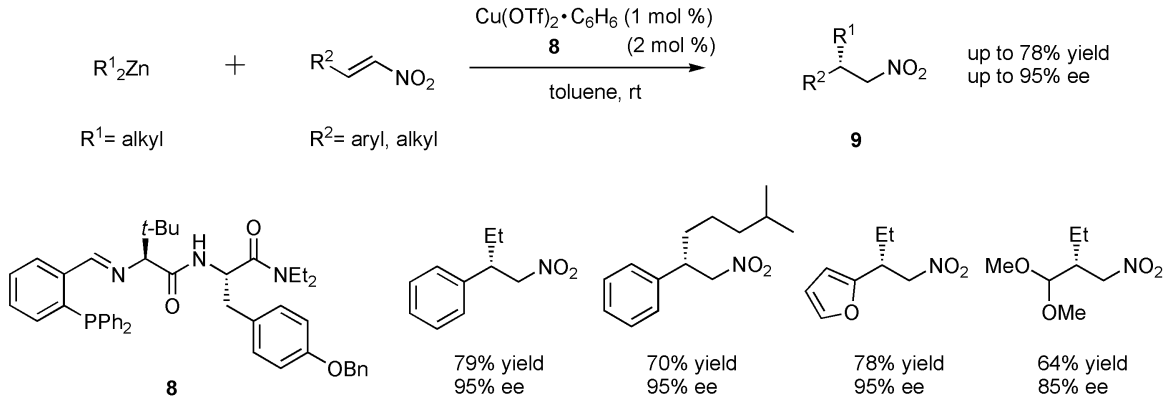
Scheme 1-6. Asymmetric nitro-Michael reaction catalyzed by chiral zinc dinuclear complex **5a**



Scheme 1-7. Asymmetric nitro-Michael reaction of ketones catalyzed by chiral **5** / zinc / magnesium complex

1.3 Asymmetric conjugate addition of organometallics catalyzed by copper catalysts

It has been reported that organometallic compounds such as dialkyl zinc undergo the asymmetric conjugate addition to nitroalkenes in the presence of copper catalysts. Representative example of this type of reaction is shown in Scheme 1-8.[23] For example, conjugate addition smoothly takes place at room temperature in the presence of 1 mol % of $Cu(OTf)_2$ and 2 mol % of chiral phosphine ligand **8**, furnishing the Michael adducts **9** with high enantiomeric excess (up to 95% ee). However, substrate scope of the reaction seems to be very limited, because of the less structural variety of organozinc compounds.

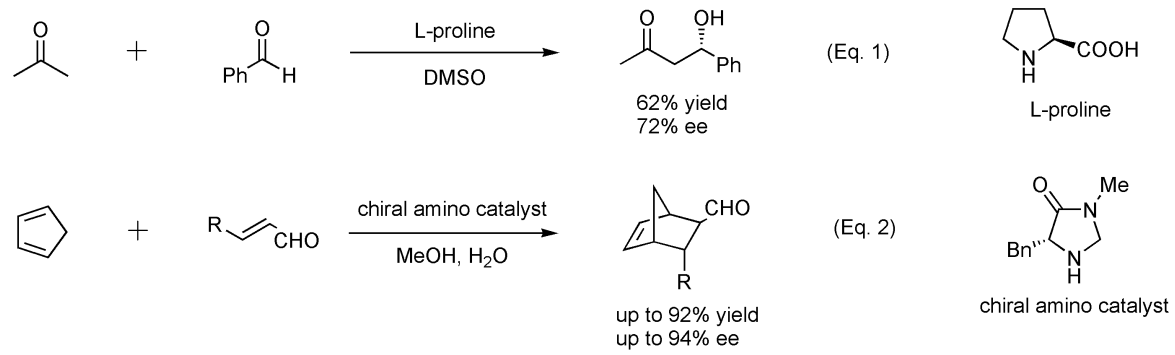


Scheme 1-8. Representative chiral copper catalyst promoted asymmetric nitro-Michael reaction of dialkyl zinc

1.4 Asymmetric nitro-Michael reaction catalyzed by organocatalysts: an overview

Asymmetric reactions catalyzed by small organic molecules (*i.e.*, organocatalysts) have enjoyed an astonishingly explosive development over the past decade.[24] An early report of organocatalysis was proline-catalyzed intramolecular aldol cyclizations reported by Hajos and Parrish in the early 1970s.[25] However, the potential of organocatalysis had been largely overlooked during the following three decades. Two independent reports appeared in 2000 have aroused the interest of synthetic chemists (Scheme 1-9). List and his co-workers reported that L-proline effectively catalyzes the asymmetric aldol reaction between benzaldehyde and acetone (Scheme 1-9, Eq. 1).[26] MacMillan's group reported that the chiral secondary amine such as chiral imidazolidinone effectively catalyzes the asymmetric Diels-Alder reaction of cyclopentadiene with α,β-unsaturated aldehydes (Scheme 1-9, Eq. 2).[27] Organocatalysts possess several advantages over the metal-based asymmetric catalysts:[28] (1) ready availability from biological substances; (2) low-toxicity; (3) most of organocatalysts are not air and moisture-sensitive; and (4) low cost. Today, asymmetric organocatalysis has become a

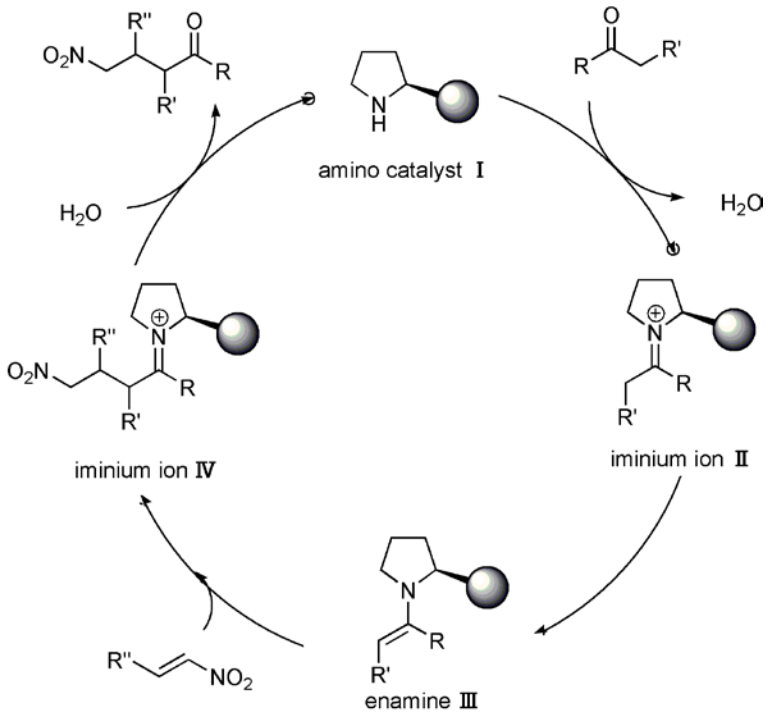
powerful tool for the diastereo- and enantioselective organic synthesis of chiral compounds under mild conditions.[29]



Scheme 1-9. Asymmetric reactions catalyzed by organocatalysts in 2000

1.5 Asymmetric nitro-Michael reaction catalyzed by enamine catalysts

Most widely used organocatalysts in the enantioselective nitro-Michael reaction are enamine catalysts (amine catalysts) and bifunctional hydrogen bonding catalysts.[30] The general mechanistic features of the nitro-Michael reaction catalyzed by enamine catalysts are shown in Scheme 1-10.[29,31]



Scheme 1-10. Mechanism of enantioselective nitro-Michael reaction catalyzed by enamine catalysts

An iminium ion Ⅱ is generated by the reversible reaction between a chiral amine catalyst Ⅰ and a carbonyl compound. The iminium ion Ⅱ is deprotonated to form the enamine intermediate Ⅲ. The enamine intermediate Ⅲ having strong nucleophilicity reacts with a nitroalkene at the β-position to create a new carbon-carbon bond. Subsequent hydrolysis of the iminium ion Ⅳ affords the Michael adduct and regenerates the chiral amine catalyst Ⅰ, which is ready to participate into a new catalytic cycle.

The high diastereo- and enantioselectivity of the secondary amine catalyzed nitro-Michael reaction would be explained by the transition states depicted in Figure 1-1.[29] The most important mechanistic feature is the geometry of enamine intermediates. The geometry of the enamine intermediates (*i.e*, (*E*)-enamine or (*Z*)-enamine) is essentially determined by the catalyst structure. Due to the steric repulsion between the bulky substituents at the α-position of the amine catalyst and the substituent at the β-position of enamine, the (*E*)-enamine is

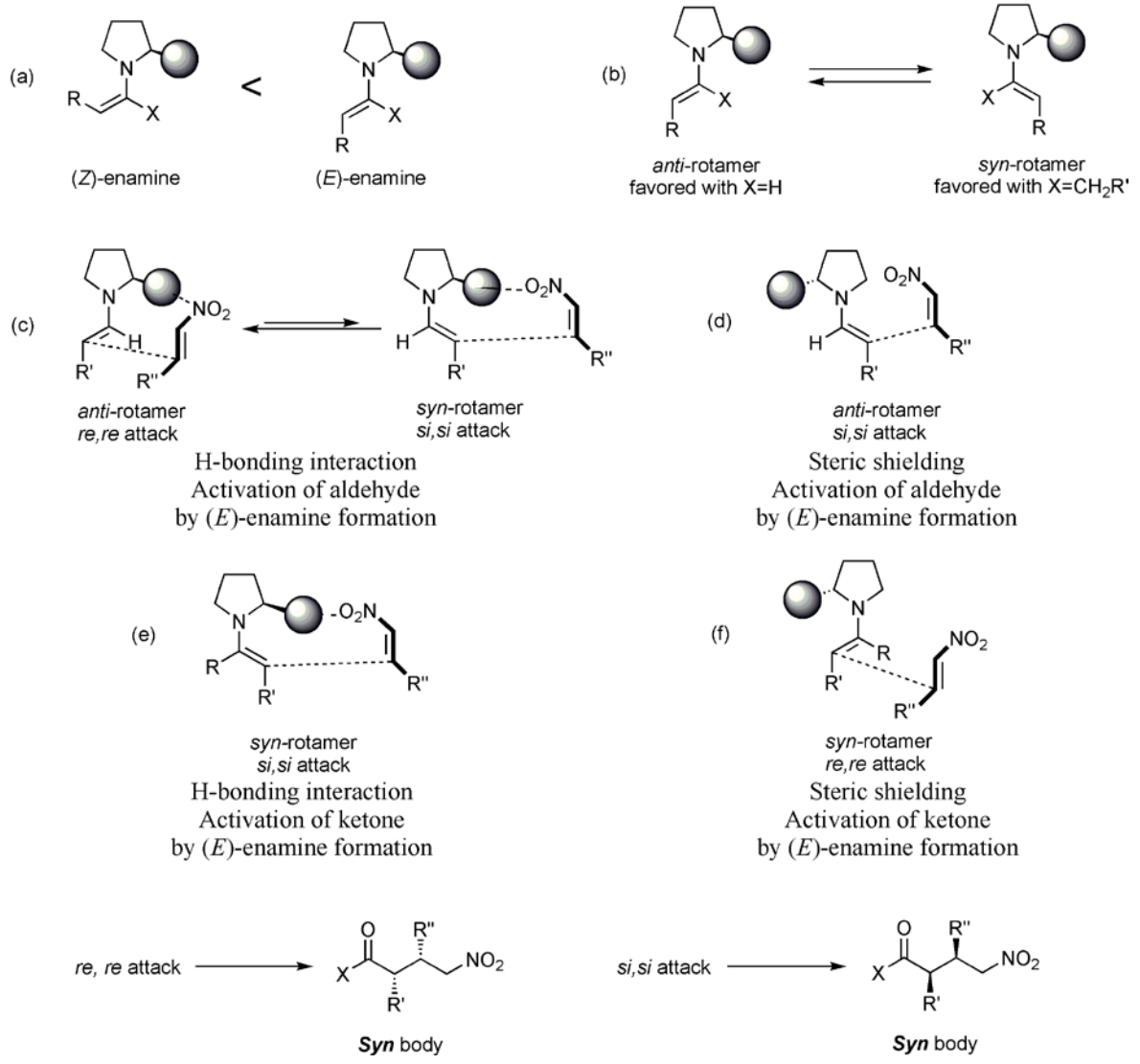
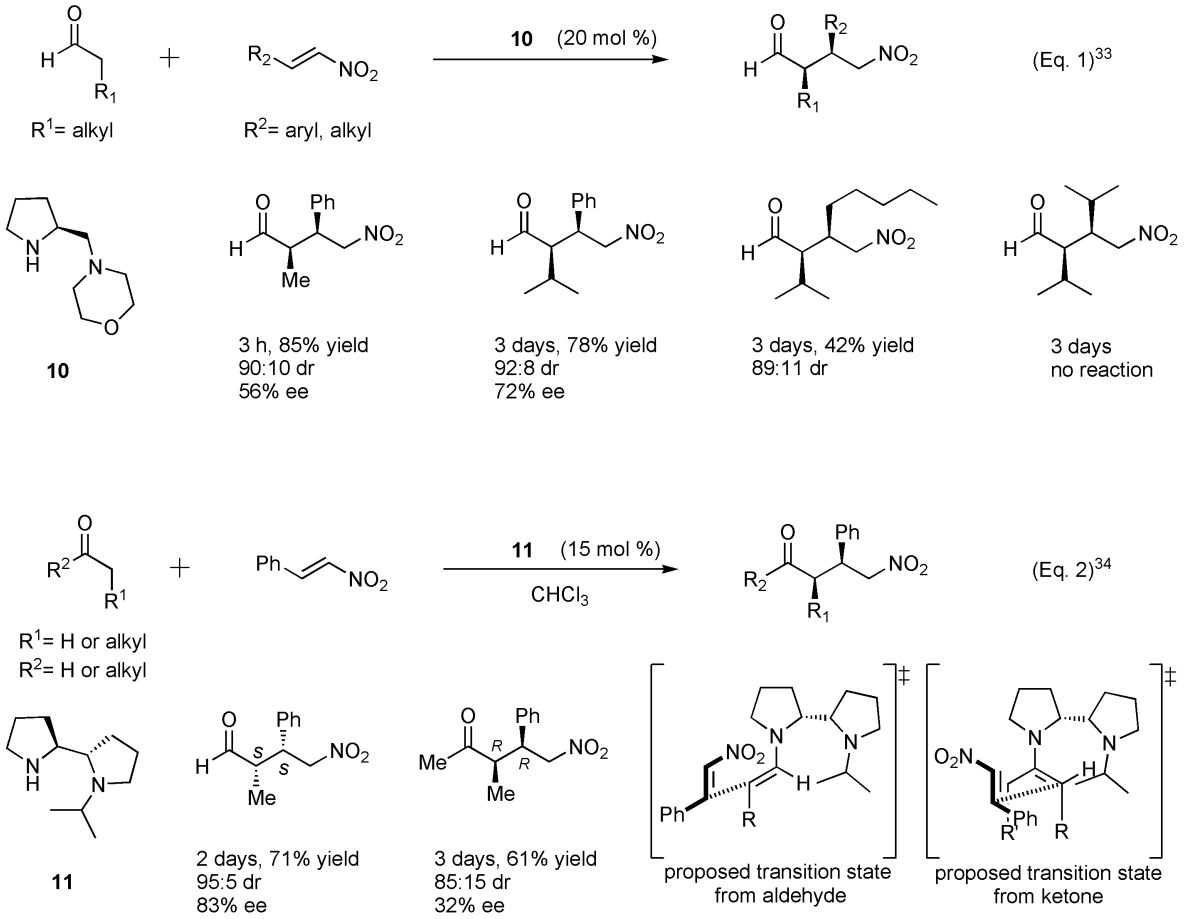


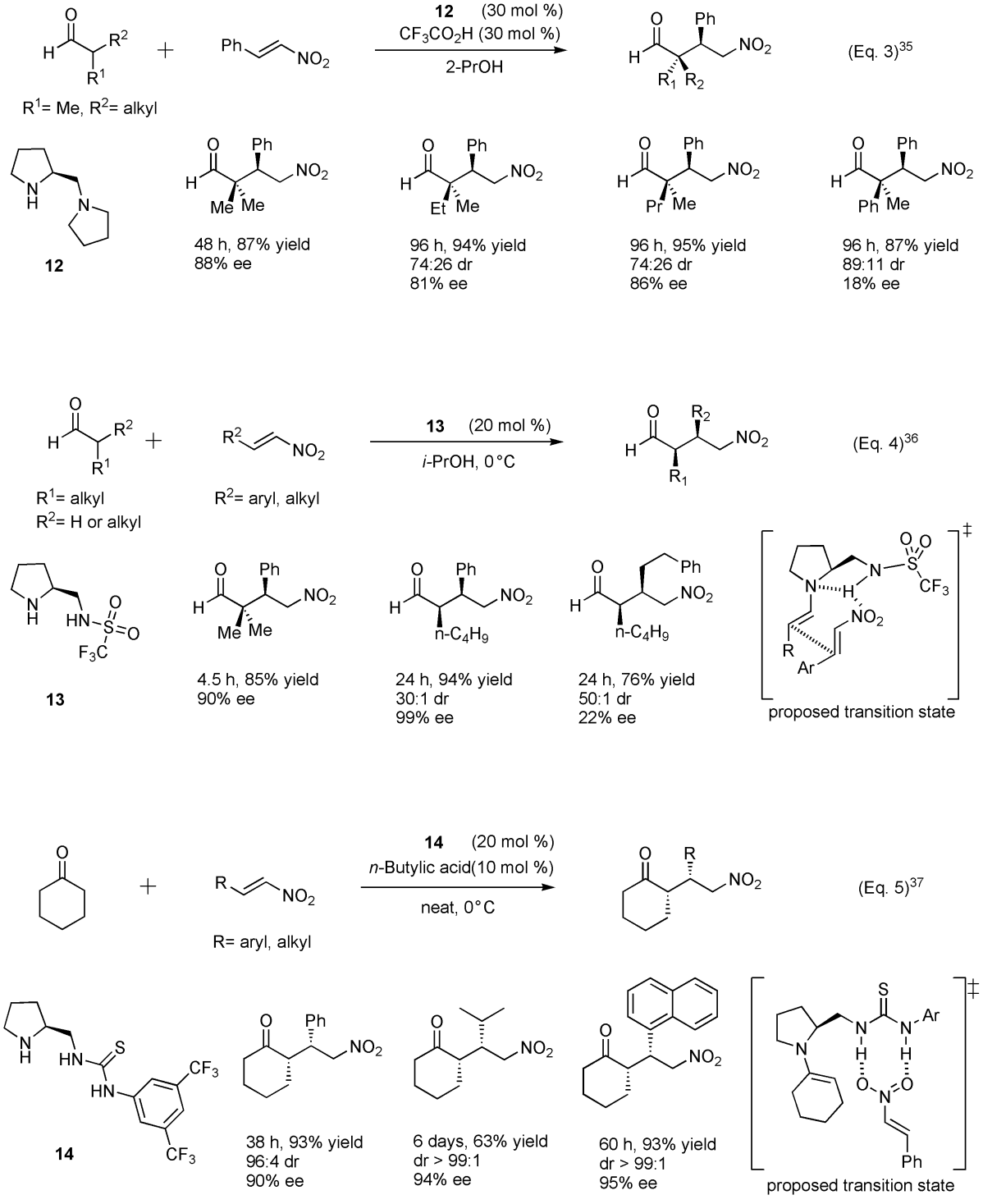
Figure 1-1. Transition states of asymmetric nitro-Michael reaction catalyzed by chiral enamine catalysts

thermodynamically favored (Figure 1-1a). The α-substituent of the amine catalyst governs the equilibrium between *anti*-rotamer and *syn*-rotamer (Figure 1-1b). Finally, the nuleophilic attack of (*E*)-enamine to nitroalkene proceeds via an acyclic synclinal transition state (Seebach's model),[32] through the two different mechanisms (hydrogen-bonding interaction or steric interaction). The conjugate addition to the nitroalkene would take place from the face of the enamine shielded by the α-substituent via hydrogen-bonding interaction (Figure 1-1c and e). In contrast, steric repulsion would determine the facial selectivity. The bulky group on the catalyst could force the attack from the open face (Figure 1-1d and f). In this scenario, the (*E*)-enamine from aldehydes and ketones favors the addition to nitroalkenes via *si,si* or *re,re* transition states, affording the *syn*-adduct predominantly.

Representative examples of asymmetric nitro-Michael reaction catalyzed by enamine catalysts are shown in Scheme 1-11. In all reactions depicted in Scheme 1-11, the reactions showed *syn*-selectivity via *si,si* or *re,re* transition states of nucleophilic attach of (*E*)-enamines to nitroalkenes.



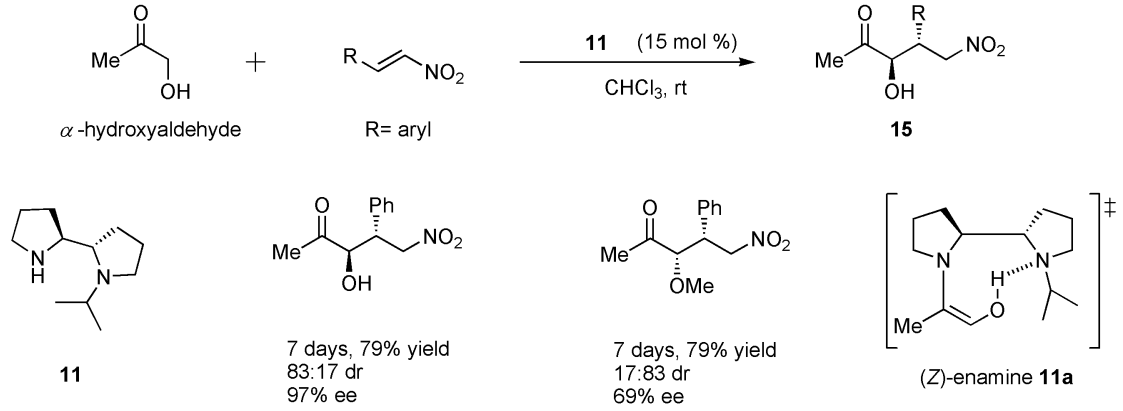
Scheme 1-11. Secondary amine catalyzed asymmetric nitro-Michael reactions



Scheme 1-11. Secondary amine catalyzed asymmetric nitro-Michael reactions (continued)

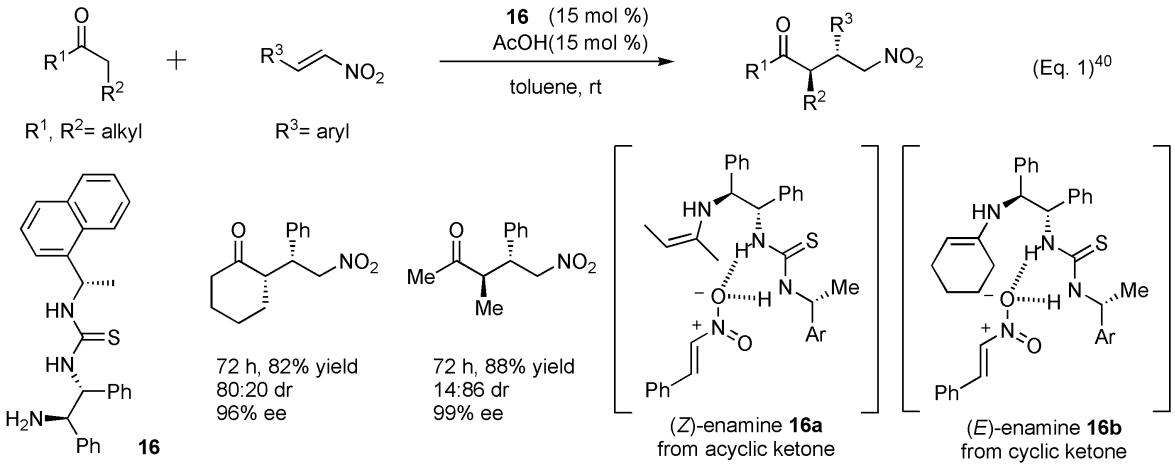
Anti-selective nitro-Michael reaction was reported in 2003, although the diastereoselectivity was moderate (Scheme 1-12).[38] Alexakis and his co-workers reported the catalytic asymmetric nitro-Michael reaction of α-hydroxyketones to nitroalkenes catalyzed by

bis-pyrrolidine **11**. With a 15 mol % of catalyst **11**, the corresponding nitro-Michael adducts **15** were obtained with moderate *anti*-selectivity and excellent enantioselectivities (up to 98% ee). In case with α-methoxyketone, the diastereoselectivity was reversed into *syn*-selectivity. The author described that the presence of a second nitrogen that fixes the conformation via a hydrogen bond to give the (*Z*)-enamine **11a** leading to *anti*-adduct.

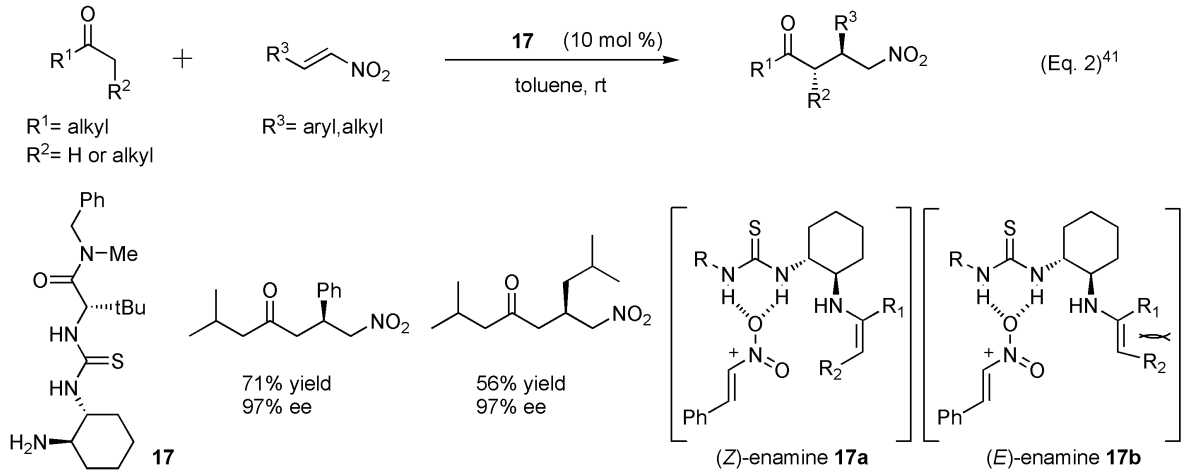


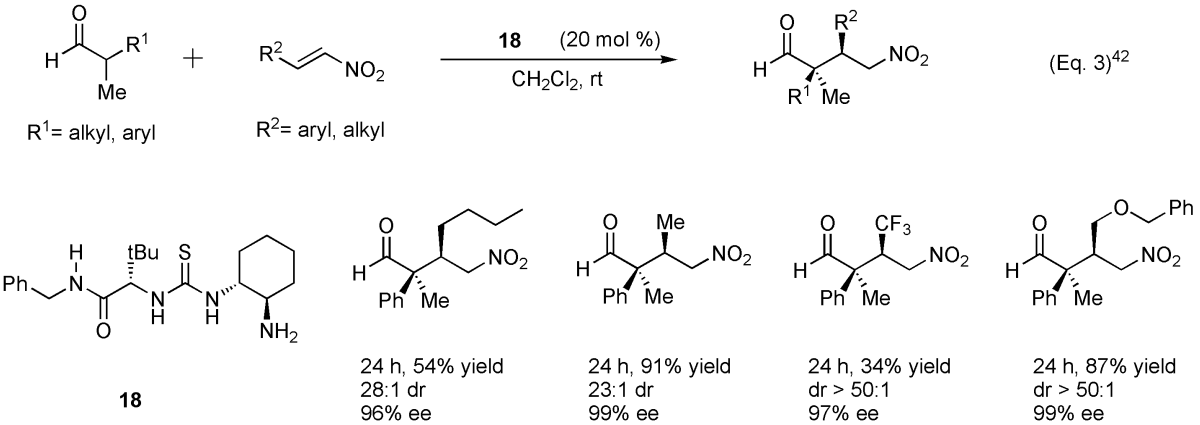
Scheme 1-12. *Anti*-selective asymmetric nitro-Michael reaction catalyzed by **11**

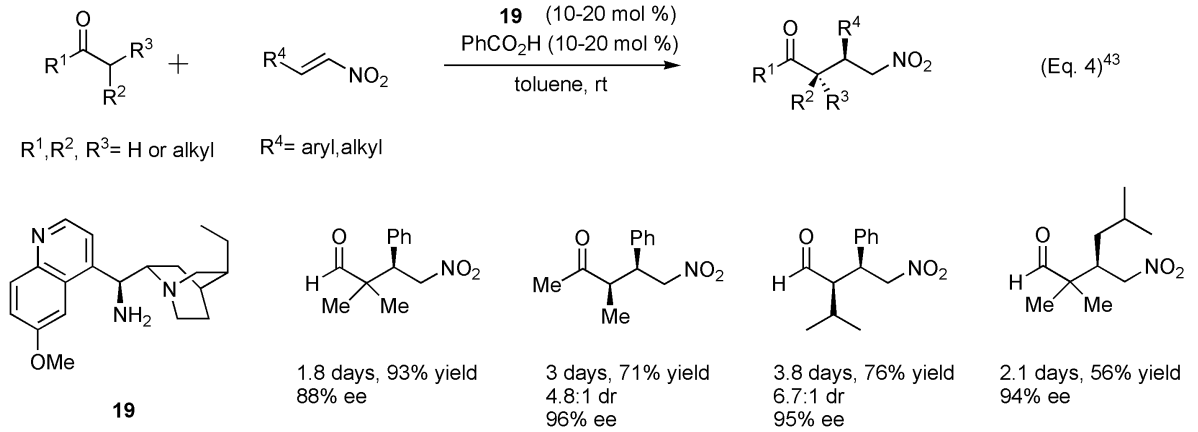
Despite of the less studies compared with those of secondary amine catalysts, primary amine catalysts took a growing importance recently.[39] The higher reactivity and the lower steric hinderance of primary amines compared with secondary amines can be helpful to promote the nitro-Michael reaction. The reduction of steric demand makes possible the pathway through a (*Z*)-enamine intermediate leading to *anti*-products. The representative examples of the nitro-Michael reaction catalyzed by chiral primary amine catalysts are summarized in Scheme 1-13. Reactions of ketones with primary amine catalysts usually form the (*Z*)-enamine intermediates, which lead to the *anti*-selective Michael addition to nitroalkenes (Scheme 1-13. Eq. 1 and 2).



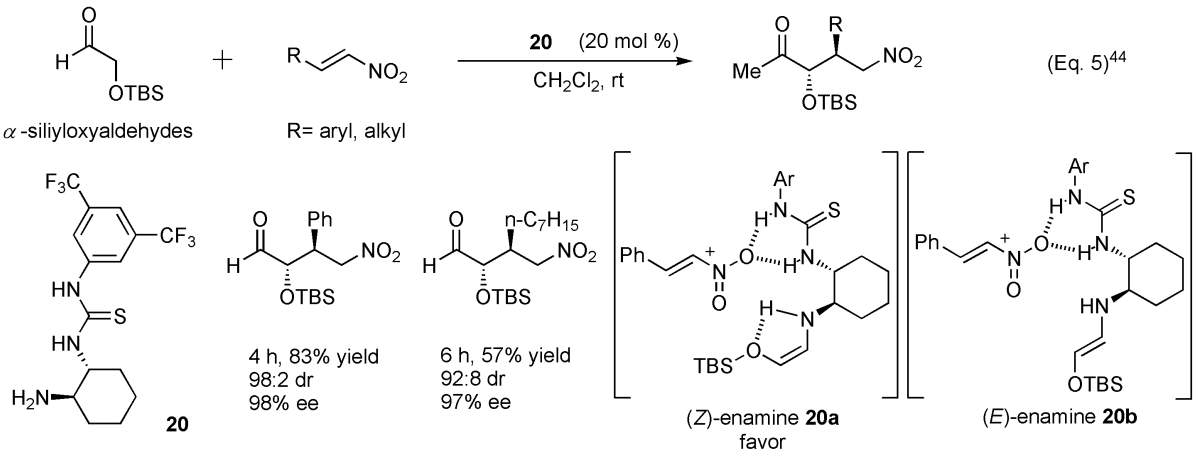
Scheme 1-13. Asymmetric nitro-Michael reactions catalyzed by chiral primary amines







Scheme 1-13. Asymmetric nitro-Michael reactions catalyzed by chiral primary amines (continued)



Scheme 1-13. Asymmetric nitro-Michael reactions catalyzed by chiral primary amines (continued)

Anti-selective nitro-Michael reaction was reported in 2009 (Scheme 1-13, Eq. 5), Barbas and his co-workers reported the *anti*-selective asymmetric nitro-Michael reaction of α-(trialkylsilyloxy)aldehydes catalyzed by **20**. The *anti*-selectivity was derived from (*Z*)-enamine. The (*Z*)-enamine is selectively formed from the α-(trialkylsilyloxy)aldehydes and catalyst, because of the hydrogen bonding between the enamine NH and oxygen atom of the siliyloxy group (**20a**). To achieve the high *anti*-selectivity of the nitro-Michael reaction, the structural modification of the aldehydes is needed (*i.e.*, substrate-control of diastereoselectivity). However, the need of the structural modification severely limits the substrate scope of the reaction.

1.6 Asymmetric nitro-Michael reaction catalyzed by H-bonding catalysts

Recently, growing interest was focused on catalytic asymmetric reaction with hydrogen-bonding catalysts (H-bonding catalysts), which allow a weak interaction such as hydrogen bonding interaction.[45] On using enamine catalysts, the Michael donors are limited to aldehydes and ketones. The H-bonding catalysts have expanded considerably this scope into 1,3-diesters, α-ketoamides, nitroalkanes as the Michael donors.[39] Its main strategy is a use of bifunctional catalyst (Figure 1-2), which incorporates both Lewis/Brønsted acid and base functionalities into a rigid chiral scaffold of catalyst molecule.[46]

They function in such a way that both nucleophilic and electrophilic substrates are activated independently and simultaneously within the same catalyst. The key associated with this approach is how to access the chiral scaffold with the following desirable features:[47] (1) rigid conformation; (2) a tight chiral environment; (3) well-defined reaction mode; and (4) good availability (easy preparation and functionalization). The chiral ligands such as BINOL, salen, diaryl prolinol and cinchona derivatives have been frequently utilized in the

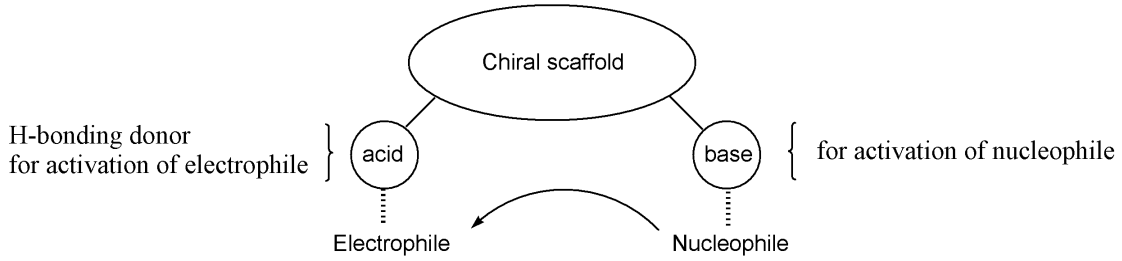


Figure 1-2. Bifunctional catalysts

bifunctional catalysts.[47] The representative examples of the reaction are shown in Scheme 1-14 to 17. Structures of the chiral H-bonding catalysts are displayed in Figure 1-3.

Takemoto and his co-workers reported the catalytic asymmetric nitro-Michael reaction of 1,3-diesters to nitroalkenes catalyzed by chiral bifunctional catalyst **21** (Scheme 1-14).[48] With a 10 mol % of catalyst **21**, the corresponding nitro-Michael products **24** were obtained in good yield with excellent enantioselectivity (up to 93% ee). However, in the reaction of β-alkyl-nitroalkenes, the enantioselectivity of the products slightly declined. The thiourea group in the catalyst **21** effectively activates the nitroalkene, while tertiary amine moiety in the catalyst **21** deprotonates 1,3-diester. In transition state **21a**, both the enolate from 1,3-diester and nitroalkene are activated independently and simultaneously within the catalyst **21**.

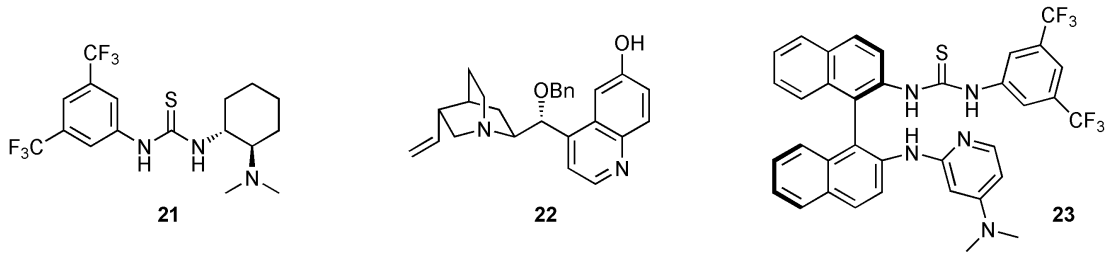
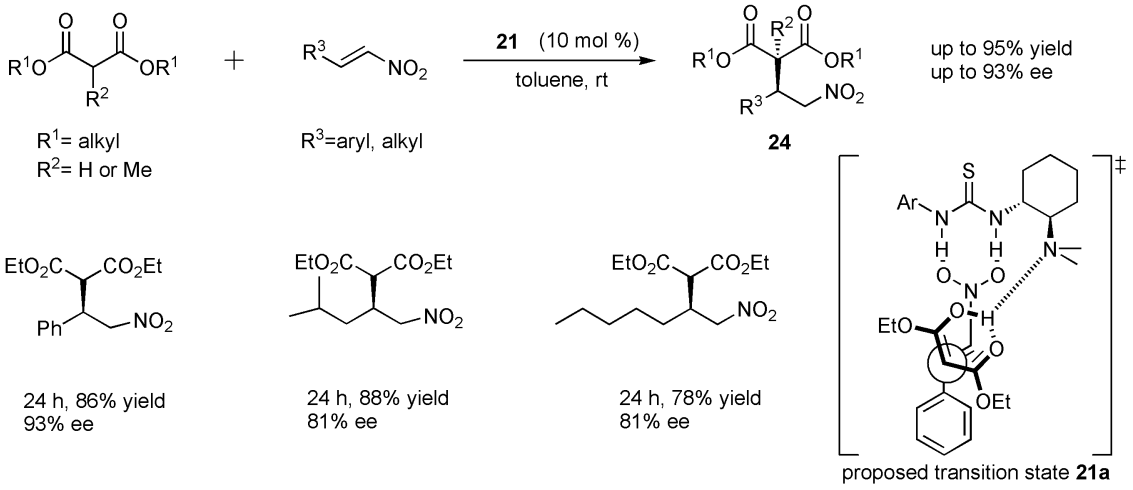
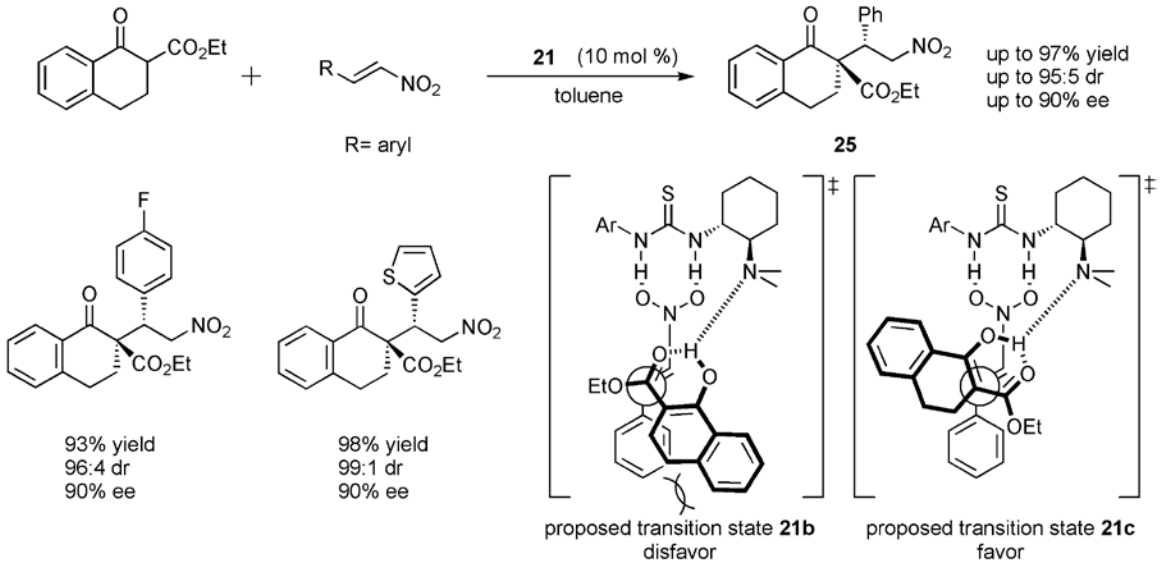


Figure 1-3. Chiral H-bonding catalysts



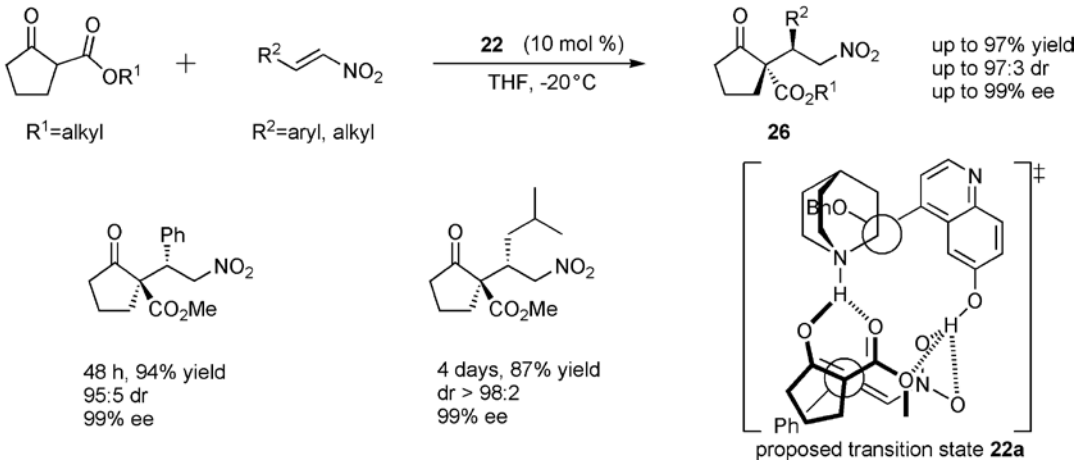
Scheme 1-14. Asymmetric nitro-Michael reaction catalyzed by chiral H-bonding catalyst **21**[48]

The bifunctional catalyst **21** was also effective in catalyzing the asymmetric nitro-Michael reaction of β-ketoesters to nitroalkenes (Scheme 1-15).[49] With a 10 mol % of catalyst **21**, the nitro-Michael addition of cyclic ketoesters to β-arlylnitroalkenes takes place to give the Michael adducts **25** having all-*carbon* quaternary stereogenic center adjacent to ternary stereogenic center. The author suggested that transition state **21c** is likely, because transition state **21b** seems to be unfavorable due to the steric repulsion.



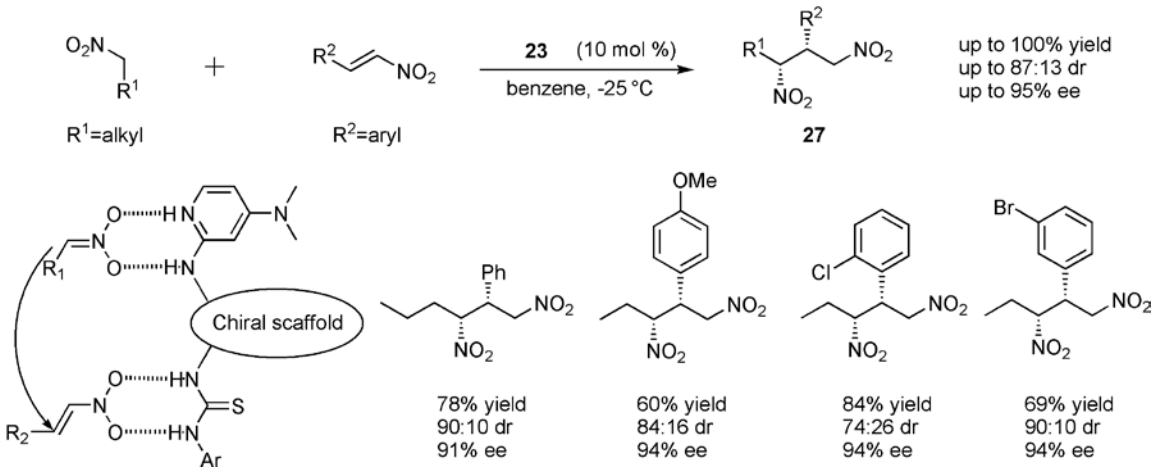
Scheme 1-15. Asymmetric nitro-Michael reaction catalyzed by chiral H-bonding catalyst **21**[49]

Cinchona alkaloid derivatives, which can be easily synthesized from natural products, are often used as bifunctional catalysts. Deng and his co-workers reported the catalytic asymmetric nitro-Michael reaction of β-ketoesters to nitroalkenes catalyzed by cinchona alkaloid derivative **22** (Scheme 1-16).[50] With a 10 mol % of catalyst **22**, the corresponding nitro-Michael products **26** were obtained in excellent yields with excellent diastereo- and enantioselectivities.



Scheme 1-16. Asymmetric nitro-Michael reaction catalyzed by chiral H-bonding catalyst **22**[50]

Wulff and his co-workers reported catalytic asymmetric nitro-Michael reaction catalyzed by BINOL-based bifunctional catalyst **23** (Scheme 1-17).[51] In the presence of a 2 mol % of catalyst **23**, the corresponding nitro-Michael products **27** were obtained in moderate to high yields and with high diastereo- and enantioselectivities (up to 95% ee). Nevertheless, a large excess of nitroalkanes (30 equiv.) was necessary to obtain the satisfactory results.



Scheme 1-17. Asymmetric nitro-Michael reaction catalyzed by chiral H-bonding catalyst **23**[51]

1.7 Major unsolved problems of the asymmetric nitro-Michael reaction catalyzed by organocatalysts

As described above, a large number of organocatalyzed asymmetric nitro-Michael reactions have been reported. However, many problems remain unsolved. The major problems associated with this chemistry of the organocatalysts are as follows:

(1) Esters (except 1,3-diesters and β-ketoesters) cannot be employed as Michael donors.

Employment of esters as Michael donors are very limited (Scheme 1-6). At the present stage of the organocatalyzed nitro-Michael reaction, little is known about diastereo- and enantioselective nitro-Michael reaction of esters. Since ester carbonyl groups cannot react with amine catalysts, the formation of the enamine intermediate is difficult.

(2) *β*-Alkylnitroalkenes cannot be employed as the Michael acceptors.

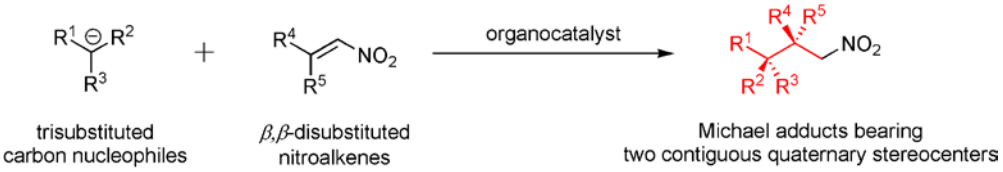
There remains a severely critical problem with the organocatalyst-promoted nitro-Michael reaction, that is, the low reactivity of *β*-alkylnitroalkenes. Thus far, the reports of the Michael reaction of *β*-alkylnitroalkenes catalyzed by H-bonding catalysts as well as enamine catalysts have been rare.[53] The low reactivity of *β*-alkylnitroalkenes is attributable to the high LUMO energy level induced by electoron-donating alkyl groups, leading to a large HOMO-LUMO gap.

(3) *Anti*-selective reactions by catalyst-control have been unknown.

Anti-selective nitro-Michael reaction is rare. An example of *anti*-selective reaction is shown in Scheme 1-13, (Eq. 5). To achieve the highly *anti*-selective nitro-Michael reaction of aldehydes, the structural modification of the aldehydes is needed (*i.e.*, substrate-control of diastereoselectivity). However, the need of the structural modification severely limits the substrate scope of the reaction.

(4) Products having two contiguous quaternary stereogenic centers have been unknown.

This is a challenging subject in organic synthesis, since catalytic asymmetric conjugate addition of trisubstituted carbon nucleophiles to *β,β*-disubstituted nitroalkene (Scheme 1-18) is very rare.[53] The significant steric repulsion between incoming carbon nucleophiles and *β,β*-disubstituted nitroalkenes seems to be the reason for the difficulty of the nitro-Michael reaction of *β,β*-disubstituted nitroalkenes. All-*carbon* quaternary stereogenic centers exist widely in natural products and biologically active compounds.[54] Therefore, catalytic enantioselective construction of all-*carbon* quaternary stereogenic center is one of the most important subjects in organic synthesis.[55]



Scheme 1-18. Asymmetric nitro-Michael reaction of trisubstituted carbon nucleophiles to *β,β*-disubstituted nitroalkenes

1.8 Purpose of this doctoral thesis

To solve these problems, the author has investigated the catalytic asymmetric vinylogous nitro-Michael reactions using 2(3*H*)-furanones as a Michael donor. The reactions have been effectively catalyzed by cinchona alkaloid derivatives as hydrogen-bonding catalysts.

This doctoral thesis consists of General Introduction as Chapter 1 followed by three chapters dealing with new reactions using novel catalysts. In Chapter 1, the present situation of the catalytic asymmetric nitro-Michael reaction is reviewed and the purpose of this doctoral thesis is described.

In Chapter 2, the highly *syn*-selective nitro-Michael addition of 2(3*H*)-furanones to nitroalkenes is described. With 0.1-5 mol % loadings of *epi*-quinine-derived catalyst, the reaction of 5-substituted 2(3*H*)-furanones with *β*-substituted nitroalkenes smoothly proceeded to give the *syn*-Michael adducts in good yields (up to 98%) with excellent diastereo- and enantioselectivities (up to > 98:2 dr, *syn* major; up to 97% ee). During the course of the investigation, the author has found that low reactive *β*-alkylsubstituted nitroalkenes smoothly

undergo the nitro-Michael reaction with 5-substituted 2(3*H*)-furanones.

In Chapter 3, the catalyst-controlled switching of diastereoselectivity from the usual *syn*-selectivity to the *anti*-selectivity of the asymmetric nitro-Michael reaction of 2(3*H*)-furanones to nitroalkenes is described. *Anti*-diastereoselectivity of the nitro-Michael reaction has been very rare. With 0.1-5 mol % loadings of *epi*-quinine-derived catalyst at room temperature, the reaction of 5-substituted 2(3*H*)-furanones with *β*-substituted nitroalkenes smoothly proceeded to give the *anti*-Michael adducts in good yields (up to 95%) with excellent diastereo- and enantioselectivities (up to 97:3 dr, *anti* major; up to 99% ee).

In Chapter 4, *epi*-quinine-catalyzed asymmetric nitro-Michael reaction of 2(3*H*)-furanones to *β*,*β*-disubstituted nitroalkenes is described. The reaction proceeded smoothly with 1-5 mol % loadings of *epi*-quinine-derived catalyst at room temperature, giving the corresponding Michael adducts in high yields (up to 93% yield) with extremely high diastereo- and enantioselectivities (up to > 98:2 dr, *syn* major; 95-99% ee). This reaction provides an effective and straightforward method for the construction of all-*carbon* quaternary stereogenic center adjacent to oxygen-containing quaternary stereogenic center.

1.9 References

(1) (a) Pinnick, H. W. *Org*. *React*. **1990**, *38*, 655.; (b) Nef, J. U. *Justus Liebigs Ann*. *Chem*. **1894**, *280*, 263.

(2) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423.

(3) (a) Larock, R. C.; In *Comprehensive Organic Transformations.*, Wiley-VCH: New York, 1989; pp. 411-415.; (b) Beck,A. K.; Seebach, D. *Chem. Ber*. **1991**, *124*, 2897.; (c) Maeri, R. E.; Heinzer, J.; Seebach, D. *Liebigs Ann*. **1995**, 1193.; (d) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem*. **1999**, *64*, 1356.; (e) Barrett, A.G. M.; Spilling, C. D. *Tetrahedron Lett*. **1988**, *29*, 5733.; (f) Loyd, D. H.; Nichols, D. E. *J. Org. Chem*. **1986**, *51*, 4294.

(4) (a) Meyer, V.; Wurster, C. *Ber*. *Dtsch. Chem. Ges*. **1873**, *6*, 1168.; (b) Kamlet, M. J.; Kaplan, L. A.; Dacons, J. C. *J. Org*. *Chem*. **1961**, *26*, 4371.

(5) Mukayama, T.; Hoshino, T. *J. Am*. *Chem*. *Soc*. **1960**, *82*, 5339.

(6) Ballini, R.; Palmieri, A.; Righi, P. *Tetrahedron* **2007**, *63*, 12099.

(7) Ballini, R.; Barboni, L.; Giarlo, G. *J. Org*. *Chem*. **2003**, *68*, 9173.

(8) Ballini, R.; Castagnani, R.; Marcantoni, E. *J. Chem*. *Soc., Perkin Trans 1* **1992**, 3161

(9) Wang, J.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem*. *Commun*. **2008**, 1232.

(10) Wilson, J. E.; Casrez, A. D.; MacMillan, D. W. C. *J. Am*. *Chem*. *Soc*. **2009**, 11332.

(11) Lu, S. -F.; Du, D. -M.; Xu, J.; Zhang, S. -W. *J. Am*. *Chem*. *Soc*. **2006**, *128*, 7418.

(12) Adams, H.; Anderson, J. C. *J. Org*. *Chem*. **1998**, *63*, 9932.

(13) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett*. **1993**, *34*, 855.

(14) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* **2002**, 2725.
(15) Barrett, A. B. M.; Graboski, G. G. *Chem. Rev*. **1986**, *86*, 751.
(16) Gnas, Y.; Glorious, F. *Synthesis* **2006**, 1899.
(17) (a) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc*. **2001**, *123*, 1004.; (b) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.; (c) Langer, W.; Seebach, D. *Helv. Chim. Acta*. **1979**, *62*, 1710.; (d) Seebach, D.; Crass, G.; Wilka, E. M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta*. **1979**, *62*, 2695.
(18) (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc*. **1999**, *121*, 10215.; (b) Watanabe, K.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc*. **2004**, *126*, 11148.
(19) Christffers, J.; Baro, A. *Angew. Chem. Int. Ed*. **2003**, *42*, 1688.
(20) Lu, S. -F.; Du, D. -M.; Xi, J.; Zhang, S. -W. *J. Am. Chem. Soc.*, **2006**, *128*, 7418.
(21) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc*. **2009**, *131*, 4572.
(22) Trost, B. M.; Hisaindee, S, *Org. Lett*. **2006**, *8*, 6003.
(23) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett*. **2004**, *6*, 2829.
(24) MacMillan, D. M. C. *Nature* **2008**, *455*, 304.
(25) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615.
(26) List, B.; Lerner, R. A.; BarbasⅢ, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395.
(27) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. M. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243.
(28) Xi, Y.; Shi, X. *Chem. Commun*. **2013**, *49*, 8583.
(29) Cordova, A.; In *Catalytic Asymmetric Conjugate Reaction*.; Wiley-VCH, Weinheil, 2010.
(30) (a) Bressy, C.; Dalko, P. I.; In *Enantioselective Organocatalysis*.; Dalko, P. I., Ed., Wiley-VCH Verlag GmbH: Weinheim, 2007; pp. 77-94.; (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed*. **2006**, *45*, 1520.; (c) Pikho, P.; In *Hydrogen Bonding in Organic Synthesis*.; Wiley-VCH Verlag GmbH; Weinheim, 2009.
(31) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun*. **2007**, 3123.
(32) (a) Seebach, D.; Golinski, J. *Helv. Chem. Acta* **1981**, *64*, 1413.; (b) Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chem. Acta* **1982**, *65*, 1637.; (c) Haner, R.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chem. Acta* **1985**, *68*, 162.
(33) Betancort, J. M.; BarbasⅢ, C. F. *Org. Lett*. **2001**, *3*, 3737.
(34) Alexakis, A.; Andrey, O. *Org. Lett*. **2002**, *4*, 3611.
(35) Masse, N.; Thayumanavan, RTanaka, F.; BarbasⅢ, C. F. *Org. Lett*. **2004**, *6*, 2527.
(36) Wang, W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed*. **2005**, *44*,1369.
(37) Cao, C. –L.; Ye, M. –C.; Sun, X. –L.; Tang, Y. *Org. Lett*. **2006**, *8*, 2901.

(38) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org*. *Chem*. **2003**, *5*, 2559.
(39) Dalko, P. I.; In *Comprehensive Enantioselective Organocatalysis*.; Dalko, P. I., Ed., Wiley-VCH Verlag GmbH: Weinheim, 2013; pp, 1013-1042.
(40) Tsogoeva, S. B.; Wei, S. *Chem*. *Commun*. **2006**, 1451.
(41) Huang, H.; Jacobsen, E. N. *J*. *Am*. *Chem*. *Soc*. **2006**, *128*, 7170.
(42) Laloude, M. P.; Chen, Y.; Jacobsen, E. N. *Angew*. *Chem*. *Int*. *Ed*. **2006**, *45*, 6366.
(43) McCooey, S. H.; Connen, S. J. *Org*. *Lett*. **2006**, *9*, 599.
(44) Uehara, H.; BarbasⅢ, C. F. *Angew*. *Chem*. *Int*. *Ed*. **2009**, *48* 9848.
(45) (a) Taylor, M. S.; Jacobsen, E. N. *Angew*. *Chem*. *Int*. *Ed*. **2006**, *45*, 1520.; (b) Pikho, P., In *Hydrogen Bonding in Organic Synthesis*., Wiley-VCH verlag GmbH: Weinheim, 2009.
(46) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc*. *Chem*. *Res*. **2008**, *41*, 655.
(47) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.
(48) Okino, T.; Hoashi, Y.; Takemoto, Y. *J*. *Am*. *Chem*. *Soc*. **2003**, *125*, 12672.
(49) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J*. *Am*. *Chem*. *Soc*. **2005**, *127*, 119.
(50) Li, H.; Wang, Y.; Tang, Z.; Wu, F.; Liu, X.; Guo, C.; Foxman, M.; Deng, Z. *Angew*. *Chem*. *Int*. *Ed*. **2005**, *44*, 105.
(51) Rabalakos, C.; Wulff, W. D. *J*. *Am*. *Chem*. *Soc*. **2008**, *130*, 13524.
(52) (a) Roux, C.; Bressy, C.; In *Comprehensive Enantioselective Organocatalysis*; Dalco, P., Ed., Wiley-VCH: Weinheim, 2013; Vol. 3; pp 1013-1042.; (b) Rios, R.; Moyano, A.; In *Catalytic Asymmetric Conjugate Reaction*; Cordóva, A., Ed.; Wiley-VCH: Weinheim, 2010; pp 191-218.
(53) (a) Kastle, R.; Wennemers, H. *Angew*. *Chem*. *Int*. *Ed*. **2013**, *52*, 7228.; (b) Chen, L. -A.; Xiaojuan, T.; Jianwet, X.; Weici, X.; Lei, G.; Meggers, E. *Angew*. *Chem*. *Int*. *Ed*. **2013**, *52*, 14021.; (c) Wang, J. -Q.; Deng, Q. -M.; Wu, L.; Xu, K.; Wu, H.; Liu, R. -R.; Gao, J. -R. *Org*. *Lett*. **2014**, *16*, 776.
(54) Liu, Y.; Han, S. -J.; Liu,W. -B.; Stoltz, B. M. *Acc*. *Chem*. *Res*. **2015**, *48*, 740.
(55) (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.; (b) Corey, E. J.; Guzman-Perez, A. *Angew*. *Chem*. *Int*. *Ed*. **1998**, *37*, 388.; (c) Bella, M.; Gasperi, T.; *Synthesis* **2009**, 1583.

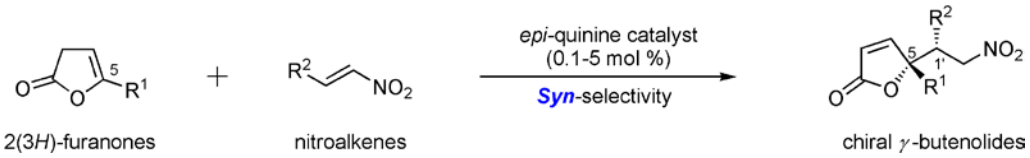
Chapter 2

Catalytic Activity of *Epi*-Quinine-Derived 3,5-Bis(trifluoromethyl)benzamide in Asymmetric Nitro-Michael Reaction of Furanones

2.1 Introduction

Among a large variety of the Michael reactions, nitroalkenes have been one of the most widely used Michael acceptors, because of the versatility of nitro groups in numerous transformations.[1] Organocatalysts employed in the asymmetric nitro-Michael reaction have been mainly bifunctional enamine catalysts,[1a,d,g] although on using the enamine catalysts, the substrates are restricted to aldehydes and ketones.[1f] This limitation can be largely overcome by bifunctional hydrogen bonding catalysts such as thiourea derivatives.[2] However, weak non-covalent hydrogen bonding activation of nitro groups often leads to moderate enantioselectivity (< 90% ee), severely limited substrate scope, and the need of substoichiometric amount of catalysts (≥ 10 mol %).[2b-j] Recently, organocatalytic diastereo- and enantioselective vinylogous Michael additions of furanone-derived dienolates to nitroalkenes have been reported as a straightforward route to highly functionalized chiral *γ*-butenolides.[3] *γ*-Butenolides are often subunits of natural products and biologically active compounds.[4] Given the great number of natural products containing chiral *γ*-butenolides, the application of reactive 2(3*H*)-furanones as a direct vinylogous nucleophile is highly promising.

Herein, the author describes the remarkable activity of *epi*-quinine-derived 3,5-bis-(trifluoromethyl)benzamide catalyst in the asymmetric Michael addition of 2(3*H*)-furanones to nitroalkenes (Scheme 2-1). In particular, this catalyst has proved to be extremely effective in promoting the nitro-Michael reaction of low reactive *β*-alkylnitroalkenes, which have been traditionally challenging substrates in the organocatalytic nitro-Michael reactions.[2,3a]



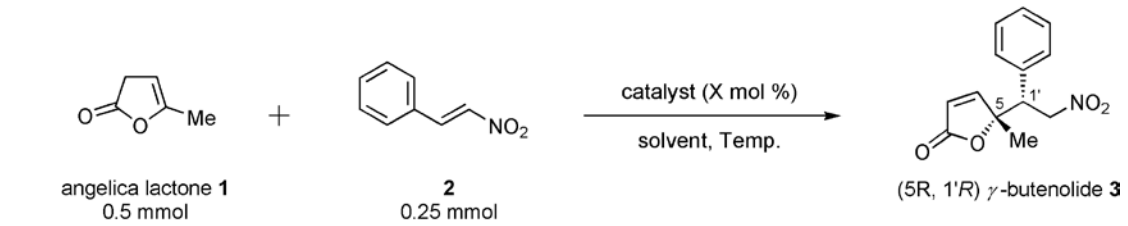
Scheme 2-1. Asymmetric nitro-Michael reaction of 2(3*H*)-furanones to nitroalkenes catalyzed by *epi*-quinine-derived catalyst

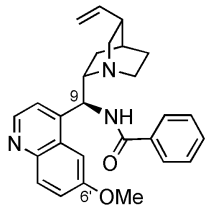
2.2 Results and Discussion

2.2.1 Catalyst scope

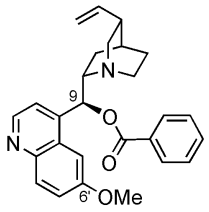
As shown in Table 2-1, the author has found that bifunctional *epi*-quinine-9-benzamide-6'-OMe catalysts are capable of promoting the Michael addition of angelica lactone **1** to (*E*)-*β*-nitrostyrene **2** with a 10 mol % catalyst loading at room temperature, affording the Michael adduct **3** (entries 1 to 6). Thus, with a 10 mol % of **4a**,[5a] the Michael adduct **3** was obtained in 57% yield with excellent diastereoselectivity, but the enantioselectivity is low (≥ 98:2 dr, *syn* major; 48% ee) (entry 6). THF is the solvent of choice (entry 6). Next, the author

Table 2-1. Catalytic asymmetric nitro-Michael reaction of **1** to **2**[a]

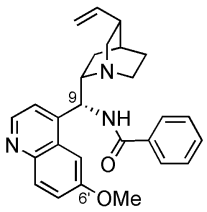




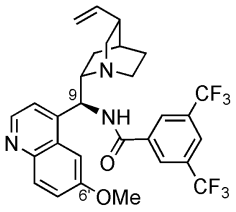
4a



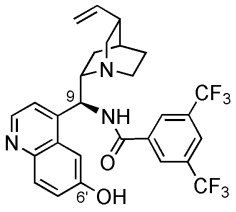
4b



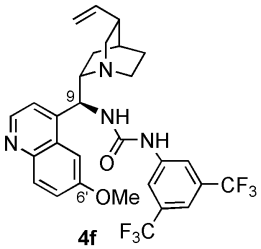
4c



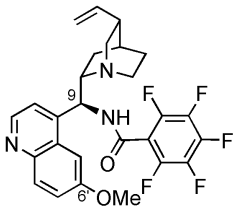
4d



4e



4f



4g

entry	catalyst	solvent	X [mol %]	T [°C]	*t* [h]	Yield [%][b]	*syn/anti*[c]	ee [%][d]
1	**4a**	CH_2Cl_2	10	rt	24	47	>98/2	44
2	**4a**	Et_2O	10	rt	24	54	>98/2	47
3	**4a**	Toluene	10	rt	24	56	>98/2	48
4	**4a**	Hexane	10	rt	24	55	>98/2	46
5	**4a**	EtOH	10	rt	24	30	66:33	27
6	**4a**	THF	10	rt	24	57	>98/2	48
7	**4b**	THF	10	rt	48	55	94:6	13
8	**4c**	THF	10	rt	96	50	87:13	4
9	**4a**	THF	10	−40	24	80	>98/2	58
10	**4d**	THF	10	−40	24	98	>98/2	90
11	**4e**	THF	10	−40	24	98	>98/2	88
12	**4f**	THF	10	−40	24	82	>98/2	−50
13	**4g**	THF	10	−40	24	78	>98/2	0
14	**4d**	$CHCl_3$	1	−40	48	98	>98/2	94

[a] Absolute configuration was assigned by analogy with compound **10ac** (Table 2-2). [b] Isolated yield. [c] Diastereomer ratio was determined by ^{1}H NMR analysis of crude material. [d] Obtained by chiral HPLC analysis.

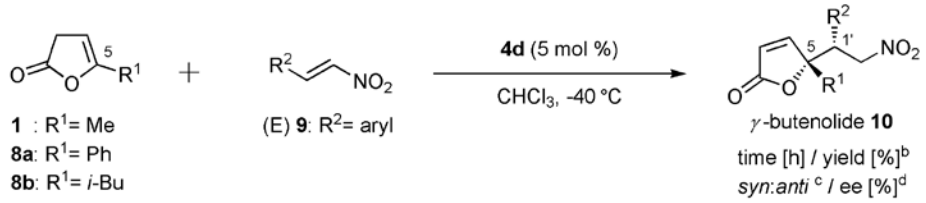
examined catalyst **4b** synthesized by replacing the 9-benzamide of **4a** with 9-benzester (entry 7). The enantioselectivity dropped considerably (13% ee), although the diastereoselectivity was very high (dr 94:6). Interestingly, diastereomeric catalyst **4c**[5b] exhibited the astonishingly reduced stereoselectivity (entry 8). A significant improvement of the catalytic performance has been attained upon the employment of *epi*-quinine-derived 3,5-bis-(trifluoromethyl)-benzamide **4d**.[5c] A 10 mol % loading of **4d** successfully catalyzed the Michael addition of **1** to **2** at −40 °C, affording the Michael adduct **3** in 98% yield with high diastereo- and enantioselectivity (> 98:2 dr, *syn* major; 90% ee) (entry 10). Catalysts **4e** and **4f** showed no improvement of the catalytic effectiveness (entries 11 and 12). With the purpose of achieving the further improvement of catalytic activity, the author prepared catalyst **4g**[5d] having pentafluorobenzamide, which is stronger electron-withdrawing group than 3,5-bis(trifluoro-methyl)benzamide. To our surprise, with a 10 mol % loading of **4g** the reaction afforded the racemic product **3** in 78% yield (entry 13). The practicability of the **4d**-catalyzed nitro-Michael reaction was demonstrated by the large scale reaction of **1** (7.5 mmol) and **2** (5 mmol) at only 1 mol % loading of **4d** in chloroform to give **3** in 98% yield with high diastereo- and enantioselectivity (> 98:2 dr, *syn* major; 94% ee) (entry 14).

2.2.2 Substrate scope

The author then turned his attention to the substrate scope of the nitro-Michael reaction in chloroform (Table 2-2). After solvent screening shown in Table 2-1, the author have noticed that chloroform brings about higher diastereo- and enantioselectivity. Table 2-2 shows that 5 mol % loadings of catalyst **4d** allowed complete conversion of the *β*-arylnitroalkenes in chloroform, giving the corresponding Michael adducts in excellent yields (90-98%) with the high level of diastereo- and enantioselectivities (> 98:2 dr; *syn* major; 92-97% ee) (entries 1 to 12). A series of *β*-arylnitroalkenes bearing electron-withdrawing and electron-releasing substituents on the aromatic rings smoothly reacted with various 5-substituted furanones in high yields (> 97%) with high diastereo- and enantioslectivities (> 98:2 dr; 92-97 % ee) (entries 4 to 7). Thus, the electronic properties of substituents on the aromatic rings of *β*-arylnitroalkenes had a no effect on the reaction. Furthermore, the substitution pattern on the aromatic rings (entries 8 to 10) and sterically demanding aromatic ring of *β*-arylnitroalkenes had also no deleterious effect on the stereoselectivities as well as the yield (entries 1 and 2).

There remains a severely critical problem with the organocatalyst-promoted asymmetric nitro-Michael reaction, that is, very low reactivity of *β*-alkylnitroalkenes. Reports of the Michael reaction of *β*-alkylnitroalkenes catalyzed by hydrogen-bonding catalysts or enamine catalysts have been rare.[1f,g,2] While a few sporadic examples of this reaction have been reported,[2b-j,3a] most of them seem to be impractical in view of the requirement of the substoichiometric amount of the catalysts (≥ 10 mol %) and the low to moderate

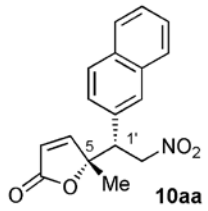
Table 2-2. Asymmetric nitro-Michael reaction catalyzed by **4d**[a]



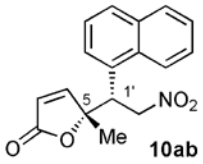
1 : R^1= Me
8a: R^1= Ph
8b: R^1= *i*-Bu

(E) **9**: R^2= aryl

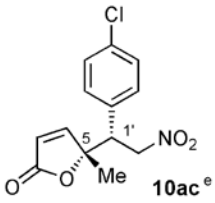
γ-butenolide **10**
time [h] / yield [%][b]
syn:*anti* [c] / ee [%][d]



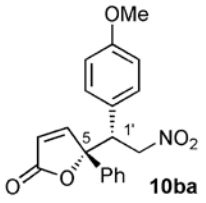
10aa
(entry 1 : **1** / **9a**)
55 h / 95% yield
>98:2 dr / 93% ee



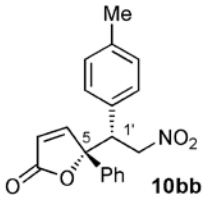
10ab
(entry 2 : **1** / **9b**)
60 h / 90% yield
>98:2 dr / 94% ee



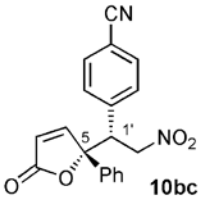
10ac [e]
(entry 3 : **1** / **9c**)
55 h / 98% yield
>98:2 dr / 92% ee



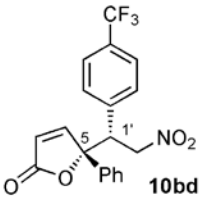
10ba
(entry 4 : **8a** / **9d**)
18 h / 97% yield
>98:2 dr / 96% ee



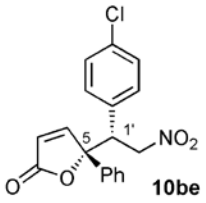
10bb
(entry 5 : **8a** / **9e**)
37 h / 97% yield
>98:2 dr / 97% ee



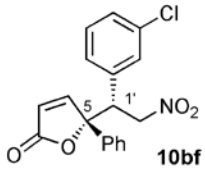
10bc
(entry 6 : **8a** / **9f**)
48 h / 98% yield
>98:2 dr / 94% ee



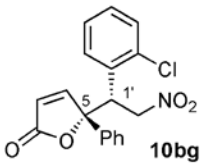
10bd
(entry 7 : **8a** / **9g**)
48 h / 98% yield
>98:2 dr / 92% ee



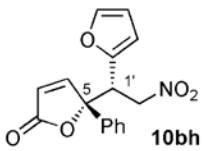
10be
(entry 8 : **8a** / **9h**)
18 h / 97% yield
>98:2 dr / 96% ee



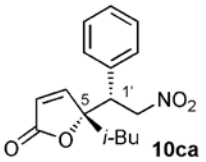
10bf
(entry 9 : **8a** / **9i**)
33 h / 96% yield
>98:2 dr / 94% ee



10bg
(entry 10 : **8a** / **9j**)
33 h / 92% yield
>98:2 dr / 96% ee



10bh
(entry 11 : **8a** / **9k**)
24 h / 95% yield
>98:2 dr / 95% ee



10ca
(entry 12 : **8b** / **2**)
48 h / 95% yield
>98:2 dr / 91% ee

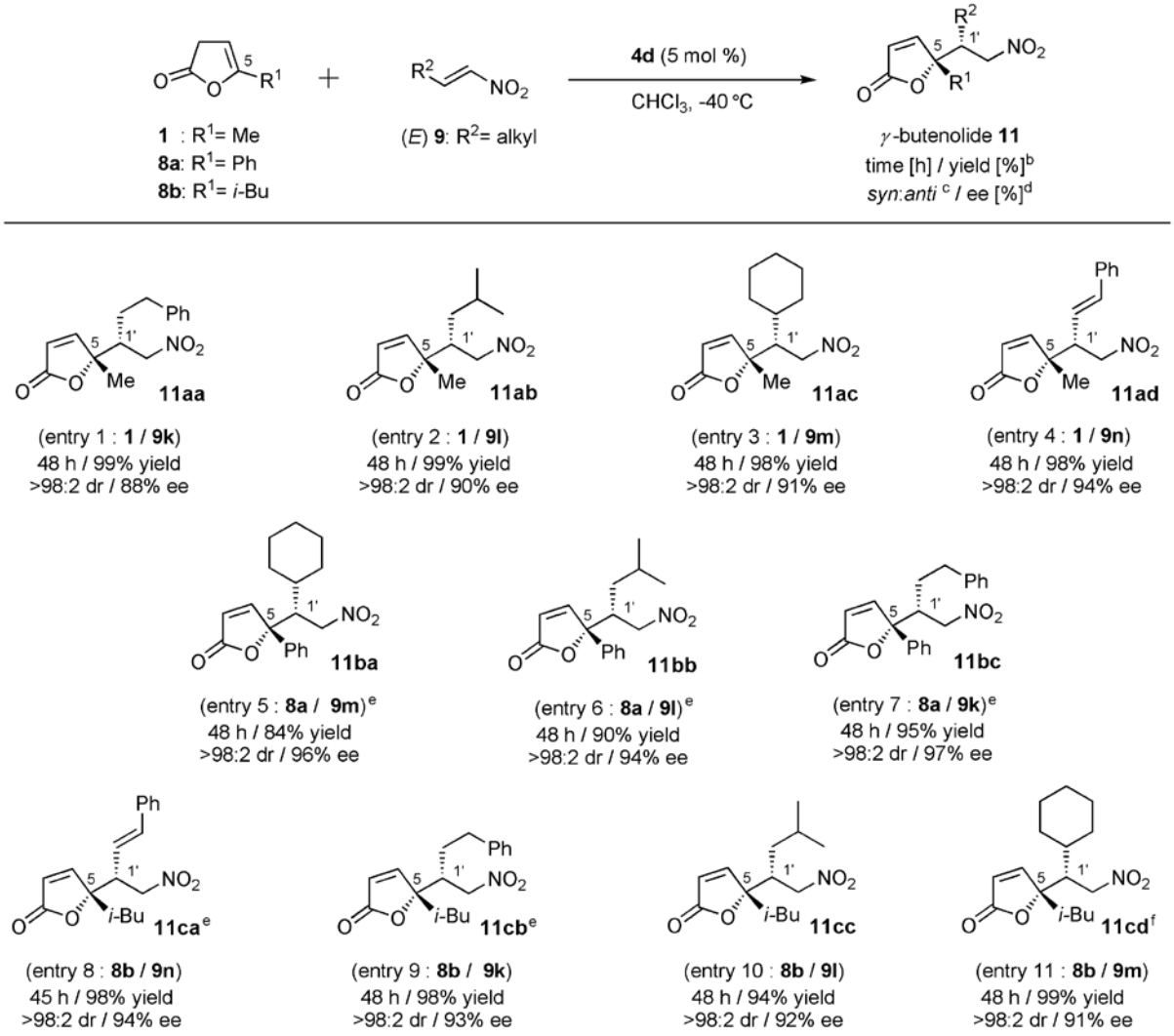
[a] Absolute configuration was assigned by analogy with compound **10ac** (entry 3). [b] Isolated yield. [c] Diastereomer ratio was determined by ^{1}H NMR analysis of crude material. [d] Obtained by chiral HPLC analysis. [e] Absolute configuration of **10ac** was determined by X-ray crystallographic analysis.

stereoselectivities (< 90% ee). Moreover, the structures of carbon nucleophiles, which can smoothly react with *β*-alkylnitroalkenes, are severely limited.[6] The low reactivity of *β*-alkylnitroalkenes is attributable to the high LUMO energy level induced by electoron-donating alkyl groups, which leads to a large HOMO-LUMO gap.

The author has pleased to find that 5 mol % loadings of catalyst **4d** are extremely effective in promoting the asymmetric nitro-Michael reaction of various 5-substituted furanones to *β*-alkylnitroalkenes at 0 °C (Table 2-3). Generally, the **4d**-catalyzed reaction of

β-alkylnitroalkenes exhibited the high yields (> 90% yield) with high diastereo- and enantioselectivities (> 98:2 dr, *syn* major; 88-96% ee) (entries 1 to 11). For example, the Michael addition of furanone **1** to sterically demanding β-cyclohexylnitroalkene **9m**, which has been challenging substrate,[2a] successfully took place, giving rise to the Michael adduct **11ac** with 91% ee (entry 3). Despite the low reactivities of **9m** and β-isobutylnitroalkene **9l**,[3a] the Michael addition of sterically demanding 5-phenylfuranone **8a** to **9l** and **9m** smoothly proceeded, affording the adducts **11ba** (96% ee) and **11bb** (94% ee) (entries 5 and 6). Thus, the present method is especially useful for constracting the sterically congested oxygen-containing quartarnary stereogenic centers adjacent to ternary stereogenic centers.[7]

Table 2-3. Catalytic asymmetric nitro-Michael reaction of furanones to (*E*)-β-alkyl- and β-alkenylnitroalkenes[a]

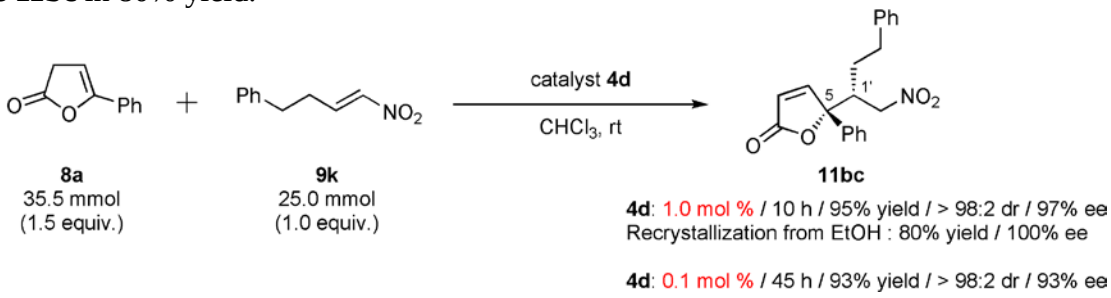


[a] Absolute configuration was assigned by analogy with compound **10ac** (Table 2-2). [b] Isolated yield. [c] Diastereomer ratio was determined by ^{1}H NMR analysis of crude material. [d] Obtained by chiral HPLC analysis. [e] Reaction was conducted at −40 °C. [f] Reaction was conducted with 10 mol % loading of **4d**.

To evaluate the potential of catalyst **4d**, the Michael additions of sterically demanding 5-isobutylfuranone **8b** to *β*-aklylnitroalkenes **9k**, **9l** and *β*-alkenylnitroalkene **9n** were carried out, giving the corresponding Michael adducts **11ca** (94% ee), **11cb** (93% ee) and **11cc** (92% ee) in high yields (entries 8 to 10). The addition of **8b** to sterically hindered nitroalkenes **9m** needed 10 mol % catalyst loading for complete substrate conversion (entry 11). However, the corresponding adduct **11cd** (91% ee) was obtained in 99% yield.

2.2.3 Large scale reaction

The author examined the large scale reaction to establish the practical reaction conditions (Scheme 2-2). When the reaction of **8a** (35.5 mmol) and **9k** (25.0 mmol) was conducted at room temperature, the author found that catalyst loading could be reduced to only 0.1-1 mol % without affecting the high diastereo- and enantioselectivity as well as the high yields of the Michael adduct **11bc** (> 98:2 dr; 93-97% ee; 93-95% yields). The reaction achieved the TON of 930.[8] Single recrystallization of the crude product from ethanol gave enantiomerically pure **11bc** in 80% yield.



Scheme 2-2. Practical reaction conditions

2.2.4 Discussion of the mechanism

To shed light on the mechanism accounting for the remarkable catalytic activity of **4d** in the asymmetric nitiro-Michael reaction, DFT calculations of the catalyst *β*-alkylnitroalkene adducts were carried out (Figure 2-1). The structure of 3,5-bis(trifluoromethyl)benzamide-*β*-isobutylnitroalkene **9l** adduct **A** as a simplified model for **4d**-**9l** adduct and the structure of thiourea-**9l** adduct **B**[1d] as a simplified model for thiourea catalyst-**9l** adduct were optimized at B3LYP/6-311++G(d,p) level at theory. Thioureas are most frequently used hydrogen-bonding catalysts in asymmetric nitro-Michel reactions.[1a,d,f] Thus, to explain the high catalytic activity of **4d**, a comparison with thiourea-based catalysts should be helpful. The results of the calculations have revealed that: (1) activation of **9l** by the double hydrogen-bondings of thioerea provides a significant decrease in the LUMO energies of **9l** (**B**, −27 Kcal mol^{-1}), while a decrease in the LUMO energy of **9l** induced by benzamide is considerally smaller (**A**, −18 Kcal mol^{-1}), but it suffices for the smooth reaction of **9l** with furanones (entries 2, 6, and

10 in Table 2-3); (2) despite the stronger hydrogen-bonding activation of **9l**, most of thiourea catalysts give unsatisfactory results of the Michael addition to *β*-alkylnitroalkenes,[2b-n,3a] (3) thiourea-**9l** adduct **B** has conformationally rigid structure due to the strong double hydrogen-bondings (hygrogen-bonding energy: 9.03 Kcal mol^{-1}).[1d,1e] In contrast, benzamide-**9l** adduct **A**, where **9l** binds to the benzamide by single hydrogen-bonding, seems to be conformationally flexible (hydrogen-bonding energy: 5.38 Kcal mol^{-1}). In general, the energy of transition state strongly depends on the angular geometry between HOMO and LUMO of reactants (*i.e.*, angles between HOMO and LUMO).[9] The calculations strongly suggest that the thiourea-**9l** adduct **B** would hinder the muximum overlap of the HOMO and LUMO, since the conformationally rigid adduct **B** would distort the angular geometry of the HOMO and LUMO from the ideal angle in sterically congested chiral environment. In contrast, conformational flexibility of benzamide-**9l** adduct **A** would permit the nearly maximum HOMO-LUMO overlap in transition state, allowing more smooth reaction via transition state of lower energy. The DFT calculations sufficiently explain the higher catalytic activity of **4d** than thiourea-based catalysts.

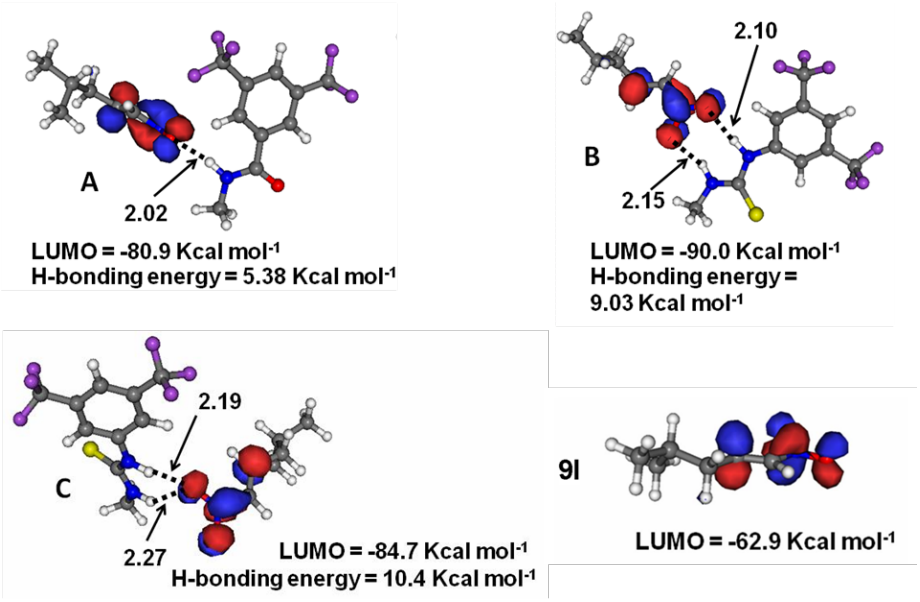


Figure 2-1. Optimized structures of benzamide-**9l** adduct (**A**) and Thiourea-**9l** adducts (**B** and **C**) optimized at B3LYP/6-311++G(d,p). Hydrogen-bond Lengths in Å

Figure 2-2 displays the simplified pre-transition state assebly model optimized at B3LYP/6-31G(d) level. Quinuclidine moiety shields the *si*-face of the nitroalkene bound to amide-hygrogen. To avoid the steric repulsion between the 5-substituent of the dienolate and the aromatic ring of the benzamide, the dienolate bound to quinuclidinium-hydrogen exposes the *si*-face to the nitroalkene. The addition of the dienolate from the *si*-face to the exposed *re*-face of the nitroalkene predicts the sence of the asymmetric induction.

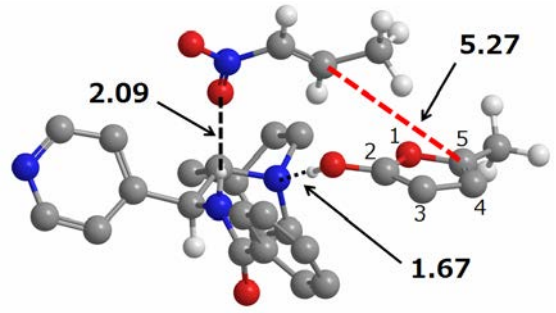
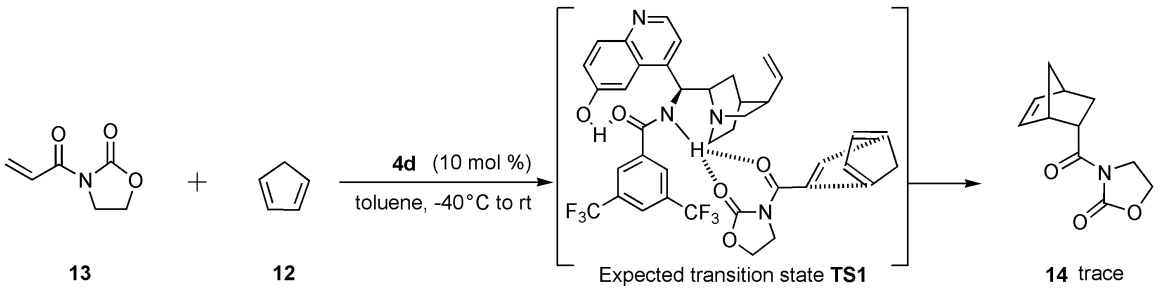


Figure 2-2. Simplified pre-transition-state assembly model optimized at B3LYP/6-31(G). Atomic distances in Å

2.3 The attempted Diels-Alder reaction catalyzed by *epi*-quinine-derived 3,5-bis(trifluoromethyl)benzamide

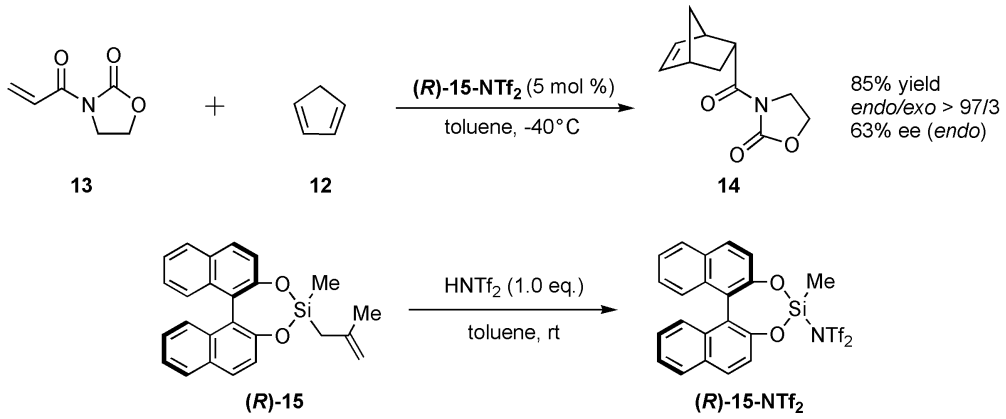
It has become apparent that *epi*-quinine-derived 3,5-bis(trifluoromethyl)benzamide catalyst **4d** can strongly activate an electrophile toward the attack of a nucleophile. The author attempted the asymmetric Diels-Alder reaction of cyclopentadiene **12** with alkenoyl-oxazolidinone **13** promoted by catalyst **4d** (Scheme 2-3). Hydrogen-bonding activation of alkenoyloxazolidinone is expected to decrease the LUMO energy of alkenoyloxazolidinone **13** (Scheme 2-3 **TS1**), leading to smaller energy gap between the HOMO of cyclopentadiene **12** and LUMO of alkenoyloxazolidinone **13**. However, when the Diels-Alder reaction was carried out with a 10 mol % of **4d** in toluene at −40 °C to room temperature, the reaction reluctantly took place to give the trace of expected the Diels-Alder adduct **14**.



Scheme 2-3. Attempt of asymmetric Diels-Alder reaction catalyzed by catalyst **4d**

Then, the author turned his attention to catalytic activity of chiral silicon Lewis acid **(*R*)-15-NTf$_2$** in this reaction (Scheme 2-4). Chiral silicon Lewis acid **(*R*)-15-NTf$_2$** was prepared in situ by protodesilylation of chiral allylsilane **(*R*)-15** with trifluoromethane-sulfonic acid ($HNTf_2$). In the presence of catalytic amount of **(*R*)-15-NTf$_2$** (5 mol %), the Diels-Alder reaction of cyclopentadiene **12** with alkenoyloxazolidinone **13** was proceeded, affording the corresponding Dieks-Alder adduct **14** in 85% yield with moderate

enantioselectivity (69% ee). This result indicates that the activation of carbonyl compounds by metal Lewis acid would be more effective than hydrogen-bonding activation.



Scheme 2-4. Asymmetric Diels-Alder reaction catalyzed by chiral silicon acid (*R*)-**15-NTf$_3$**

2.4 Summary

In summary, the author has developed highly enantioselective nitro-Michael reaction of 2(3*H*)-furanones with very low reactive *β*-alkylnitroalkenes catalyzed by a novel *epi*-quinine-amide **4d**. The DFT calculations revealed that the conformational flexibility of the catalyst **4d**-nitroalkene adducts plays a critical role in the high asymmetric induction. This result is entirely unexpected, since asymmetric organocatalysts are usually designed to achieve the conformational rigidity (*e.g.*, a series of iminium catalysts and thiourea-based catalysts).[2]

2.5 References

(1) For recent reviews on organocatalytic asymmetric nitro-Michael reactions and the application to organic synthesis, see: (a) Somanatham, R.; Chávez, D.; Servin, F. A.; Romero, J. A.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; de Parrod, C. A.; González, J. S. *Curr. Org. Chem*. **2012**, *16*, 2440.; (b) Chauhan, P.; Chimni, S. S. *RSC. Adv* **2012**, 2, 737.; (c) Raimond, W.; Bonne, D.; Rodriguez, J. *Angew. Chem. Int. Ed*. **2012**, *51*, 40.; (d) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051.; (e) Xi, Y.; Shi, X. *Chem. Commun*. **2013**, *49*, 8583.; (f) Roux, C.; Bressy, C.; In *Comprehensive Enantioselective Organocatalysis*; Dalco, P., Ed., Wiley-VCH: Weinheim, 2013; Vol. 3; pp 1013-1042.; (g) Rios, R.; Moyano, A.; In *Catalytic Asymmetric Conjugate Reaction*; Cordóva, A., Ed.; Wiley-VCH: Weinheim, 2010; pp 191-218.

(2) For selected examples of the nitro-Michael reaction promoted by bifunctional H-bonding catalysts, see: (a) McCoorey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.*

2005, *44*, 6367.; (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.; (c) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.; (d) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.; (e) Basle, O.; Raimondi, W.; del Mar Sanchez Duque, M.; Bonne, D.; Constantieux, T.; González, J. S. *Org. Lett*. **2010**, *12*, 5246.; (f) Uehara, H.; Barbas III, C.F. *Angew. Chem. Int.* Ed. **2009**, *48*, 9848.; (g) Tan B.; Hernández-Torres, G.; Barbas III, C. F. *Angew. Chem. Int. Ed*. **2012**, *57*, 5381.; (h) Corbett, M. T.; Xu, Q.; Johnson, J. S. *Org. Lett.* **2014**, *16*, 2362.; (i) Cao, C. -L.; Ye, M. -C.; Sun, X. -L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901.; (j) Cui, B. -D.; Han, W. -Y.; Wu, Z. -J.; Zhang, X. -M, Yuan, W. -C. *J. Org. Chem.* **2013**, *78*, 8833.; (k) Rabalakos, C.; Wulff. W. D. *J. Am. Chem. Soc.* **2008,** 130, 13524.; (l) Hynes, P. S.; Stranges, D.; Stupple, P. A.; Guarna, A.; Dixon, D. J. *Org. Lett.* **2007**, *9*, 2107.; (m) Cui, B. -D.; Han, W. -Y.; Wu, Z. -J.; Zhang, X. -M, Yuan, W. -C. *J. Org. Chem*. **2013**, *78*, 8833.; (n) Noole, A.; Järving, I.; Werner, F.; Lopp, M.; Malkov, A.; Kangert. *J. Org. Chem*. **2013**, *78*, 8833.

(3) (a) Manna, M. S.; Kumar, V. Mukherjee, S. *Chem. Commun.* **2012**, *48*, 5193.; (b) Terada, M.; Ando, K. *Org. Lett.* **2011**. *13*, 2026.; (c) Kumar, V.; Ray, B.; Rathi, P.; Mukherjee, S. *Syntesis* **2013** *45*, 1641. A similar reaction was independently reported by the autor.: (d) Hatanaka, Y.; Sekikawa, T.; Kitagawa, M.; Minami, T. The 92nd Annual Meeting of Chem. Soc. Jpn. **2012** March, Yokohama, Abstract (1K5-50A) is available from The Chemical Society of Japan as a CD (http://chemistry.or.jp). The reaction using chiral Zn catalyst was reported. However, the substrates are restricted to unsubstituted furanones: (e) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572.

(4) (a) Alali, F. Q.; Liu, X. -X.; McLaughlin, J. L. *J. Nat. Prod.**1999**, 62*, 504.; (b) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 609.

(5) (a) Huang, Y.; Yang, L.; Shao, P.; Zhao. Y. *Chem. Sci.* **2013**, *4*, 3275.; (b) Brunner, H.; Buegler, J. *Bull. Soc. Chim. Belg.* **1997**, *106*, 77.; (c) For similar H-bonding catalyst bearing trifluoromethyl group, see: Shao, Q.; Chen, J.; Tu, M.; Piotorawski, D. V.; Huang, Y. *Chem. Commun*. **2013**, *49*, 11098.; (d) Rana, N. K.; Selvokumar, S.; Singh, V. D. *J. Org. Chem*. **2010**, *75*, 2089.

(6) Compounds with very low pK_a values such as cyclohexyl Meldrum's acid (pK_a in DMSO = 7-8) and α-nitroacetates (pK_a in DMSO = 9) can react with β-alkylnitroalkenes at 1-3 mol % loadings of bifunctional H-bonding catalysts: (a) Kimmel, K. L.; Weaver, J. D.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 121.; (b) Li, Y. -Z.; Li, F.; Tian, P.; Lin, G. -Q. *Eur. J. Org. Chem.* **2013**, 1558.

(7) For a review, see: Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

(8) Development of low-loading asymmetric organocatalysts (≤ 3 mol %) has received considerable attention. Review: Giacolone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R.

Chem. Soc. Rev. **2012**, *41*, 2406.

(9) Houk, K. N.; Paddon-Row, M. N.; Rondon, N. G.; Wu, Y. -D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Richard, Y. L.; Loncharich, R. J. *Science* **1986**, *231*, 1108.

2.6 Experimental Section

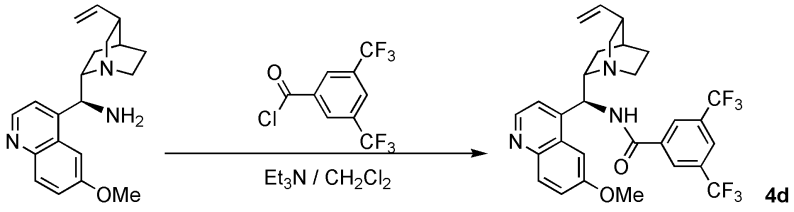
2.6.1 Materials and methods

General Methods: All manipulations were carried out under nitrogen atmosphere using Schlenk tube technique. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a BRUKER-300 spectrometer. Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ (7.26 ppm) for ^{1}H NMR, and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as internal standards respectively. Infrared spectra were measured on a JASCO FT/IR-230 in Nujol mulls. All the melting points were measured by using Yanagimoto micro melting point apparatus under inert atmosphere and are uncorrected. Solvents were purified as follows: tetrahydrofuran, diethylether and hexane by distillation from benzophenone ketyl under nitrogen; dichloromethane and chloroform by distillation from calcium hydride. Optical rotation was measured on RUDOLPH AUTOPOL IV digital polarimeter. Analytical HPLC was performed on a Shodex Model RI-72 instrument using Daicel CHIRALPACK AD-3 (4.6 × 150 mm), and Daicel CHIRALPACK AD-H (4.6 × 150 mm). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Facility of Osaka City University.

Materials: *Epi*-quinine derivatives **4a**,[1] **4b**,[1] and **4g**[2] were prepared according to the literature procedure. Quinine derivative **4c** was prepared according to the literature procedure.[3] *Epi*-quinine derivatives **4f** and angelica lactone **1** were obtained from Aldrich. Nitroalkenes **9a**-**9n** were prepared according to the literature procedure.[4] 5-Substituted 2(3*H*)-furanones **8a** and **8b** were prepared according to the literature procedure.[5]

2.6.2 Preparation of catalysts

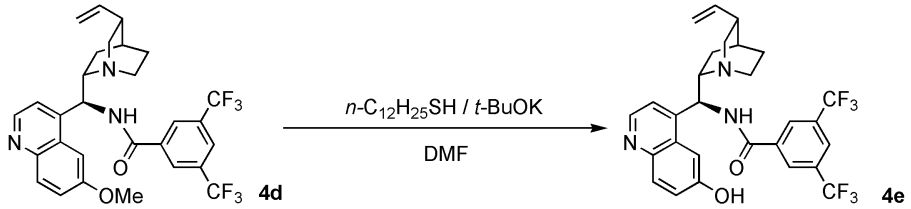
N-[(8a, 9*S*)-6'-methoxycinchonan-9-yl]-3,5-bis(trifluoromethyl)benzamide **4d**



To a solution of (8a, 9*S*)-6'-methoxycinchonan-9-amine[6] (3.218 g, 9.95 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (4.2 mL) and 3,5-bis(trifluoromethyl)benzoyl chloride (2.17 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 12 h. The reaction mixture was brought to rt., and washed with saturated $NaHCO_3$ and brine. The aqueous phase was

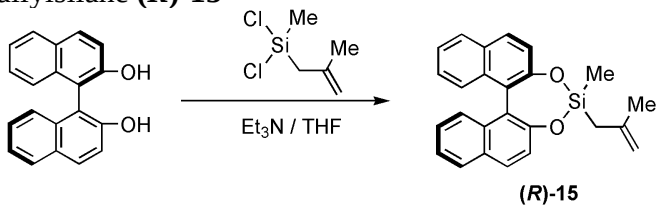
extracted with CH_2Cl_2 (2 × 10 mL). Combined CH_2Cl_2 layer was dried over $MgSO_4$, and concentrated under reduced pressure. Obtained crude material was purified by silica-gel column chromatography (CH_2Cl_2 : EtOAc = 1 : 1), to give 4.33 g (7.60 mmol, 77%) of compound **4d**. as a colorless solid.: mp 135-137 °C; $[\alpha]_D^{23}$ −99.8 (*c* 0.11, $CHCl_3$), IR (nujol), 1637, 1282, 1175, 1130, 905 cm^{-1}; ^1H NMR(300 Mz, $CDCl_3$); δ 0.85-1.02 (m, 1H), 1.45-1.50 (m, 1H), 1.52-1.70 (m, 3H), 2.28 (br s, 1H), 2.59-2.79 (m, 2H), 2.90-3.30 (m, 3H), 3.93 (s, 3H), 4.89-4.97 (m, 2H), 5.41 (br s, 1H), 5.68 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H), 7.19-7.35 (m, 2H), 7.63 (d, *J* = 2.4 Hz, 1 H), 7.81 (br s, 1H), 7.90 (s, 1H), 7.97 (d, *J* = 9.3 Hz, 1H), 8.17 (s, 2H), 8.67 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 26.3, 27.2, 38.6, 46.7, 49.4, 55.7, 60.0, 76.7, 101.3, 115.7 , 117.6, 121.2, 122.4, 124.8, 126.2, 127.8, 128.3, 129.4, 131.2, 132.0, 132.1, 132.4, 132.9, 136.4, 138.0, 140.0, 145.0, 147.7, 158.3, 164.8; HRMS (FAB+) calcd for $C_{29}H_{28}F_6N_3O_2$, $(M+H)^+$: 564.2086, found: 564.2083.

N-[(8a, 9*S*)-6'-hydroxycinchonan-9-yl]-3,5-bis(trifluoromethyl)benzamide **4e**



To a solution of *t*-BuOK (1.87 g, 16.7 mmol) in DMF (50 mL), *n*-$C_{12}H_{25}SH$ (5.3 mL, 22.2 mmol) was added and stirred at room temperature for 2 h. The solution of compound **4d** (3.13 g, 5.55 mmol) dissolved in DMF (20 mL) was added to the reaction mixture, and stirred at 110 °C for 12 h. The reaction mixture was brought to rt., and washed with aqueous HCl (1*N*) and brine. The aqueous phase was extracted with Et_2O (2 × 10 mL). Combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. Obtained crude material was purified by silica-gel column chromatography (CH_2Cl_2 : EtOAc: MeOH = 10 : 10 : 1), to give 2.01 g (3.66 mmol, 65%) of compound **4e**. as a colorless solid.: mp 154-157 °C; $[\alpha]_D^{23}$ −38.3 (*c* 0.1, $CHCl_3$), IR (nujol) 3254, 1618, 1279, 1136, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.65-0.85 (m, 1H), 0.92 (br s, 1H), 1.03-1.26 (m, 2H), 1.26-1.74 (m, 2H, the peaks overlap with the peak of water.), 2.15-2.35 (m, 1H), 2.55-2.95 (m, 2H), 2.95-3.35 (m, 2H), 3.35-3.70 (m, 1H), 4.75-5.05 (m, 2H), 5.40-5.80 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.39 (br s, 1H), 7.60-7.90 (m, 3H), 8.06 (s, 2H), 8.49 (br s, 1H), 8.59 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 25.9, 27.2, 28.9, 29.2, 31.9, 39.2, 41.1, 55.5, 105.0, 115.2, 121.0, 122.6, 124.7, 125.1, 127.7, 131.3, 131.6, 132.1, 136.0, 140.7, 143.5, 146.5, 156.6, 165.2; HRMS (FAB+) calcd for $C_{28}H_{26}F_6N_3O_2$, $[M+H]^+$: 550.1929, found: 550.1932.

Preparation of chiral allylsilane **(*R*)-15**

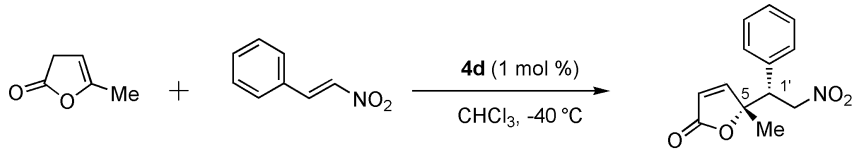


To a solution of dichloro(2-methyl-2-propenyl)silane (2.0 mL, 12.5 mmol) in THF (50 mL) was added a solution of triethylamine (4.35 mL, 31.2 mmol) and (*R*)-1,1'-bi(2-naphthol) (2.98 g, 10.4 mmol) in THF (50 mL). The solution was stirred at room temperature for 2 h, and then filtered to remove triethylammonium salt. After removal of the solvent, residue was extracted with dry pentane (30 mL) for three times. Removal of the solvent under reduced pressure gave **(*R*)-15** as a colorless solid in 85% (3.38 g), which was recrystallized from hexane: mp 198 °C; $[\alpha]^{23}_{D}$ −342.3 (*c* 1.21, $CHCl_3$), IR (nujol) 3050, 2961, 1617, 987, 857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 3H), 1.72-1.74 (m, 5H), 4.66 (m, 1H), 4.69 (m, 1H), 7.13-7.31 (m, 8H), 7.13-7.14 (m, 4H), 7.24-7.31 (m, 4H), 7.80-7.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.0, 25.2, 25.3, 111.6, 121.4, 121.6, 121.8, 121.9, 124.3, 126.0, 126.1 127.0, 127.1, 128.2, 130.1, 130.2, 130.4, 130.5, 133.6, 140.0, 150.3, 150.4 ; ^{29}Si NMR (60 Mz, $CDCl_3$) δ 7.51; HRMS (FAB+) calcd for $C_{25}H_{22}O_2Si$: M^+ 382.1389, found 382.1390.

2.6.3 Preparation of substrates

Experimental procedures for the Michael Addition of furanones to *β*-arylnitroalkenes

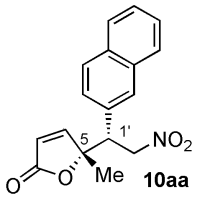
Reaction of angelica lactone to *β*-nitrostyrene: Compound **3** (Table 2-1, Entry 14)



To a solution of nitroalkene **2** (725 mg, 5 mmol) and catalyst **4d** (28 mg, 0.05 mmol) in $CHCl_3$ (5 mL) was added angelica lactone **1** (735 mg, 673 μL, 7.5 mmol) at −40 °C. The resulting solution was stirred for 48 h at −40 °C. After removal of solvent under reduced pressure, the crude material was purified by silica gel column chromatography (CH_2Cl_2 : hexane = 1 : 1), to give 1.21 g (4.9 mmol, 98%) of compound **3** as a colorless solid.: mp 93-95 °C; $[\alpha]_D^{23}$ +193.4 (*c* 1.26, $CHCl_3$), IR (KBr) 3095, 1761, 1558, 700, 645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.46 (s, 3H), 3.94 (dd, *J* = 9.6, 5.1 Hz, 1H), 4.63-4.85 (m, 2H), 5.83 (d, *J* = 5.7 Hz, 1H), 7.06-7.14 (m, 2H), 7.21-7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 50.8, 75.5, 88.4, 121.7, 128.5, 128.9, 129.3, 134.4, 158.0, 171.3; HRMS (FAB+) calcd for $C_{13}H_{14}NO_4$, $(M+H)^+$: 248.0923, found: 248.0924. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-H column; flow rate 1.0 mL/min; hexane : EtOH =

18 : 1; (5*S*, 1'*S*) t_R = 18.5 min, (5*R*, 1'*R*) t_R = 23.9 min). Absolute configuration was assigned by analogy with compound **10ac**.

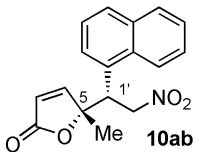
Typical procedure for the asymmetric nitro-Michael addition of 2(3H)-furanones to *β*-arylnitroalkenes: Compound **10aa** (Table 2-2, Entry 1)



10aa

To a solution of nitroalkene **9a** (50 mg, 0.25 mmol) and catalyst **4d** (7 mg, 0.0125 mmol) in $CHCl_3$ (0.25 mL) was added angelica lactone **1** (50 mg, 45 μL, 0.25 mmol) at −40 °C. The resulting solution was stirred for 55 h at −40 °C. After removal of solvent under reduced pressure, the crude material was purified by silica gel column chromatography (CH_2Cl_2 : hexane = 1 : 1), to give 71 mg (0.24 mmol, 95%) of compound **10aa** as a colorless solid.: mp 151-152 °C; $[\alpha]_D^{23}$ +212.4 (*c* 0.1, $CHCl_3$), IR (nujol) 1748, 1556, 1140, 1100, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.47 (s, 3H), 4.08 (dd, *J* = 9.3, 5.4 Hz, 1H), 4.75-4.92 (m, 2H), 5.77 (d, *J* = 5.7 Hz 1H), 7.18 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.24 (d, *J* = 5.7 Hz, 2H), 7.38-7.47 (m, 2H), 7.56 (d, *J* = 1.0 Hz, 1H), 7.66-7.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 50.9, 75.6, 88.5, 121.7, 125.5, 126.9, 126.9, 127.8, 128.0, 129.3, 131.9, 133.2, 133.3, 158.1, 171.3; HRMS (FAB+) calcd for $C_{17}H_{16}NO_4$, $(M+H)^+$: 298.1079, found: 298.1086. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (93% ee) was determined through chiral HPLC analysis (Daicel AD-H column; flow rate 1 mL/min; hexane : EtOH = 50 : 1; (5*R*, 1'*R*) t_R = 34.5 min, (5*S*, 1'*S*) t_R = 37.4 min). Absolute configuration was assigned by analogy with compound **10ac**.

Compound **10ab** (Table 2-2, Entry 2)

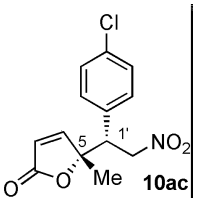


10ab

Colorless solid: mp 159-161 °C; $[\alpha]_D^{23}$ +153.5 (*c* 0.1, $CHCl_3$), IR (nujol) 1748, 1552, 1139 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.51 (s, 3H), 4.90-5.03 (m, 3H), 5.62 (d, *J* = 5.7 Hz, 1H), 7.17 (d, *J* = 5.7 Hz, 1H), 7.27 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.36 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.45 (ddd, *J* = 8.7, 6.9, 1.4 Hz, 1H), 7.52 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.81 (dd, *J* = 8.7, 1.2 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 43.1, 76.0, 88.7, 121.5, 122.2, 124.7, 125.4, 126.2, 127.3, 129.4, 129.5, 130.7, 131.9, 134.1, 157.7, 171.4; HRMS (FAB+) calcd for $C_{17}H_{16}NO_4$, $(M+H)^+$: 297.1079, found:

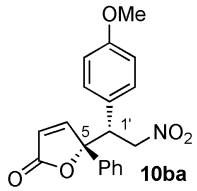
298.1080. ^{1}H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 5 : 1; (5*R*, 1'*R*) t_R = 39.1 min, (5*S*, 1'*S*) t_R = 52.5 min). Absolute configuration was assigned by analogy with compound **10ac**

Compound **10ac** (Table 2-2, Entry 3)



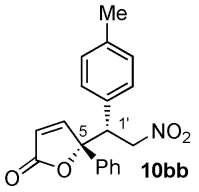
Colorless solid: mp 117-118 °C; $[\alpha]_D^{23}$ +170.2 (*c* 0.12, $CHCl_3$), IR (nujol) 3045, 1741, 1551, 1201, 1118 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.48 (s, 3H), 3.90 (dd, *J* = 10.2, 5.1 Hz, 1H), 4.69 (dd, *J* = 13.5, 10.5 Hz, 1H), 4.83 (dd, *J* = 13.5, 5.1 Hz, 1H), 5.82 (d, *J* = 5.7 Hz, 1H), 7.05 (dd, *J* = 8.4 Hz, 2H), 7.20 (m,3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 50.1, 75.4, 88.0, 121.9, 129.6, 129.7, 132.9, 135.0, 157.9, 171.1; HRMS (CI+) calcd for $C_{13}H_{13}{}^{35}ClNO_4$: $(M+H)^+$: 282.0533, found: 282.0539 ^{1}H NMR analysis of the crude products indicated that *syn/anti* ratio was > 98/2. The enantiomeric excess (92% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 7 : 1; (5*R*, 1'*R*) t_R = 38.9 min, (5*S*, 1'*S*) t_R = 47.0 min). Absolute configuration was determined by X-ray crystallographic analysis.

Compound **10ba** (Table 2-2, Entry 4)



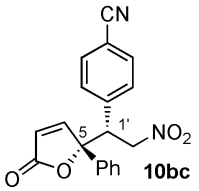
Colorless solid: mp 186-188 °C; $[\alpha]_D^{23}$ −45.7 (*c* 0.2, $CHCl_3$); IR (nujol) 1740, 1544, 1252, 1110, 815 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 3.68 (s, 3H), 4.19 (dd, *J* = 11.1, 3.9 Hz, 1H), 4.39 (dd, *J* = 13.2, 3.9 Hz, 1H), 4.84 (dd, *J* = 13.2, 11.1 Hz, 1H), 5.61 (d, *J* = 5.7 Hz, 1H), 6.75 (d, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 7.28-7.51 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5, 55.3, 75.7, 91.1, 114.5, 120.0, 124.8, 125.1, 129.2, 129.7, 129.8, 136.8, 158.2, 159.9, 171.5; HRMS (EI+) calcd for $C_{19}H_{17}NO_5$: M^+: 339.1107, found: 339.1107. ^{1}H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (96% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 4 : 1; (5*R*,1'*R*) t_R = 22.4 min, (5*S*,1'*S*) t_R = 35.6 min). Absolute configuration was assigned by analogy with compound **10ac**.

Compound **10bb** (Table 2-2, Entry 5)



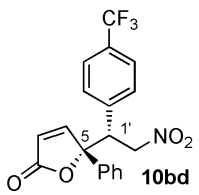
Colorless solid: mp 195-197 °C; $[\alpha]_D^{23}$ −59.5 (*c* 0.1, $CHCl_3$), IR (nujol) 3102, 1747, 1552, 1187, 823, 760, 722, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 2.21 (s, 3H), 4.19 (dd, *J* = 13.5, 3.9Hz, 1H), 4.39 (dd, *J* = 13.5, 11.1 Hz, 1H), 4.87 (dd, *J* = 13.5, 11.1 Hz, 1H), 5.59 (d, *J* = 5.7 Hz, 1H), 7.02 (dd, *J* = 8.4, 8.1 Hz, 4H), 7,26-7.50 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 51.8, 75.6, 91.0, 120.0, 124.8, 128.5, 129.2, 129.6, 129.9, 130.2, 136.8, 138.8, 158.1, 171.5; HRMS (FAB+) calcd for $C_{19}H_{18}NO_4$, $(M+H)^+$: 324.1236, found 324.1239. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 5 : 1; (5*R*, 1'*R*) t_R = 24.6 min, (5*S*, 1'*S*) t_R = 27.0 min). Absolute configuration was assigned by analogy with compound **10ac**.

Compound **10bc** (Table 2-2, Entry 6)



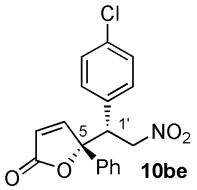
Colorless solid: mp 245-247 °C; $[\alpha]_D^{23}$ −8.6 (*c* 0.04, $CHCl_3$), IR (nujol) 1750, 1552, 815, 759, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 4.29 (dd, *J* = 11.4, 3.9 Hz, 1H), 4.45 (dd, *J* = 14.1, 3.9 Hz, 1H), 4.90 (dd, *J* = 14.1, 11.1 Hz, 1H), 5.67 (d, *J* = 5.4 Hz, 1H), 7.34 -7.95 (m, 8H), 7.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1, 75.1, 90.2, 113.3, 118.1, 120.7, 124.7, 129.6, 129.7, 130.0, 132.0, 136.0, 138.8, 157.4, 170.7; HRMS (FAB+) calcd for $C_{19}H_{15}N_2O_4$, $(M+H)^+$: 335.1032, found: 335.1035. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 4 : 1; (5*S*, 1'*S*) t_R = 43.9 min, (5*R*, 1'*R*) t_R = 87.7 min). Absolute configuration was assigned by analogy with compounds **10ac**

Compound **10bd** (Table 2-2, Entry 7)



Colorless solid: mp 187-190 °C; $[\alpha]_D^{23}$ -93.9 (*c* 0.2, $CHCl_3$), IR (nujol) 1757, 1556, 1378, 1120, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 4.30 (dd, *J* = 11.4, 3.9 Hz, 1H), 4.45 (dd, *J* = 11.4, 5.7 Hz, 1H), , 4.91 (dd, *J* = 13.8, 11.4 Hz, 1H), 5.66 (d, *J* = 8.2 Hz, 1H), 7.03-7.60 (m, 10H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 51.9, 75.3, 90.4, 120.5, 124.8, 126.2, 126.3, 129.2, 129.6, 129.9, 136.2, 137.5, 157.6, 170.9; HRMS (FAB+) calcd for $C_{19}H_{15}F_3NO_4$, $(M+H)^+$: 378.0953 found: 378.0958; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (92% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 9 : 1; (5*S*, 1'*S*) t_R = 26.8 min, (5*R*, 1'*R*) t_R = 28.5 min). Absolute configuration was assigned by analogy with compounds **10ac**

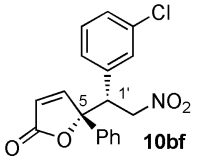
Compound **10be** (Table 2-2, Entry 8)



10be

Colorless solid: mp 204-205 °C; $[\alpha]_D^{23}$ −79.6 (*c* 0.1, $CHCl_3$), IR (nujol) 1751, 1119, 817, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 4.22 (dd, *J* = 11.1, 3.9 Hz, 1H), 4.41 (dd, *J* = 13.5, 3.9 Hz, 1H), 4.84 (dd, *J* = 8.7 Hz, 1H), 5.65 (d, *J* = 5.4 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.30-7.46 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.6, 75.4, 90.6, 120.4, 124.8, 129.4, 129.5, 129.8, 130.0, 132.0, 135.0, 136.4, 157.8, 171.1; HRMS (FAB+) calcd for $C_{18}H_{15}{}^{35}ClNO_4$, $(M+1)^+$: 344.0690, found: 344.0696: ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (96% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1 mL/min; hexane : EtOH = 9 : 1; (5*S*, 1'*S*) t_R = 37.6 min, (5*R*, 1'*R*) t_R = 46.3 min). Absolute configuration was assigned by analogy with compound **10ac**.

Compound **10bf**[11] (Table 2-2, Entry 9)

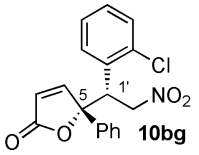


10bf

Colorless solid: mp 207-208 °C; $[\alpha]_D^{25}$ −81.5 (*c* 0.2, $CHCl_3$), IR (nujol) 1768, 1555, 1192, 1098, 798, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 4.20 (dd, *J* = 11.4, 3.9 Hz, 1H), 4.41 (dd, *J* = 11.4, 3.6 Hz, 1H), 4.87 (dd, *J* = 13.8, 11.1 Hz, 1H), 5.67 (d, *J* = 5.7 Hz, 1H), 7.10 -7.25 (m, 5H), 7,30-7.50 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9, 75.3, 90.5, 120.4, 124.8, 126.3, 129.3, 129.4, 129.5, 129.9, 130.6, 135.1, 135.5, 136.4, 157.7, 171.1; HRMS (FAB+)

calcd for $C_{18}H_{15}{}^{35}ClNO_4$, $(M+H)^+$: 344.0690, found: 344.0691. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 9 : 1; (5*S*, 1'*S*) t_R = 19.2 min, (5*R*, 1'*R*) t_R = 31.0 min). Absolute configuration was assigned by analogy with compound **10ac**.

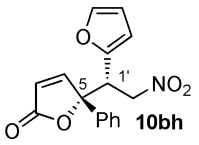
Compound **10bg** (Table 2-2, Entry 10)



10bg

Colorless solid: mp 160-161 °C; $[\alpha]_D{}^{23}$ −137.7 (*c* 0.13, $CHCl_3$), IR (nujol) 1773, 1552, 1100, 751, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 4.45 (dd, *J* = 13.8, 3.6 Hz, 1H), 4.90-4.98 (m, 1H), 5.07 (dd, *J* = 13.8, 3.6 Hz, 1H), 5.81 (d, *J* = 5.7 Hz, 1H), 7.14-7.26 (m, 2H), 7.28-7.38 (m, 3H), 7.40-7.75 (m, 2H), 7.75-7.50 (m, 2H), 7.57 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.1, 74.8, 91.0, 120.3, 124.7, 127.9, 128.0, 129.5, 129.9, 130.1, 130.3, 131.3, 135.1, 136.5, 157.3, 171.3,; HRMS (FAB+) calcd for $C_{18}H_{15}ClNO_4$, $(M+H)^+$: 344.0690, found: 344.0687; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (96% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 9 : 1; (5*S*, 1'*S*) t_R = 23.9 min, (5*R*, 1'*R*) t_R = 28.6 min). Absolute configuration was assigned by analogy with compound **10ac**.

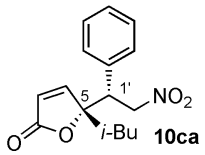
Compound **10bh** (Table 2, Entry 11)



10bh

Colorless solid: mp 58-60 °C; $[\alpha]_D{}^{23}$ −54.3 (*c* 0.2, $CHCl_3$), IR (nujol) 3069, 2961, 1324, 964, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 4.41 (m, 2H), 4.78 (m, 1H), 5.77 (d, *J* = 5.7 Hz, 1H), 6.16-6.23 (m, 2H), 7.26 (m, 1H), 7.28- 7.43 (m, 5H), 7.54 (d, *J* = 5.7, 1H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 46.2, 74.0, 90.4, 109.9, 111.0, 120.2, 124.9, 129.4, 129.6, 136.1, 143.1, 147.5, 157.2, 171.1; HRMS (FAB+) calcd for $C_{16}H_{14}NO_5$, $(M+H)^+$: 300.0872, found: 300.0875; ^1H NMR analysis of the crude products indicated *syn*:*anti* ratio was > 98:2. The enantiomeric excess (95% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 0.5 mL/min; hexane : EtOH = 4.5 : 1; (5*R*, 1'*R*) t_R = 27.0 min, (5*S*, 1'*S*) t_R = 44.0 min). Absolute configuration was assigned by analogy with compound **10ac**.

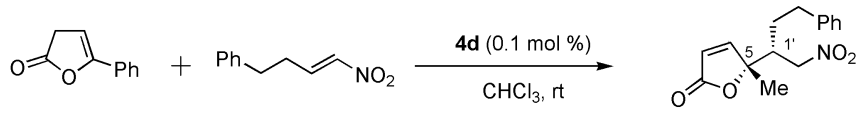
Compound **10ca** (Table 2-2, Entry 12)



10ca

Colorless solid: mp 104-105 °C; $[\alpha]_D^{23}$ +129.1 (*c* 0.1, $CHCl_3$), IR (nujol) 1757, 1545, 1194, 1116, 931, 820, 723, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.82 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 1.48 (m, 1H, the peak overlaps with water peak), 1.62 (dd, *J* = 14.7, 5.7 Hz, 1H), 1.81 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.95 (dd, *J* = 9.5, 5.1 Hz, 1H), 4.65-4.80 (m, 2H), 5.87 (d, *J* = 5.7 Hz, 1H), 7.04 -7.12 (m, 2H), 7.14 -7.21 (m, 2H), 7.21 -7.32 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 24.0, 24.6, 44.5, 50.7, 75.7, 91.2, 122.5, 128.6, 128.9, 129.3, 134.4, 157.2, 171.6; HRMS (FAB+) calcd for $C_{16}H_{20}NO_4$, $(M+H)^+$: 290.3343, found: 290.3340. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (91% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 0.5 mL/min; hexane : EtOH = 9 : 1; (5*R*, 1'*R*) t_R = 12.8 min, (5*S*, 1'*S*) t_R = 14.9 min). Absolute configuration was assigned by analogy with compound **10ac**.

Experimental procedures for the Michael addition of furanones to *β*-alkylnitroalkenes: compound **11bc** (Scheme 2-3)

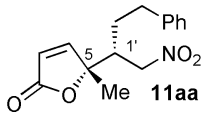


8a 33.5 mmol (1.5 eq.) **9k** 25 mmol (1.0 eq.) **11bc**

To a solution of nitroalkene **9k** (4.43 g, 25 mmol) and catalyst **4d** (14 mg, 0.025 mmol(0.1 mol % based on **9k**)) in $CHCl_3$ (30 mL) was added furanone **8a** (5.69 g, 35.5 mmol) at room temperature. The resulting solution was stirred for 45 h. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (CH_2Cl_2), to give 7.84 g (23.3 mmol, 93%) of compound **11bc** as a colorless solid.: mp 152-154 °C; $[\alpha]_D^{26}$ −171.5 (*c* 0.1, $CHCl_3$), IR (nujol) 1761, 1552, 1192, 699, 644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.63 (m, 2H), 2.48 (m, 1H), 2.58 (m, 1H), 3.10 (m, 1H), 4.22-4.38 (m, 2H), 6.00 (d, *J* = 5.7 Hz, 1H), 6.97-7.05 (m, 2H), 7.01-7.35 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8, 33.9, 44.1, 76.2, 92.0, 120.7, 125.0, 126.7, 128.5, 128.8, 129.2, 129.5, 136.9, 140.3, 157.8, 171.4; HRMS (FAB+) calcd for $C_{20}H_{20}NO_4$, $(M+H)^+$: 338.1392, found: 338.1389. ^1H NMR analysis of the crude products indicated that *syn/anti* ratio was > 98/2. The enantiomeric excess (93% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 36 : 1; (5*S*, 1'*S*) t_R = 73.3 min,

(5*R*, 1'*R*) t_R = 77.8 min). Absolute configuration was assigned by analogy with compound **10ac**.

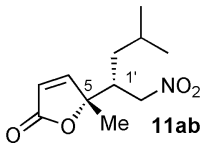
Compound **11aa** (Table 2-3, Entry 1)



11aa

Colorless solid: mp 90-91 °C; $[\alpha]_D^{26}$ +44.9 (*c* 0.15, $CHCl_3$), IR (nujol) 1755, 1554, 1208, 1114, 724, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.41 (s, 3H), 1.45-1.65 (m, 1H), 1.65-1.82 (m, 1H), 2.45-2.60 (m, 1H), 2.60-2.75 (m, 2H), 4.28(dd, *J* = 13.5, 5.7 Hz, 1H), 4.47 (dd, *J* = 13.5, 6.3 Hz, 1H), 6.04 (d, *J* = 6.0 Hz, 1H), 7.02-7.10 (m, 2H), 7.10-7.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 30.4, 33.6, 43.7, 75.4, 89.2, 122.1, 126.7, 128.5, 128.9, 140.2, 158.0, 171.3; HRMS (CI+) calcd for $C_{11}H_{18}NO_4$, $(M+H)^+$, 228.1236, found: 228.1229; ^1H NMR analysis of the crude products indicated that *syn/anti* ratio was > 98/2. The enantiomeric excess (88% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 1 : 36; (5*R*, 1'*R*) t_R = 23.7 min, (5*S*, 1'*S*) t_R = 39.6 min). Absolute configuration was assigned by analogy with compound **10ac**.

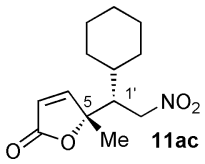
Compound **11ab** (Table 2-3, Entry 2)



11ab

Colorless solid: mp 56-57 °C; $[\alpha]_D^{26}$ +27.0 (*c* 0.1, $CHCl_3$), IR (nujol) 1748, 1552, 1139, 1105, 949, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.83 (d, *J* = 6.6 Hz, 6H), 1.10-1.20 (m, 2H), 1.46 (s, 3H), 1.50 (sep, *J* = 6.6 Hz, 1H), 2.74 (m, 1H), 4.18 (dd, *J* = 13.8, 4.8 Hz, 1H), 4.40 (dd, *J* = 13.8, 6.9 Hz, 1H), 6.07 (d, *J* = 5.7 Hz, 1H), 7,30 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 22.9 23.4, 25.0, 37.4, 42.4, 75.7, 89.5, 122.0, 158.1, 171.5; HRMS (FAB+) calcd for $C_{11}H_{17}NO_4$, M^+: 227.1158, found: ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (90% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 36 : 1; (5*S*, 1'*S*) t_R = 55.3 min, (5*R*, 1'*R*) t_R = 70.3 min). Absolute configuration was assigned by analogy with compound **10ac**.

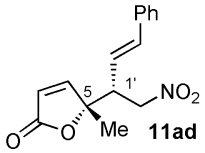
Compound **11ac** (Table 2-3, Entry 3)



11ac

Colorless solid; mp 106-107 °C; $[\alpha]_D^{26}$ +25.0 (*c* 0.01, $CHCl_3$), IR (nujol) 1754, 1552, 1211, 1098, 946, 829 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.70-1.30 (m, 5H), 1.30-1.80 (m, 9H), 2.70 (m, 1H), 4.37 (m, 2H), 6.06 (d, *J* = 5.0 Hz, 1H), 7.40 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 25.9, 26.9, 26.7, 28.5, 32.7, 38.6, 49.2, 73.0, 90.3, 121.6, 158.8, 171.5; HRMS (FAB+) calcd for $C_{13}H_{20}NO_4$, $(M+H)^+$: 254.1392, found: 254.1389. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (91% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 9 : 1; (5*S*, 1'*S*) t_R = 15.6 min, (5*R*, 1'*R*) t_R = 23.5 min). Absolute configuration was assigned by analogy with compound **10ac**.

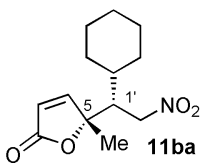
Compound **11ad** (Table 2-3, Entry 4)



11ad

Colorless oil: $[\alpha]_D^{23}$ +196.2 (*c* 0.13, $CHCl_3$), IR (thin film) 3082, 3029, 1755, 1553, 1212, 1116, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.50 (s, 3H), 3.48 (ddd, *J* = 10.2, 9.6, 4.5 Hz, 1H), 4.30 (dd, *J* = 12.3, 10.2 Hz, 1H), 4.58 (dd, *J* = 12.3, 5.7 Hz, 1H), 5.79 (dd, *J* = 15.6, 9.6 Hz, 1H), 6.05 (d, *J* = 5.7 Hz, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 7.13-7.32 (m, 5H), 7.36 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 48.9, 75.7, 88.3, 121.3, 122.0, 126.8, 128.8, 128.9, 135.5, 137.2, 158.0, 171.3; HRMS (FAB+) calcd for $C_{15}H_{16}NO_4$, $(M+H)^+$: 274.1079, found: 274.1074. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 18 : 1; (5*R*, 1'*R*) t_R = 53.0 min, (5*S*, 1'*S*) t_R = 86.1 min). Absolute configuration was assigned by analogy with compound **10ac**.

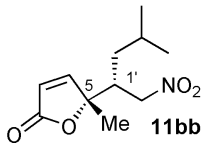
Compound **11ba** (Table 2-3, Entry 5)



11ba

Colorless solid: mp 180-182 °C; $[\alpha]_D^{23}$ −153.9 (*c* 0.1, $CHCl_3$), IR (nujol) 1755, 1553, 827, 745, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.80-1.25 (m, 5H), 1.40-1.75 (m, 6H), 3.09 (m, 1H), 4.25 (dd, *J* = 14.1, 4.5 Hz, 1H), 4.45 (dd, *J* = 14.1, 7.2 Hz, 1H), 6.03 (d, *J* = 5.7 Hz, 1H), 7.25-7.35 (m, 5H), 7.63 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 26.5, 26.9, 28.8, 33.0, 38.2, 50.1, 73.0, 93.2, 120.2, 125.1, 129.1, 129.5, 137.7, 158.5, 171.7; HRMS (FAB+) calcd for $C_{18}H_{22}NO_4$, $(M+H)^+$: 316.1549, found 316.1556; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 0.5 mL/min; hexane : EtOH = 36 : 1; (5*S*, 1'*S*) t_R = 33.2 min, (5*R*, 1'*R*) t_R = 51.5 min). Absolute configuration was assigned by analogy with compound **10ac**.

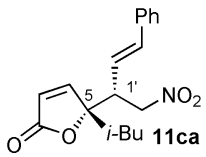
Compound **11bb** (Table 2-3, Entry 6)



11bb

Colorless solid: mp 96-98 °C; $[\alpha]_D^{23}$ −193.7 (*c* 0.10, $CHCl_3$), IR (nujol) 1754, 1555, 1199, 954, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.80 (d, *J* = 6.3, 3H), 0.84 (d, *J* = 6.3, 3H), 1.14-1.25 (m, 2H), 1.42 (sep, *J* = 6.3 Hz, 1H, the peak overlaps with water peak), 3.13 (m, 1H), 4.23 (m, 2H), 6.05 (d, *J* = 5.7 Hz, 1H), 7.25-7.00 (m, 5H), 7.52 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 23.0, 26.5, 37.0, 43.2, 77.4, 92.3, 120.6, 125.1, 129.2, 129.5, 137.0, 157.9, 171.6; HRMS (FAB+) calcd for $C_{16}H_{20}NO_4$, $(M+H)^+$: 290.1392, found. 290.1396; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : *i*-PrOH = 50 : 1; (1*R*, 1'*R*) t_R = 49.7 min, (1*S*, 1'*S*) t_R = 63.0 min). Absolute configuration was assigned by analogy with compound **10ac**.

Compound **11ca** (Table 2-3, Entry 8)

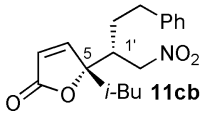


11ca

Colorless solid: mp 110-112 °C; $[\alpha]_D^{23}$ +195.9 (*c* 0.10, $CHCl_3$), IR (nujol) 1762, 1543, 1118, 929, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.83 (d, *J* = 6.6 Hz,3H), 0.85 (d, *J* = 6.6 Hz, 3H), 1.53 (sept, *J* = 6.6 Hz,1H), 1.67 (dd, *J* = 14.7, 6.0 Hz, 1H), 1.82 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.53 (ddd, *J* = 10.5, 9.6, 4.2 Hz, 1H), 4.24 (dd, *J* = 12.3, 10.5 Hz, 1H), 4.53 (dd, *J* = 12.3, 4.2 Hz, 1H), 5.78 (dd, *J* = 15.9, 9.6 Hz, 1H), 6.10 (d, *J* = 5.7 Hz, 1H), 6.51 (d, *J* = 15.9 Hz,

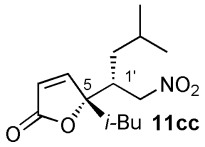
1H), 7.15-7.31 (m, 5H), 7.34 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 24.1, 24.4, 44.5, 48.6, 75.6, 91.0, 121.5, 122.8, 126.8, 128.7, 128.8, 135.5, 137.1, 157.2, 171.5; HRMS (EI+) calcd for $C_{18}H_{21}NO_4$, M^+: 315.1471, found: 315.1473. ^{1}H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 36 : 1; (1*R*, 1'*R*) t_R = 34.3 min, (1*S*, 1'*S*) t_R = 52.8 min). Absolute configuration was assigned by analogy with compound **10ac**.

Compound **11cb** (Table 2-3, Entry 9)



Colorless oil: $[\alpha]_D^{23}$ +27.5 (*c* 0.15, $CHCl_3$), IR (nujol) 1763, 1556, 1200, 1126, 925, 828, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.78 (dd, *J* = 6.3, 1.5 Hz, 6H), 1.36 (sep, *J* = 6.3 Hz, 1H), 1.48-1.55 (m, 2H), 1.74-1.83 (m, 2H), 2.43-2.59 (m, 1H), 2.59-2.83 (m, 2H), 4.22 (dd, *J* = 13.8, 5.4 Hz, 1H), 4.36 (dd, *J* = 13.8, 6.0 Hz, 1H), 6.09 (d, *J* = 5.7 Hz, 1H), 7.01-7.30 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 24.1, 24.2, 30.1, 33.7, 43.3, 43.7, 75.1, 92.0, 123.0, 126.7, 128.5, 128.8, 140.2, 156.8, 171.5; HRMS (EI+) calcd for $C_{18}H_{23}NO_4$, M^+: 317.1627, found: 317.1629. ^{1}H NMR analysis of the crude products indicated that *syn*:*anti* ratio is > 98:2. The enantiomeric excess (93% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 50 : 1; (5*R*, 1'*R*) t_R = 49.7 min, (5*S*, 1'*S*) t_R = 63.1 min). Absolute configuration was assigned by analogy with compounds **10ac**.

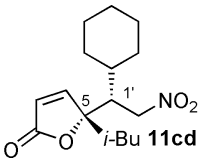
Compound **11cc** (Table 2-3, Entry 10)



Colorless solid: mp 82-84 °C; $[\alpha]_D^{23}$ +0.82 (*c* 0.21, $CHCl_3$), IR (nujol) 1758, 1560, 1196, 1116, 925 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.72-0.99 (m, 12H), 1.00-1.24 (m, 2H), 1.48 (m, 2H, the peaks overlap with peak of water), 1.60 (dd, *J* = 14.4, 7.5 Hz, 1H), 1.79 (dd, *J* = 14.4, 6.1 Hz, 1H), 2.79 (m, 1H), 4.11 (dd, *J* = 13.8, 5.0 Hz, 1H), 4.13 (dd, *J* = 13.8, 6.0 Hz, 1H), 6.12 (d, *J* = 5.7 Hz, 1H), 7.23 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 21.6, 23.5, 23.7, 24.2, 24.4, 26.1, 29.9, 37.9, 42.3, 43.8, 75.6, 92.2, 123.0, 156.8, 171.6; HRMS (CI+) calcd for $C_{14}H_{24}NO_4$, $(M+H)^+$: 270.1705, found 270.1700. ^{1}H NMR analysis of the

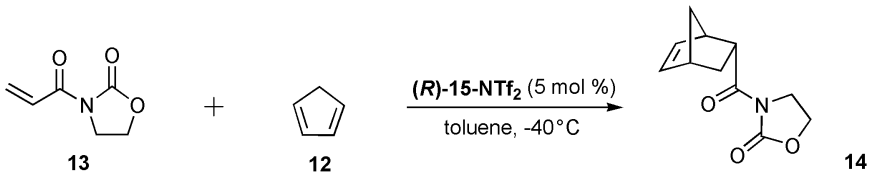
crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (92% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 0.5 mL/min; hexane : EtOH = 50 : 1; (5*R*, 1'*R*) t_R = 37.9 min, (5*S*, 1'*S*) t_R = 39.9 min). Absolute configuration was assigned by analogy with compound **10ac**.

Compound **11cd** (Table 2-3, Entry 11)



Colorless oil: $[\alpha]_D^{23}$ +9.3 (*c* 0.2, $CHCl_3$), IR (nujol) 3091, 1763, 1557,1205, 1128, 926, 829 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.83 (dd, *J* = 6.3, 4.5 Hz, 6H), 0.90-1.45 (m, 4H), 1.45-1.90 (m, 10H), 2.77, (t, *J* = 1.2 Hz, 1H), 4.27 (d, *J* = 5.7 Hz, 2H), 6.15 (d, *J* = 5.7 Hz, 1H), 7.32 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 24.2, 24.4, 25.9, 26.4, 26.8, 28.6, 33.0, 38.5, 44.9, 49.2, 72.8, 93.0, 122.5, 151.4, 171.5; HRMS (FAB+) calcd for $C_{16}H_{25}NO_4$, M^+: 295.1784, found: 295.1781. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was > 98:2. The enantiomeric excess (91% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 36 : 1; (5*S*, 1'*S*) t_R = 25.1 min, (5*R*, 1'*R*) t_R = 29.6 min). Absolute configuration was assigned by analogy with compound **10ac**.

3-[(1*R*, 2*R*, 4*R*)-Bicyclo[2.2.1]hept-5-enecarbonyl]oxazolidin-2-one **14**



To a solution of allylsilane (*R*)-**15** (122 mg, 0.20 mmol) in toluene (10 mL) was added a solution of trifluoromethanesulfonimide ($HNTf_2$) (0.5 M in toluene, 0.4 mL, 0.20 mmol) at room temperature. After stirring for 2 h at room temperature, the solution was cooled to −78 °C. A solution of 3-(2-propenoyl)oxazolidin-2-one **13** (1.13 g, 8 mmol) in toluene (20 mL) was added dropwise at −78 °C, followed by addition of cyclopentadiene **12** (2.0 mL, 1.59 g, 24 mmol). Stirring was continued for 6 h at −78 °C and at the end of reaction, triethylamine (1 mL) was added. Evaporation under reduced pressure afforded a brown oil which was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 1) to yield 1.41 g of **14** as a colorless solid (7.0 mmol, 85%). ^1H NMR analysis of the crude products indicated *endo*:*exo* ratio was > 97:3. The enantiomeric excess (85% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 0.5 mL/min; hexane : *i*-PrOH

= 50 : 1; *endo* 2S t_R = 30.1 min, *endo* 2*R*t_R = 33.5 min). Absolute configuration was determined in comparison with reported optical rotation: $[\alpha]^{25}_D$ +131.4 (*c* 1.0, $CHCl_3$)

2.6.4 Computational data

(a) Optimized Structure of Benzamide-*β*-Isobutylnitroalkene **9l** Adduct (**A**) (B3LYP/6-311++G(d,p)) (Fig. 2-1)

DFT GRID SWITCH THRESHOLD = 3.00E-04

TOTAL ENERGY = -1554.4384544292

COORDINATES OF ALL ATOMS ARE (ANGS)

ATOM	CHARGE	X	Y	Z
H	1.0	0.3841408597	4.9419488707	-1.7824866382
H	1.0	0.4679513950	5.1409527865	-0.0289178118
H	1.0	-3.8812958474	-0.1748719976	-0.4409220945
C	6.0	-4.7546456855	0.3955179775	1.4589409782
C	6.0	0.0325277179	4.5421085693	-0.8299209645
N	7.0	0.3950330172	3.1392548757	-0.6887716146
H	1.0	-1.0521516758	4.6167386100	-0.7897599262
C	6.0	1.6879366690	2.7637901930	-0.5607621744
O	8.0	2.6184568442	3.5657720802	-0.5696133922
C	6.0	1.9608559728	1.2838409032	-0.4001379454
H	1.0	-0.3570180994	2.4781099612	-0.5440997263
C	6.0	1.0696878303	0.2759329306	-0.7826060231
C	6.0	1.4190051002	-1.0591807591	-0.6163059016
H	1.0	0.1109815963	0.5174575609	-1.2164792696
C	6.0	0.4803633307	-2.1637586027	-1.0248038240
C	6.0	2.6530800342	-1.4124939818	-0.0707320620
H	1.0	2.9124782734	-2.4533409417	0.0633127296
C	6.0	3.5404072143	-0.4093726686	0.2961366169
C	6.0	4.8808772776	-0.7511209117	0.8929676976
C	6.0	3.2011136415	0.9313446500	0.1265675881
H	1.0	3.8872335374	1.7263345798	0.3864182194
C	6.0	-3.8534493895	0.3809182988	0.4807520826
N	7.0	-2.6898568253	1.2432350906	0.5586867472
O	8.0	-2.4210083138	1.8355458307	1.6005737526
O	8.0	-2.0303640080	1.3430705486	-0.4906400393
C	6.0	-6.0358551090	-0.3730059368	1.4961701009

H	1.0	-4.5334795802	1.0309415262	2.3105233913
F	9.0	1.0042323953	-2.9398054922	-2.0073398464
F	9.0	-0.7065216092	-1.6991381187	-1.4803719363
F	9.0	0.2050872397	-2.9965269732	0.0141381598
F	9.0	5.9013059958	-0.2209418826	0.1758253204
F	9.0	5.0911597165	-2.0867253231	0.9578815292
F	9.0	5.0023229925	-0.2678225189	2.1552355801
H	1.0	-6.8152171700	0.3061844755	1.8604194444
H	1.0	-5.9327607411	-1.1205120510	2.2952459228
C	6.0	-6.5053856948	-1.0607745753	0.2019716074
C	6.0	-7.7334466535	-1.9328064840	0.4971980699
H	1.0	-5.6960105794	-1.7187635577	-0.1356052348
C	6.0	-6.8287149024	-0.0580581173	-0.9184496989
H	1.0	-8.0374112883	-2.4960114729	-0.3874080436
H	1.0	-8.5795434182	-1.3098296819	0.8013864836
H	1.0	-7.5362799932	-2.6452337655	1.3007203820
H	1.0	-7.0668039081	-0.5823739479	-1.8473994443
H	1.0	-6.0042781093	0.6212774861	-1.1311635529
H	1.0	-7.6961137036	0.5516511568	-0.6485920073

(b) Thiourea-*β*- Isobutylnitroalkene **9l** Adduct (**B**) (B3LYP/6-311++G(d,p)) (Fig. 2-1)

DFT GRID SWITCH THRESHOLD = 3.00E-04

TOTAL ENERGY = -1932.7152206768

COORDINATES OF ALL ATOMS ARE (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	2.2055069533	-1.8185008860	-0.2184433790
C	6.0	-5.6740115580	-0.0586793038	-0.2427488346
C	6.0	3.5264842024	-1.4810853179	0.0587987156
H	1.0	-4.1592491279	-1.5950272833	-0.1196172382
C	6.0	3.8278623325	-0.1433818815	0.2990671893
C	6.0	-6.8904962955	-0.9022912971	-0.4453103360
C	6.0	2.8503176321	0.8474744772	0.2668268521
H	1.0	-5.7846779197	1.0202064929	-0.2360166667
C	6.0	1.5260017994	0.5033689456	-0.0309075350
C	6.0	1.2174375296	-0.8439881435	-0.2714558549
N	7.0	0.4527039626	1.4050930513	-0.0440226666

C	6.0	0.4067595974	2.7702162925	-0.2675158482
N	7.0	-0.8441040184	3.2672404734	-0.1155512001
C	6.0	1.8205710921	-3.2624311306	-0.3961305665
C	6.0	5.2597973543	0.2487618728	0.5594918336
F	9.0	1.4273514273	-3.8257488415	0.7788707363
F	9.0	2.8432784675	-4.0155420924	-0.8619725514
F	9.0	0.7843247860	-3.4170293213	-1.2578782557
F	9.0	5.9574811908	-0.7486361076	1.1585686735
F	9.0	5.3589461308	1.3376923765	1.3547691717
F	9.0	5.9184401445	0.5420624555	-0.5915766649
S	16.0	1.7071901042	3.7349764677	-0.7062010011
H	1.0	4.2951467328	-2.2393867718	0.0914868827
H	1.0	3.1031688279	1.8757105298	0.4630597053
H	1.0	0.1988447466	-1.1258448137	-0.4990253877
H	1.0	-0.4470929407	0.9407631816	0.0087643910
H	1.0	-1.6085208879	2.6353218002	0.0845387787
C	6.0	-1.2097132385	4.6461179600	-0.3997558507
H	1.0	-0.5835078933	5.3361028550	0.1648630487
H	1.0	-1.0978800657	4.8784022570	-1.4609998008
H	1.0	-2.2501476842	4.7778443942	-0.1055189825
N	7.0	-3.2959145052	0.3181649273	0.0020196110
C	6.0	-4.4435739988	-0.5544465613	-0.1155666580
O	8.0	-2.1861591794	-0.2337902915	-0.0026073460
O	8.0	-3.4518257125	1.5392325558	0.0974631049
C	6.0	-8.1588633077	-0.4248961760	0.3014717553
C	6.0	-9.3425591019	-1.3094606143	-0.1142026998
H	1.0	-8.3644875610	0.6008924878	-0.0235072530
C	6.0	-7.9725534199	-0.4228409052	1.8223069688
H	1.0	-6.6739521697	-1.9424971330	-0.1881746665
H	1.0	-7.1156987677	-0.8865952541	-1.5187610366
H	1.0	-10.2733278191	-0.9624872148	0.3375437555
H	1.0	-9.1814870831	-2.3421395943	0.2065656059
H	1.0	-9.4729001118	-1.3115477146	-1.1983110866
H	1.0	-8.8684360981	-0.0474801461	2.3225404773
H	1.0	-7.1361049756	0.2057573730	2.1356227352
H	1.0	-7.7887462672	-1.4356582028	2.1902840241

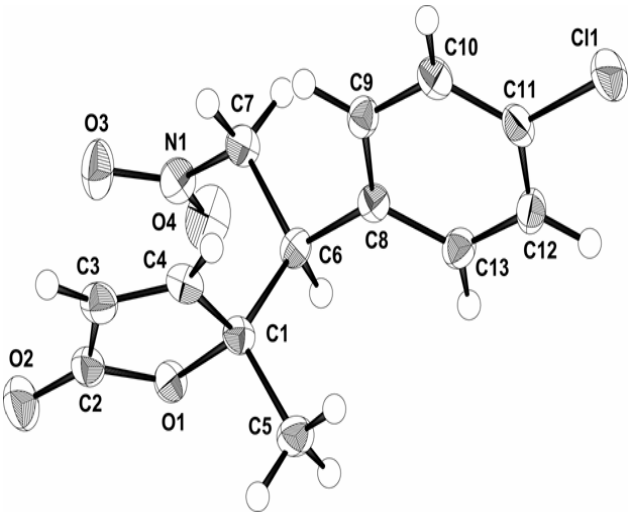
(c) Simplified Pre-Transition-State Assembly Model Optimized at B3LYP/6-31(G) (Fig. 2-2)
DFT GRID SWITCH THRESHOLD = 3.00E-04
TOTAL POTENTIAL ENERGY = -3348.0633944829
COORDINATES OF ALL ATOMS ARE (ANGS)

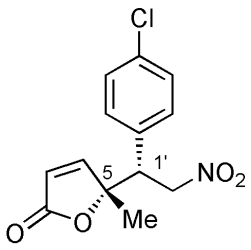
ATOM	CHARGE	X	Y	Z
C	6.0	0.2034827419	2.9123273167	-1.3263855513
C	6.0	-0.5921615919	4.2538899298	-1.3105240820
N	7.0	0.0533307552	2.1976331507	-0.0310130527
C	6.0	-1.2753615719	4.4034762889	0.0679072096
C	6.0	-1.3663150548	1.8775487823	0.2854857532
C	6.0	-0.1960325455	4.3968153278	1.1709837646
C	6.0	-2.2108703534	3.1951771874	0.2907776048
C	6.0	-1.9842516667	0.8082328575	-0.6530167542
C	6.0	-3.3911304908	0.3827600581	-0.2148715266
C	6.0	0.5892236654	3.0571149583	1.0595507666
C	6.0	-3.8318032554	0.3611045388	1.1123896593
C	6.0	-5.1247337752	-0.0804784986	1.3987838278
N	7.0	-1.1472953005	-0.3737581874	-0.8021685431
C	6.0	0.4405190801	-4.3259317450	-1.2702888231
H	1.0	-1.0436589343	-2.9856085330	-0.4852931978
H	1.0	-0.1127041372	2.2403518472	-2.1281646895
H	1.0	1.2773743644	3.0806425294	-1.4527635322
H	1.0	0.0756182020	5.1007004528	-1.4979936035
H	1.0	-1.3439438750	4.2676286564	-2.1063359975
H	1.0	0.1401929124	-5.1463917415	-0.6261442403
H	1.0	-1.8537653324	5.3354742083	0.1065001239
H	1.0	-1.3217964204	1.4485012506	1.2930095626
H	1.0	-0.6643929645	4.5007758284	2.1556836515
H	1.0	-2.7603977192	3.2990248230	1.2335894752
H	1.0	-2.9683457406	3.1657626379	-0.4990753636
H	1.0	-2.0608253990	1.2243079844	-1.6608524001
C	6.0	1.4771683420	-4.4969616622	-2.1941763430
H	1.0	0.5409219833	2.4737711607	1.9857590699
H	1.0	1.6478435198	3.2162312252	0.8451420685
H	1.0	1.9939987173	-5.4508528125	-2.2586744078
C	6.0	-0.5553714303	-0.7042887574	-1.9905711075

C	6.0	1.8306045461	-3.4464899496	-3.0442997774
H	1.0	3.4904827804	-2.9043155580	3.5243618630
H	1.0	3.8747673310	-2.1972620772	1.9268624289
H	1.0	3.7090245470	-1.1476789759	3.3158263932
C	6.0	-0.2223512567	-3.0991083738	-1.1878422421
C	6.0	1.1594845016	-2.2262650189	-2.9679206302
H	1.0	0.4809214052	5.2493738685	1.0561849196
O	8.0	-0.6003479433	0.0301088455	-2.9825333170
H	1.0	1.0196967459	1.0102151928	0.0069562842
C	6.0	0.1392421139	-2.0380141120	-2.0238886313
H	1.0	-0.9425739687	-0.9218950156	0.0256047819
C	6.0	3.3063585742	-2.0590363673	2.8555487405
C	6.0	1.8544077004	-1.8820255065	2.5481580204
C	6.0	0.9005308452	-2.6609959692	3.0679212056
N	7.0	-0.4975355419	-2.4732357694	2.7363174777
O	8.0	-1.2926338158	-3.2916913326	3.1949239525
O	8.0	-0.8287600725	-1.5131813950	2.0224111206
H	1.0	1.5772111878	-1.0889338657	1.8550134650
H	1.0	1.0553363854	-3.4959631972	3.7446993601
C	6.0	5.5956509807	2.8866206371	0.4932776788
C	6.0	4.8155028710	1.6812108265	0.1003544030
C	6.0	5.1486554492	0.4993535960	-0.4764339449
C	6.0	3.9507436585	-0.2792887714	-0.5999134331
C	6.0	2.9553132844	0.4796035636	-0.0686490573
H	1.0	6.1444460385	0.2080090304	-0.7907683858
H	1.0	3.7904139267	-1.2577565722	-1.0309416764
O	8.0	3.4507562603	1.6912788097	0.3638504639
O	8.0	1.6780666853	0.1994452979	0.1603394376
H	1.0	5.2300417087	3.7959795181	-0.0055448857
H	1.0	6.6444865929	2.7435690983	0.2058072373
H	1.0	5.5643358816	3.0701233068	1.5774738143
H	1.0	2.6239959662	-3.5812664249	-3.7772270258
H	1.0	1.4048422676	-1.4038541859	-3.6289243303
H	1.0	-3.1874230848	0.6802175287	1.9258790757
H	1.0	-5.4794141196	-0.0850490414	2.4305757079
N	7.0	-5.9943503950	-0.5095414671	0.4755921944
C	6.0	-5.5624977021	-0.5035874545	-0.7935784565

C	6.0	-4.2975212548	-0.0712357421	-1.1827571905
H	1.0	-6.2709378027	-0.8588080071	-1.5427767784
H	1.0	-4.0123839915	-0.0878944309	-2.2334535119

2.6.5 X-ray structure of (5*R*, 1'*R*)-10ac





(5*R*, 1'*R*)-10ac

2.6.6 References

(1) Huang, Y.; Yang, L.; Shao. P.; Zhao, Y. *Chem., Sci*. **2013**, *14*, 3275.

(2) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089.

(3) (a) Brunner, H.; Buegler, J. *Bull. Soc. Chim. Bel*. **1997**, *106*, 77.; (b) Taggi, A. E.; Hafez, A. M.; Wack. H.; Young, B.; Durry, W. J.; Lektka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831.

(4) (a) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829.; (b) Xia, X. -Z.; Shu, K. -G.; Ji, Y. -F.; Yang, A.; Shaukat, X. -Y.; Liang. Y. -M. *J. Org. Chem*. **2010**, *75*, 2893.; (c) Bassas, O.; Huuskonen, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem*. **2009**, 1340.

(5) Marshall, J. A.; Wolf, M. A.; Wallence, E. M. *J. Org. Chem*., **1997**, *62*, 367.

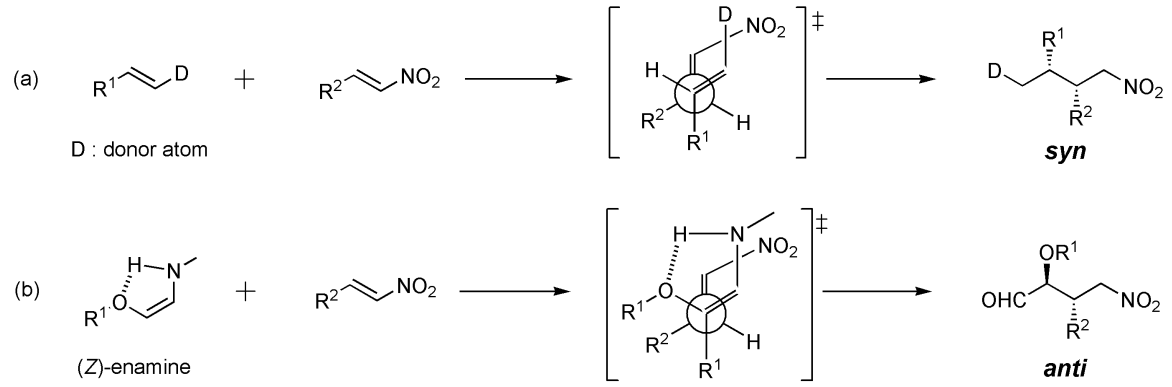
(6) Cornaggia, F.; Manoni, E.; Torrente, S.; Tallon, S.; Connon, S. J. *Org. Lett.* **2012**, *14*, 1850.

Chapter 3

Anti-Selective Asymmetric Nitro-Michael Reaction of Furanones: Diastereocontrol by Catalyst

3.1 Introduction

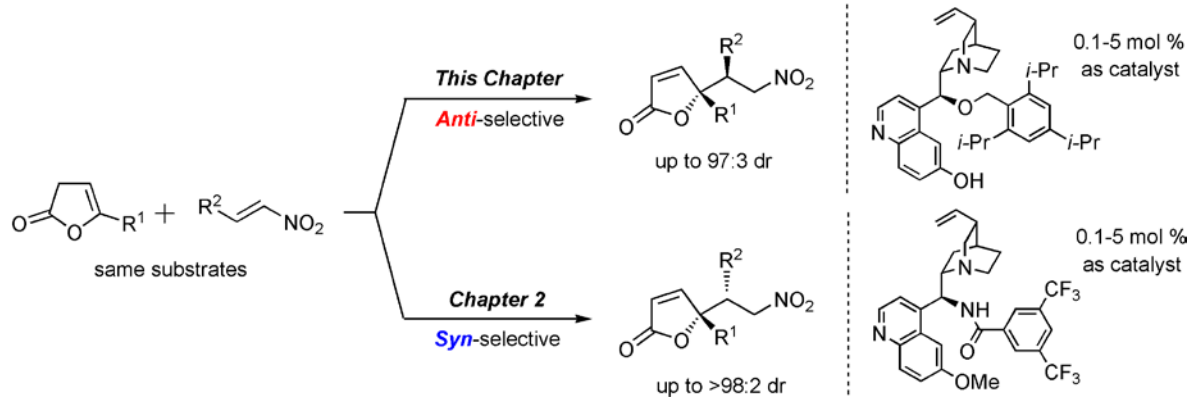
Among a large variety of the asymmetric Michael reactions, nitroalkenes have been one of the most widely used Michael acceptors, because of the synthetic importance of chiral nitroalkanes, which undergo facile *β*-alkylation reactions and interconversions to important organic functional groups.[1] Although a large number of the nitro-Michael reactions catalyzed by enamine catalysts and bifunctional hydrogen-bonding catalysts have been reported, these reactions exclusively exhibit *syn*-selectivity.[2] The predominant *syn*-selectivity of the nitro-Michael reaction is explained by the transition state model proposed by Seebach, in which donor atoms and acceptor atoms are situated close to each other (Scheme 3-1a).[3] The first example of the *anti*-selective nitro-Michael reaction of aldehydes promoted by enamine catalyst was reported by Barbas and his co-workers.[4] They have achieved the high *anti*-selectivity of nitro-Michael reaction by introducing an alkoxy group to the *α*-carbon of aldehydes. The reaction of *α*-alkoxyaldehydes with enamine catalysts predominantly forms (*Z*)-enamines stabilized by intramolecular hydrogen-bonding, giving *anti*-Michael adduct via Seebach's transition state model (Scheme 3-1b). Their strategy is a substrate-controlled diastereoselectivity, which is a typical synthetic protocol.[5]



Scheme 3-1. Seebach's transition state model of nitro-Michael reaction

The author reports herein the catalyst-controlled switching from the *syn*-selectivity of the asymmetric nitro-Michael reaction of furanones to the *anti*-selectivity (Scheme 3-2). Catalyst-control of the diastereoselectivity of an organic reaction is more practical and expedient than the substrate-control, since the need of modifying the substrate to achieve the high diastereoselectivity severely limits the substrate scope. To the best of the author's knowledge, a successful organocatalyst-controlled diastereoselectivity of the nitro-Michael reaction is very rare.[1] Moreover, catalyst-controlled switching from high *syn*-selectivity (> 90:10 dr) to high *anti*-selectivity (> 90:10 dr) of an asymmetric reaction using the same substrates seems to be seldom[4d]. In Chapter 2, the author has described the asymmetric nitro-Michael reaction of 2(3*H*)-furanones to give chiral *γ*-butenolides catalyzed by

epi-quinine-derived 3,5-bis(trifluoromethyl)benzamide, which exclusively exhibits the high *syn*-selectivities (> 98:2 dr) as well as the excellent enantioselectivities (> 90% ee) (Scheme 3-2).[6] The extremely high *syn*-selectivity of this reaction affords a perfect opportunity to investigate the catalyst-controlled switching of the diastereoselectivity.

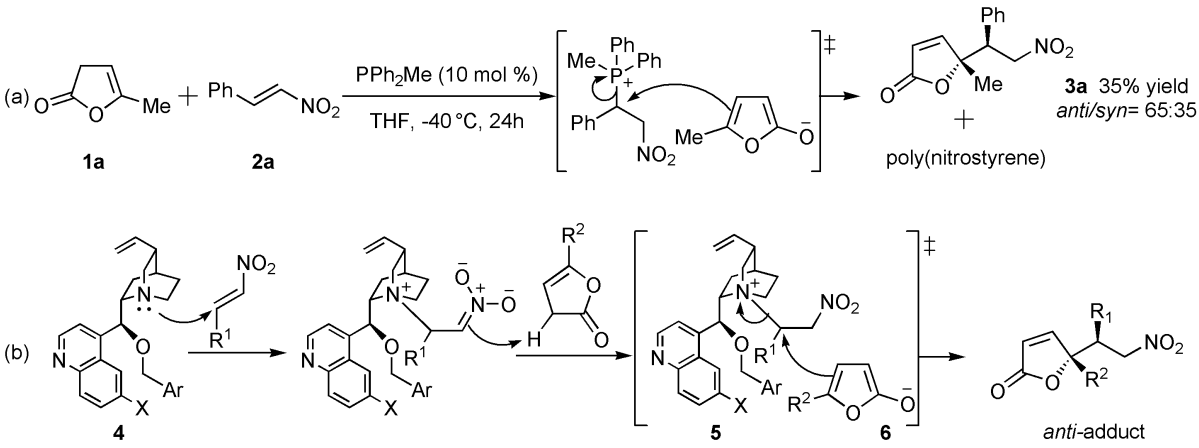


Scheme 3-2. Catalyst-controlled switching of diastereoselectivity

3.2 Results and Discussion

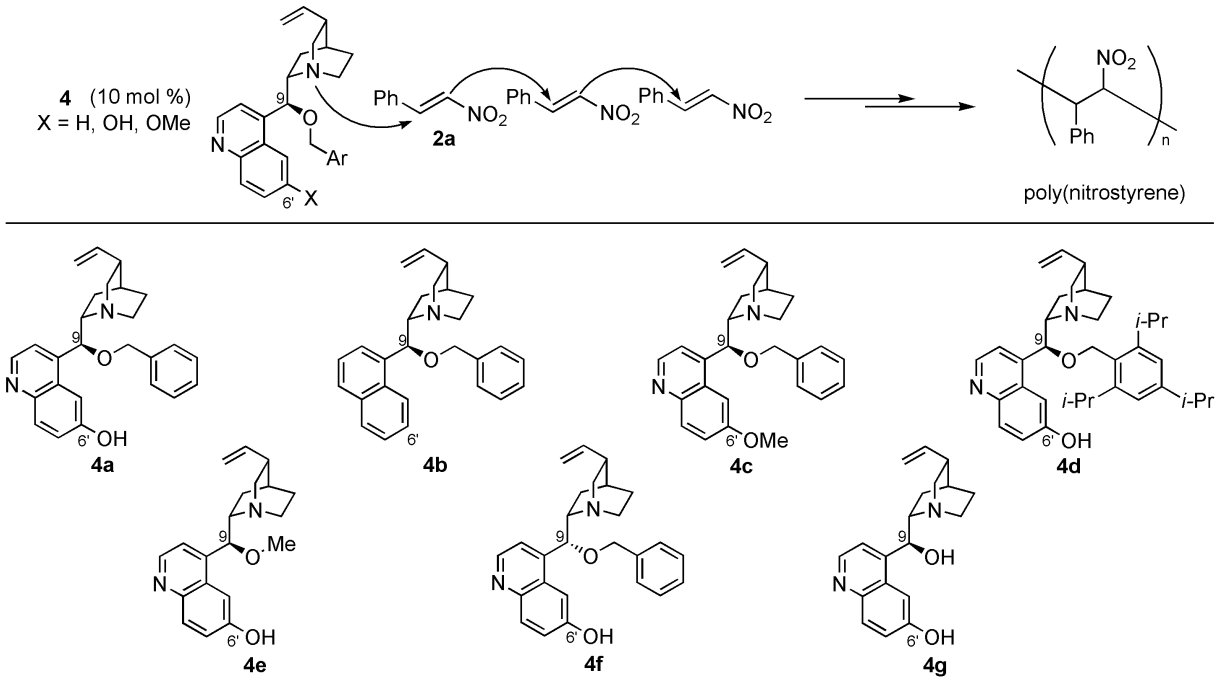
3.2.1 Polymerization of (*E*)-*β*-nitrostyrene by *epi*-quinine-derived catalyst

The author has found that a 10 mol % loading of PPh_2Me catalyzes the nitro-Michael reaction of angelica lactone **1a** with nitrostyrene **2a** in THF at −40 °C, giving the corresponding adduct **3a** (Scheme 3-3a). The reaction mechanism likely involves conjugate addition of PPh_2Me to **2a**.[7] The crucial aspect of the reaction is the moderate *anti*-selectivity (*anti*:*syn* = 65:35). Based on this result, the author has made an assumption that the quinuclidine nitrogen of *epi*-quinine-derived catalysts **4** would undergo the conjugate addition to nitroalkenes, giving nitroammonium intermediate **5** (Scheme 3-3b).[8] Analogously to the PPh_2Me-catalyzed nitro-Michael reaction, the nucleophilic substitution of **5** with dienolate **6** is expected to afford *anti*-adduct.



Scheme 3-3. *Anti*-selective nitro-Michael reaction

With the purpose of evaluating the nucleophilicity of the quinuclidine nitrogen, the polymerization of (*E*)-*β*-nitrostyrene **2a** promoted by *epi*-quinines **4** was carried out at 10 mol % loadings of *epi*-quinines **4** in THF at the room temperature (Scheme 3-4).



Scheme 3-4. *Epi*-quinine derivatives-promoted polymerization of nitrostyrene

The reaction furnished poly(nitrostyrene) as an insoluble material, whose structure was determined by elementary analysis. The author has observed that bifunctional *epi*-quinine-derived catalyst **4a**, **4d**, **4e** and **4g** are capable of promoting the polymerization of **2a** to give polymer in quantitative yield. The rate of polymerization strongly depends on the structures of the catalysts. *Epi*-quinine-derived **4d** bearing 6'-OH and sterically demanding 9-OCH_2[2,4,6-tri(isopropyl)phenyl] substituent exhibited the lower reaction rate of the polymerization of **2a**, compared to **4a**, **4e**, and **4g**, which completed the polymerization within 10 min. In contrast, the replacement of 6'-OH of **4a** with 6'-H (**4b**) and the replacement of 6'-OH of **4a** with 6'-OMe (**4c**)[9a] profoundly depresses the activity for the polymerization reaction. Quinine-derived **4f**[9b] bearing 6'-OH (diastereomer of **4a**) failed to promote the polymerization. These results conclusively reveal that the 6'-OH of *epi*-quinine derivatives are essential for the nucleophilic activation of nitrostyrene **2a**. The ^{13}C NMR spectra of the mixture of **4a** and nitrostyrene **2a** (**4a**:**2a** = 1:2, in C_6D_6) indicated that $\delta(^{13}C)$ of the *β*-carbon of **2a** did not shift upon the addition of **4a**, indicating the very weak interaction between the quinuclidine nitrogen and nitrostyrene **2a**. In order to reveal the role of 6'-OH group of *epi*-quinine-derived catalysts **4a**, **4d**, **4e**, and **4g**, the author carried out theoretical calculations (Figure 3-1).

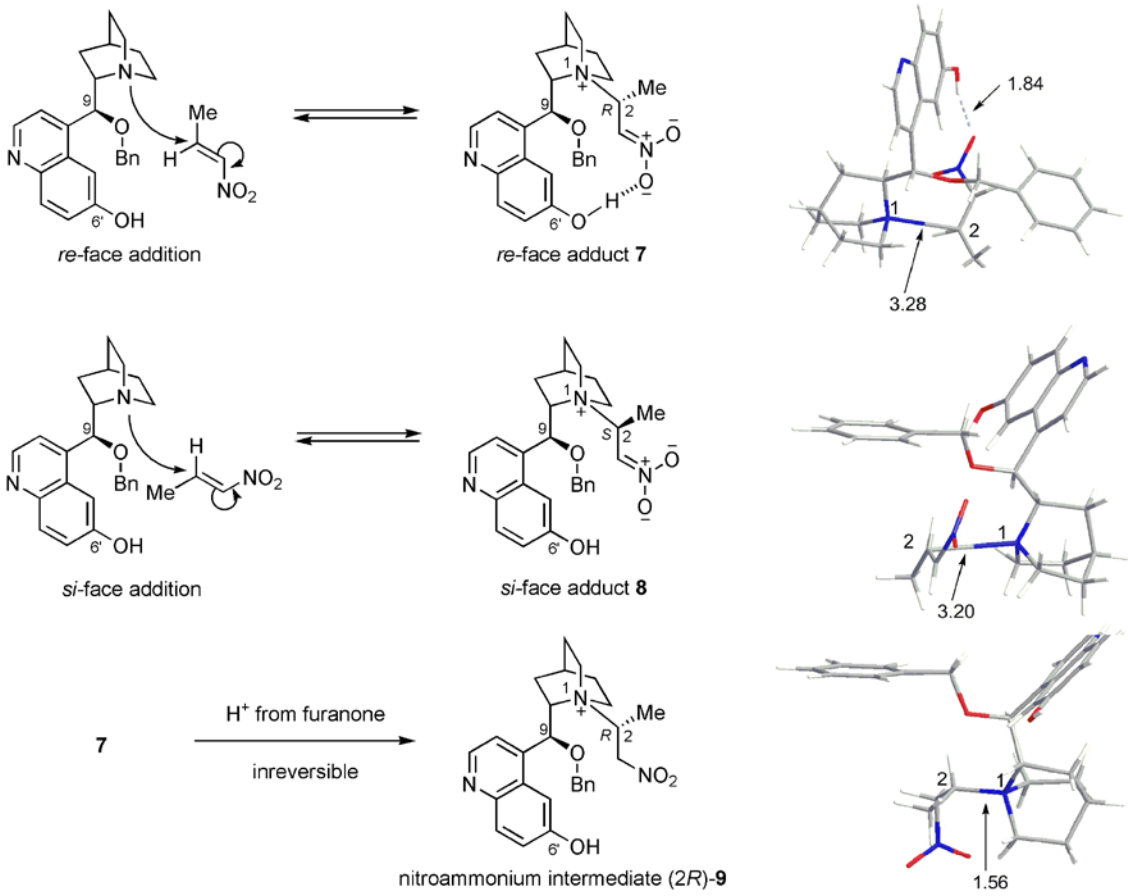


Figure 3-1. Simplified models of *re*-face and *si*-face adducts optimized at B3LYP/6-31G(d). Atomic distances in Å.

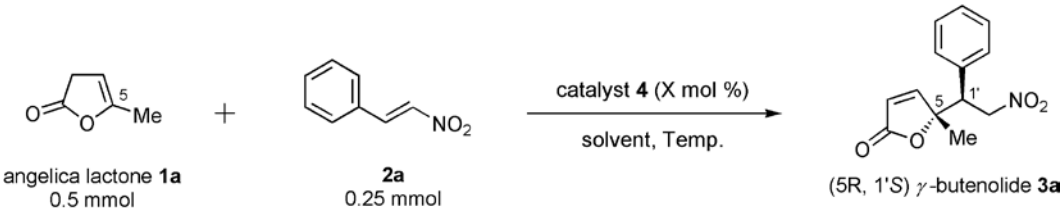
The simplified structures of the Michael adducts formed by the conjugate addition of the quinuclidine N (1) to the *re*- and *si*-face of nitroalkene were optimized at B3LYP/6-31G(d). The results of the calculations are wholly surprising. The structure of optimized *re*-face adduct **7** discloses the very weak interaction between the quinuclidine N(1) and nitroalkene as indicated by the very long N(1)-C(2) bond length (3.28 Å), but an intramolecular hydrogen-bonding between 6'-OH and nitronate oxygen effectively stabilize the *re*-face adduct **7**. The long N(1)-C(2) bond length would be ascribed to the strong electrostatic repulsion between the nitrate moiety and N(1), which bears a considerable negative charge (−0.3868: Mulliken). The formal positive charge on N(1) can be neutralized by electron releasing from five neighboring hydrogen atoms in germinal positions relative to N(1).[10] On the contrary, the *si*-face adduct **8** cannot form an intramolecular hydrogen-bonding between 6'-OH and nitronate oxygen. Consequently, the *si*-face adduct **8** dissociates into the catalyst and the nitroalkene due to the electrostatic repulsion between the negatively charged N(1) and the nitronate moiety. The N(1)-C(2) bond length of the *si*-face adduct **8** (3.20 Å) is roughly comparable to the sum of van der Waals radii of N and C (3.25 Å).[11] The electrostatic

repulsion between N(1) and C(2) of the *re*-face adduct **7** is reduced when **7** is protonated by furanone (Figure 3-1). Resulting nitroammonium intermediate (2*R*)-**9** is considered thermodynamically stable; the N(1)-C(2) bond length of 1.56 Å is normal as a N-C covalent bond.[12] The DFT calculations strongly suggested that the conjugate addition of the quinuclidine N(1) to the nitroalkene would occur predominantly at the *re*-face of the nitroalkene, affording the nitroammonium intermediate (2*R*)-**9**.

3.2.2 Catalyst scope

As expected from the *anti*-selectivity of the PPh_2Me-catalyzed nitro-Michael reaction, *epi*-quinine derivatives are capable of catalyzing the conjugate addition of angelica lactone **1a** to nitrostyrene **2a** with *anti*-selectivity (Table 3-1). For example, 10 mol % loading of **4a**, the Michael adduct **3a** was obtained with high diastereo- and enantioselectivity (93:7 dr, *anti* major; 93% ee), while the yield was very low (35% yield) (entry 1). Catalysts **4e** and **4g** showed no improvement of the diastereoselectivity (entries 2 and 3). Although the diastereo- and enantioselectivity dropped considerably (78:22 dr, *anti* major; 86% ee), catalyst **4d** effectively suppressed the polymerization of **2a**, increasing the yield of **3a** (66% yield) (entry 4). This is apparently due to the inhibition of the polymerization by sterically demanding 9-OCH_2[2,4,6-tri(isopropyl)phenyl] substituent. Catalysts **4b**, **4c** and **4f,** which failed to

Table 3-1. Catalytic asymmetric nitro-Michael reaction of **1a** to **2a**[a]



angelica lactone **1a** 0.5 mmol + **2a** 0.25 mmol → (5R, 1'S) γ-butenolide **3a**

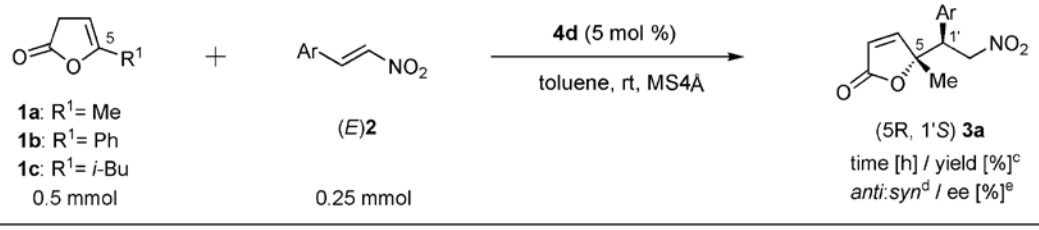
entry	catalyst	X [mol %]	solvent	T [°C]	t [h]	Yield [%][b]	*anti/syn* [c]	ee [%][d]
1	4a	10	THF	-40	20	35	93/7	93
2	4e	10	THF	-40	20	51	88/12	87
3	4g	10	THF	-40	20	56	70/30	71
4	4d	10	THF	-40	24	66	78/22	86
5	4b	10	THF	-40	50	62	30/70	(2) [e]
6	4c	10	THF	-40	50	60	26/74	(0) [e]
7	4f	10	THF	-40	84	47	7/93	(35) [e]
8 [f]	4d	10	toluene	rt	0.5	71	90/10	95
9 [f]	4d	5	toluene	-20	48	69	94/6	97

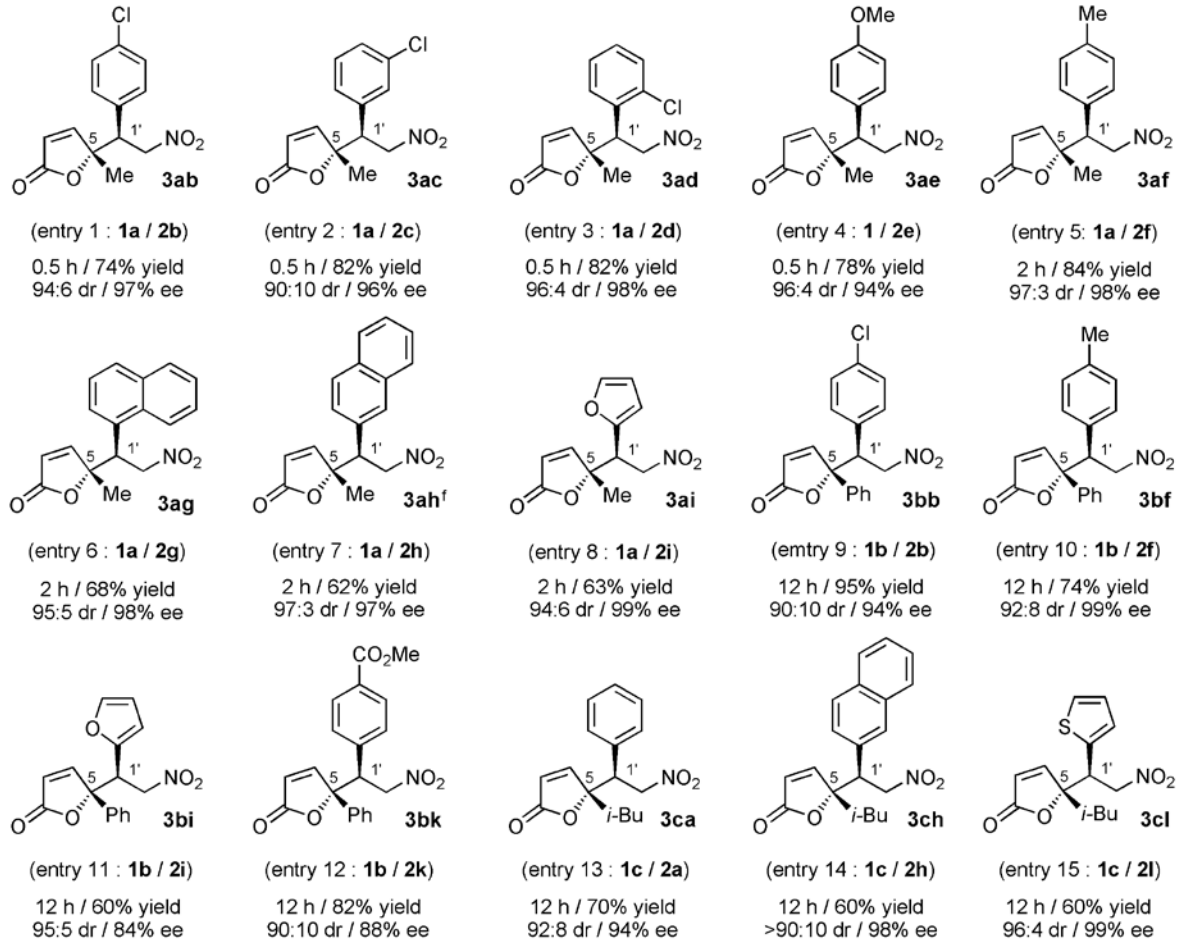
[a]Absolute configuration was assigned by analogy with compound **3ah** (Table 3-2, entry 7). [b] Isolated yield. [c] Diastereomer ratio was determined by ^{1}H NMR analysis of crude material. [d] Obtained by chiral HPLC analysis. [e] Ee value of *syn* body. [f] Reaction was conducted in the presence of MS 4 Å (50 mg).

catalyze the polymerization of nitrostyrene, while the *syn*-selective reaction promoted by these catalysts (entries 4 to 7). The screening of solvents with **4d** revealed that toluene is the solvent of choice (entry 8). To the author's delight, addition of 4 Å MS into the reaction mixture considerably improved the diastereoselectivity without affecting the high enantioselectivity (96:4 dr, *anti* major; 97% ee) (entry 9). Furthermore, catalyst loading as low as 5 mol % can be achieved.

3.2.3 Substrate scope

Table 3-2. Catalytic asymmetric nitro-Michael reaction catalyzed by **4d**[a,b]

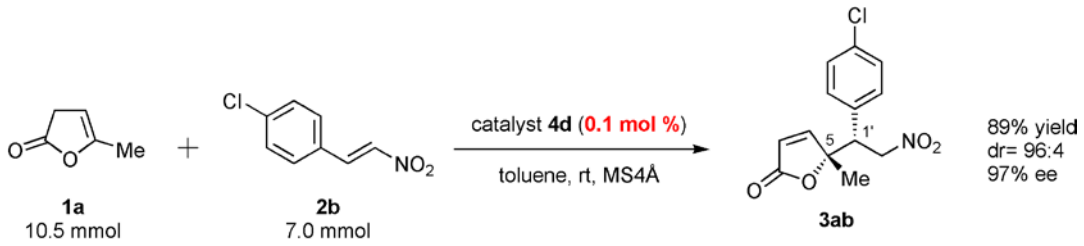




[a] Absolute configuration was assigned by analogy with compound **3ah** (entry 7). [b] Reaction was conducted in the presence of 4 Å MS (50 mg) otherwise noted. [c] Isolated yield. [d] Diastereomer ratio was determined by ^{1}H NMR analysis of crude material. [e] Obtained by chiral HPLC analysis. [f] Absolute configuration of **3ah** was determined by X-ray crystallographic analysis.

The author then turned our attention to the substrate scope of the *anti*-selective nitro-Michael reaction promoted by novel catalyst **4d**. Table 3-2 shows that 5 mol % loadings of **4d** allowed complete conversion of the substrates in toluene at room temperature, giving the corresponding *anti*-Michael adducts in good yields (60-95% yield) with the high level of diastereo- and enantioselectivities (88:12-97:3 dr, *anti* major; 84-99% ee).[13] *β*-Arylnitroalkenes **2** bearing electron-withdrawing and electron-releasing substituents on the aromatic ring smoothly reacted with 5-substituted furanones **1** in good yields (78-82%) with high diastereo- and enantioselectivities (90:10-96:4 dr; 88-94% ee) (entries 4 and 12). Thus,

Furthermore, the substitution pattern on the aromatic rings (entries 1 to 3) as well as sterically demanding aromatic ring of *β*-(*E*)-arylnitroalkenes **2g** and **2h** had also no deleterious effect on the diastereo- and enantioselectivity (entries 6 and 7). The Michael additions of sterically demanding 5-isobutylfuranone **1c** to *β*-arylnitroalkenes **2a**, **2h** and **2l** smoothly proceeded, giving the *anti*-adducts **3ca** (94% ee), **3ch** (98% ee) and **3cl** (99% ee) in moderate-to-high yields (entries 13 to 15). To evaluate the potential of catalyst **4d**, the nitro-Michael addition of more sterically demanding 5-phenylfuranone **1b** (A-value of Ph = 3.0 Kcal mol^{-1}; *cf*. Me = 1.70 Kcal mol^{-1})[14] to *β*-arylnitroalkenes **2** were carried out, affording the *anti*-adducts with high diastereo- and enantioselectivities (> 90:10 dr; 84-99% ee) (entries 9 to 12). Thus, the present method is especially useful for constructing the sterically congested oxygen-containing quaternary stereogenic centers adjacent to ternary stereogenic centers.[15] When the large scale reaction of **1a** (10.5 mmol) and **2b** (7 mmol) was conducted at room temperature, the author found that the catalyst loading could be reduced to only 0.1 mol % without affecting the high diastereo- and enantioselectivity as well as the high yield of the Michael adduct **3ab** (96:4 dr, *anti* major; 97% ee; 89% yield; TON = 890) (Scheme 3-5).[16]



Scheme 3-5. Practical Reaction Conditions

3.3 Summary

In summary, the author has developed the highly *anti*-selective nitro-Michael reaction of furanones by the catalyst-controlled switching of diastereoselectivity. Preliminary DFT calculations suggest that *anti*-selective nitro-Michael addition of aldehydes is promising under the similar conditions.

3.4 References

(1) For selected recent review of organocatalytic asymmetric nitro-Michael reactions and the application to organic synthesis, see: (a) Somanatham, R.; Chávez, D.; Servin, F. A.; Romero, J. A.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; de Parrod, C. A.; González, J. S. *Curr. Org. Chem.* **2012,** *16*, 2440.; (b) Chauhan, P.; Chimni, S. S. *RSC. Adv*, **2012**, *2*, 737.; (c) Raimondi, W.; Bonne, D.; Rodriguez, J. *Angew. Chem., Int. Ed*. **2012**, *51*, 40.; (d) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051.; (e) Xi, Y.; Shii, X. *Chem. Commun*. **2013**, *49*, 8583.; (f) Roux, C.; Bressy, C. In *Comprehensive Enantioselective Organocatalysis*; Dalco P., Ed.; Wiley-VCH: Weinheim, 2013, Vol. 3, pp. 1013-1042.; (g) Rios, R.; Moyano, A. In *Catalytic Asymmetric Conjugate Reaction*; Cordóva, A.; Ed.; Wiley-VCH: Weinheim, 2010; pp. 191-218.

(2) As a Michael donor, ketones exhibit *anti*-selectivity in the nitro-Michael reaction, see: (a) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559.; (b) Tsogoeva, S. B.; Wei, S. *Chem. Commun*. **2006**, 1451.; (c) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170.; (d) Enders, D.; Chow, S. *Eur. J. Org. Chem.* **2006**, 4578.; (e) Mandal, T. Zhao, C.-G. *Angew. Chem. Int. Ed*. **2008**, *47*, 7714.

(3) (a) Seebach, D.; Goliński, J. *Helv. Chim. Acta* **1981**, *64*, 1413.; (b) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 8822.; (c) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 71.; (d) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc*. **2012**, *134*, 6741.

(4) (a) Uehara, H.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 9848.; (b) Uehara, H.; Imashiro, R; Hernández-Torres, G.; Barbas III, C. F. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20672.; (c) Imashiro, R.; Uehara, H.; Barbas III, C. F. *Org. Lett.* **2010**, *12*, 5250. Addition of organic bases promote the *anti*-selective Michael addition of aldehydes to α,β-unsaturated esters: (d) Hong, B. -C.; Dange, N. S.; Yen, P. J.; Lee, G. -H.; Liao, J.-H. *Org. Lett*. **2012**, *14*, 5346.

(5) (a) For review, see: Cao, L. -L.; Gao, B. -L.; Ma, S. -T.; Liu, Z. -P. *Curr. Org. Chem.* **2010**, *14*, 889.; (b) Charette, A. B.; Andre, B.; Lindsay, V. *Top. Curr. Chem.* **2014**, *343*, 33.; (c) Chemler, S. R.; Copeland, D. A. *Top. Heterocycl. Chem.* **2013**, *32*, 1861.

(6) (a) Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2015**, *17*, 3026.; (b) Manna, M. S.; Kumar, V.; Mukherjee, S. *Chem. Commun.* **2012**, *48*, 5193.; (c) Terada, M; Ando, K. *Org. Lett.* **2011**, *13*, 2026. γ-Butenolides are often subunits of natural products and biologically active compounds. For review, see: (d) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.; (e) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 609.

(7) Lee, C. -J.; Jang, Y. -J.; Wu, Z. -Z.; Ling, W. *Org. Lett.* **2012**, *14*, 1906.

(8) Syder, H. R.; Hamln, W. E. *J. Am. Chem. Soc.* **1950**, *72*, 5082.
(9) (a) Mandal, T.; Zhao. C. -G. *Angew. Chem. Int. Ed.* **2008**, *47*, 7714.; (b) He, P.; Liu, X.; Shi, J.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 936.
(10) Chandra, A.; Chen, Z.; Hatanaka, T.; Minami, T.; Hatanaka, Y. *Organometallics*, **2013**, 32, 3575.
(11) Mantina, M.; Chamberlin, A. C.; Valero, R.; Cramer, C. J.; Truhal, D. G. *J. Phys. Chem. A*, **2009**, *113*, 5806.
(12) Pyykkö, P.; Atsumi, M. *Chem. Eur. J*. **2009**, *15*, 186.
(13) All substrates listed in Table 3-2 undergo extremely high *syn*-selective nitro-Michael reaction in the presence of *epi*-quinine-derived 3,5-bis(trifluoromethyl)benzamide catalyst, see ref. 6a.
(14) (a) Eliel, E. L. ; Wilson, S. H. *Stereochemistry of Organic Compounds*, Wiley, New York, 1993, pp. 696-697.; (b) Eliel, E. L.; Wilson, S. H.; Doyl, M. P. *Basic Organic Chemistry*, Wiley, New York, 2001, pp. 443-444.
(15) For review, see: Bella, M.; Gaspert. *Synthesis* **2009**, 1583.
(16) Most of the compounds **3** listed in Table 3-2 are highly crystalline materials, which can be easily recrystallized from EtOH to give the enantiomerically pure **3**.
(17) For the X-ray analysis of **3ah**: See Experimental Section.

3.5 Experimental Section

3.5.1 Materials and methods

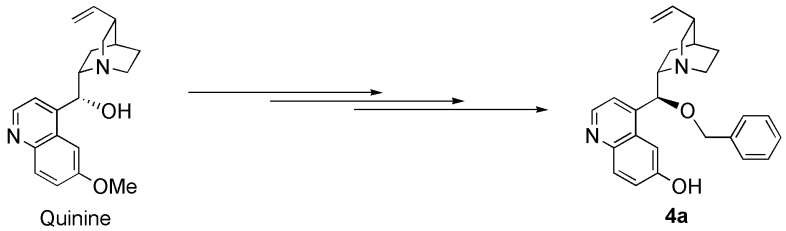
General Methods: All manipulations were carried out under nitrogen atmosphere using Schlenk tube technique. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a BRUKER-300 spectrometer. Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ (7.26 ppm) for ^{1}H NMR, and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as internal standards respectively. Infrared spectra were measured on a JASCO FT/IR-230 in Nujol mulls. All the melting points were measured by using Yanagimoto micro melting point apparatus under inert atmosphere and are uncorrected. Solvents were purified as follows: tetrahydrofuran, diethylether and hexane by distillation from benzophenone ketyl under nitrogen; dichloromethane and chloroform by distillation from calcium hydride. Optical rotation was measured on RUDOLPH AUTOPOL IV digital polarimeter. Analytical HPLC was performed on a Shodex Model RI-72 instrument using Daicel CHIRALPACK AD-3 (4.6 × 150 mm), and Daicel CHIRALPACK AD-H (4.6 × 150 mm). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Facility of Osaka City University.

Materials: *Epi*-quinine derivative **4c** was prepared according to the literature procedure.[1] Quinine derivative **4f** was prepared according to the literature procedure.[2] Angelica lactone **1a** was obtained from Aldrich. (8a, 9S)-6'-methoxy-9-hydroxycinchonan was obtained from

Fluka. Nitroalkenes **2b**-**2j** were prepared according to the literature procedure.[3] 5-Substituted 2(3*H*)-furanones **1b** and **1c** were prepared according to the literature procedure.[4] (8a, 9*S*)-6',9-dihydroxycinchonan **4g** and (8a, 9*R*)-6'-methoxy-9-hydroxycinchonan were prepared according to the literature procedure.[5] (9*S*)-9-(Phenylmethoxy)cinchonin **4b** was prepared according to the literature procedure.[6] (8a, 9*S*)-9-hydroxycinchonan was obtained from Inno ChemTech. (8a, 9*R*)-6'-methoxy-9-hydroxycinchonan was obtained from Tokyo Kasei. (8a, 9*S*)-6'-hydroxy-9-hydroxycinchonan and (8a, 9*S*)-6'-hydroxy-9-methoxycinchonan **4e** were obtained from ChinaChimca.

3.5.2 Preparation of catalysts

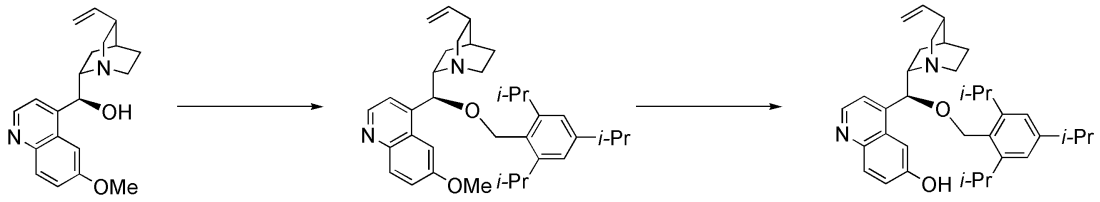
[(8a, 9*S*)-6'-hydroxy-9-(phenylmethoxy)]cinchonan **4a**



To a solution of quinine (3.1 g, 9.25 mmol) in THF (60 mL) was added triethylamine (2.96 mL) and methanesulfonyl chloride (2.0 g, 17.6 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). Combined CH_2Cl_2 layer was dried over $MgSO_4$, and concentrated under reduced pressure. Obtained crude material was subjected to next step without purification. To a solution of the clued product in water (54 mL) was added D-tartaric acid (1.37 g, 9.12 mmol). The resulting reaction mixture was refluxed for 1 h. Powder of $NaHCO_3$ was added slowly. After ceasing of gas evolution, the reaction mixture was extracted by CH_2Cl_2 (3 × 10 mL) and combined organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure gave (8a, 9*S*)-6'-methoxy-9-hydroxycinchonan, which was used for next step after the short column purification. To a DMF solution (10 mL) of NaH (100 mg) and crude (8a, 9*S*)-6'-methoxy-9-*hydr*oxycinchonan (0.97 g, 3.08 mmol) was added benzylchloride (0.43 g. 3.39 mmol). The resulting reaction mixture was stirred at room temperature for 12 h. The reaction mixture was poured into the mixture of brine (20 mL) and ethylacetate (20 mL), then washed with 1N HCl. The organic layer was washed with sat. $NaHCO_3$. Subsequently, organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded (8a, 9*S*)-6'-methoxy-9-(benzyl)cinchonan, which was used next step without isolation. To a DMF solution (3 mL) of crude (8a, 9*S*)-6'-methoxy-9-(benzyl)chonan (440 mg, 1.1 mmol) and potassium *tert*-butoxide (280 mg, 2.1 mmol) was added dodecanethiol (0.85 g, 4.25 mmol). The reaction mixture was stirred at room temperature for 2 h, then heated to 110 °C for 12 h. The reaction mixture

was poured into the mixture of ethylacetate (20 mL) and 1N HCl (10 mL), and extracted by CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, and condensed under reduced pressure, giving the crude product. Obtained crude material was purified by silica-gel column chromatography (CH_2Cl_2 : MeOH = 9 : 1), to give 360 mg (0.90 mmol) of compound **4a**. as a colorless solid: mp 153-156 °C; $[\alpha]_D^{23}$ −74.2 (*c* 0.36, $CHCl_3$), IR (nujol), 4334, 1615, 1456, 1376, 1243, 1089 cm^{-1}; ^1H NMR(300 Mz, $CDCl_3$); δ 0.61 (dd, *J* = 13.5, 8.1 Hz, 1H), 1.04-1.30 (m, 1H), 1.31-1.62 (m, 2H), 1.15 (s, 1H), 2.25 (br s, 1H), 2.55-2.80 (m, 2H), 2.88 (m, 1H), 3.34 (dd, *J* = 13.2, 10.2 Hz, 1H), 3.80 (br s, 1H), 3.93 (d, *J* = 12.3 Hz, 1H), 4.45 (d, *J* = 12.3 Hz, 1H), 4.77 (d, *J* = 10.2 Hz, 1 H), 4.84 (d, *J* = 17.1 Hz, 1H), 5.50-5.70 (m, 1H), 6.84 (br s, 1H), 8.17 (s, 2H), 7.03-7.25 (m, 5H), 7.40 (dd, *J* = 9.3, 1.8 Hz, 1H), 8.01(d, *J* = 9.0 Hz, 1H), 8.54 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.16, 25.4, 27.4, 27.5, 39.9, 49.8, 56.0, 70.4, 76.7, 94.7, 115.6, 123.3, 128.1, 128.4, 128.6, 129.4, 132.0, 134.8, 137.0, 140.9, 144.5, 156.9; HRMS (FAB+) calcd for $C_{26}H_{29}N_2O_2$, $(M+H)^+$ 401.2229, found: 401.2227.

[(8a, 9*S*)-6'-hydroxy-9-[2,4,6-tri(isopropyl)phenylmethoxy]cinchonan **4d**

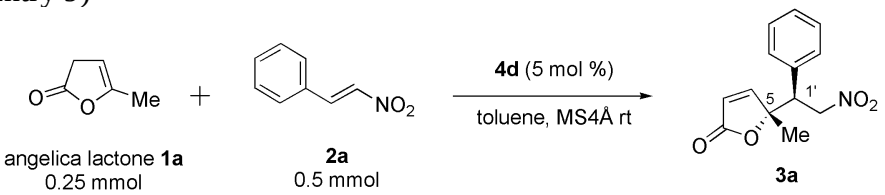


The solution of (8a, 9*R)*-6'-methoxy-9-hydroxycinchonan (2.1 g, 6.5 mmol), and NaH (0.39 g, 16.2 mmol) in DMF (21 mL) was stirred for 2 h at room temperature. To the solution, 2, 4, 5-triisopropyl)benzylchloride (3.27 g, 13.0 mmol) was added at 0 °C. The resulting solution was stirred for 12 h at room temperature. After the careful addition of brine, the reaction mixture was extracted with 1N HCl (3 × 20 mL). Obtained aqueous solution was treated with sat. NH_4OH and extracted with Et_2O (3 × 10 mL). Organic layer was dried over $MgSO_4$, followed by removal of the solvent under reduced pressure, giving [(8a, 9S)-6'-methoxy-9-[2,4,6-tri(isopropyl)phenylmethoxy]cinchonan, which was subjected to next step without isolation (3.4 g, 6.45 mmol). The solution of potassium *t*-butoxide (1.87 g, 16.6 mmol) and 1-dodecanethiol (5.3 mL, 22 mmol) in DMF (23 mL) was stirred for 2 h at room temperature. To this solution, a solution of crude [(8a, 9S)-6'-methoxy-9-[2,4,6-tri(isopropyl)phenyl-methoxy]cinchonan (3.0 g, 5.7 mmol) in DMF (20 mL) was added dropwise and heated to 110 °C for 12 h. After cooling of the reaction mixture, the solution was treated with 1N HCl and extracted with Et_2O (4 × 10 mL). After the treatment of organic phase with sat. NH_4OH, aqueous phase was extracted with Et_2O (4 × 10 mL). Combined organic layer was dried over

$MgSO_4$ and concentrated under reduced pressure, giving a solid product. Purification by column chromatography (Et_2O : MeOH = 10 : 1) gave **4d** (1.44 g, 2.7 mmol, 42%) as a colorless solid.: mp 127-129 °C; $[\alpha]_D^{25}$ +157.4 (*c* 0.11, $CHCl_3$), IR (nujol), 4327, 2910, 1617, 1462, 1240, 1054 cm^{-1}; ^1H NMR(300 Mz, $CDCl_3$); δ 0.99 (d, *J* = 6.6 Hz, 7H), 1.06-1.16 (m, 1H), 1.60-1.40 (m, 3H), 2.19 (br s, 1H), 2.63-2.77 (m, 3H), 2.95-3.14 (m, 3H), 3.26 (m, 1H), 3.41 (q, *J* = 7.2 Hz, 1H), 33.57 (q, *J* = 7.2 Hz, 1H), 4.68 (q, *J* = 10.2 Hz, 1 H), 4.81-4.90 (m, 3 H), 5.60 (q, *J* = 7.8 Hz, 1H), 6.84 (s, 2H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.44 (br s, 2H), 7.70 (m, 1H); 7.92 (d, *J* = 9.9 Hz, 7H), 8.63 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 15.3, 22.7, 24.0, 24.0, 24.2, 24.6, 27.7, 27.8, 29.2, 31.6, 34.3, 39.5, 56.0, 64.3, 65.9, 114.7, 120.9,122.5, 128.4, 130.8, 141.3, 143.0, 146.0, 148.6, 149.0, 156.7; HRMS (FAB+) calcd. for $C_{35}H_{47}N_2O_2$, $(M+H)^+$: 527.3638, found: 527.3635.

3.5.3 Preparation of substrates

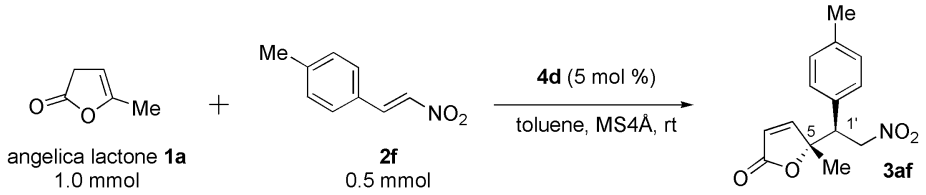
Experimental procedure for the Michael addition of furanones **1a** to (*E*)-*β*-nitrostyrene **2a** (Table 3-1, Entry 9)



To a solution of nitroalkene **2a** (74.5 mg, 0.5 mmol), catalyst **4d** (6.8 mg, 0.013 mmol) and MS4Å (50 mg) in toluene (0.5 mL) was added angelica lactone **1a** (24.5 mg, 0.25 mmol) at -40 °C. The resulting solution was stirred for 12 h. After removal of solvent under reduced pressure, the crude material was purified by silica gel column chromatography (CH_2Cl_2 : hexane = 1 : 1), giving 43 mg (0.17 mmol, 69%) of compound **3a** as a colorless solid.: mp 57-59 °C; $[\alpha]_D^{23}$ −66.4 (*c* 0.8, $CHCl_3$), IR (nujol) 1758, 1556, 1456, 1377, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.26 (s, 3H), 3.74(dd, *J* = 7.2, 7.2 Hz, 1H), 4.62 (d, *J* = 7.8 Hz, 2H), 6.07 (d, *J* = 5.7 Hz, 1H), 7.23-7.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 50.3, 75.6, 88.2, 121.6, 128.8, 129.2, 129.2, 134.5, 159.4, 171.4; HRMS (FAB+) calcd for $C_{13}H_{14}NO_4$, $(M+H)^+$: 248.0923, found: 248.0925. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 4:96. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : EtOH = 100 : 1; (5*R*, 1'*S*) t_R = 22.2 min, (5*S*, 1'*R*) t_R = 26.2 min). Absolute configuration was assigned by analogy with compound **3ah** (Table 3-2, entry 7).

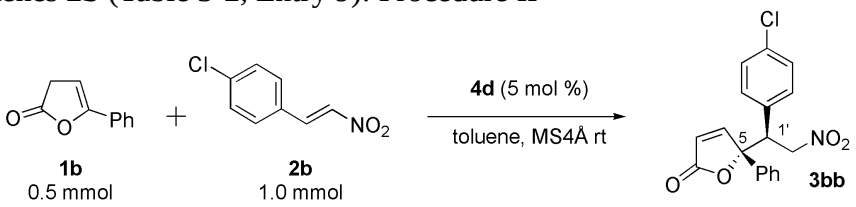
Representative experimental procedure for the asymmetric Michael Addition of furanones **1a** and **1c** to *β*-arylnitroalkenes: Procedure I.

Reaction of angelica lactone **1a** with (*E*)-*β*-nitroalkene **2f** (Table 3-2, Entry 5)



To a solution of nitroalkene **2f** (82 mg, 0.5 mmol), catalyst **4d** (13 mg, 0.025 mmol) and MS4Å (50mg) in toluene (0.5 mL) was added angelica lactone **1a** (98 mg, 1.0 mmol) at room temperature. The resulting solution was stirred for 2 h. After removal of solvent under reduced pressure, the crude material was purified by silica gel column chromatography (CH_2Cl_2 : hexane = 1 : 1), to give 97 mg (0.37 mmol, 74%) of compound **3af** as a colorless solid.: mp 45-48 °C; $[\alpha]_D^{23}$ −109.7 (*c* 0.8, $CHCl_3$), IR (nujol) 2923, 1749, 1556, 817, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.25 (s, 3H), 2.28 (s, 3H), 3.69 (t, *J* = 7.5 Hz, 1H), 4.62 (d, *J* = 7.5 Hz, 2H), 6.06 (d, *J* = 5.8 Hz, 1H), 7.08-7.15 (m, 4H), 7.31 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 22.4, 50.2, 75.7, 88.8, 121.6, 128.9, 129.1, 129.9, 131.4, 138.8, 159.5, 171.5; HRMS (FAB+) calcd for $C_{14}H_{16}NO_4$, $(M+H)^+$: 262.1079, found: 262.1081. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 3:97. The enantiomeric excess (98% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : EtOH = 100 : 1; (5*R*, 1'*S*) t_R = 27.5 min, (5*S*, 1'*R*) t_R = 49.8 min). Absolute configuration was assigned by analogy with compound **3ah** (Table 3-2, entry 7).

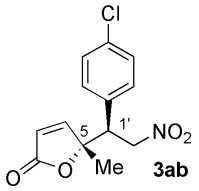
Representative experimental procedure for the asymmetric nitro-Michael addition of furanone **1b** to nitroalkenes **2b** (Table 3-2, Entry 9): Procedure II



To a solution of nitroalkene **2b** (184 mg, 1.0 mmol), catalyst **4d** (13 mg, 0.025 mmol) and MS4Å (50mg) in toluene (0.5 mL) was added lactone **1b** (80 mg, 0.5 mmol) at room temperature. The resulting solution was stirred for 12 h. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (CH_2Cl_2 : hexane = 1 : 1), to give 136 mg (0.48 mmol, 95%) of compound **3bb** as a colorless solid.: mp 126-129 °C; $[\alpha]_D^{25}$ −95.7 (*c* 0.1, $CHCl_3$), IR (nujol) 1764, 1556, 1458, 11376, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 4.13 (dd, *J* = 8.7, 6.3 Hz, 1H), 4.54 (dd, *J* = 13.8, 8.4 Hz, 1H), 4.49 (dd, *J* = 13.8, 6.6 Hz, 1H) 6.10 (d, *J* = 5.7 Hz 1H), 6.89 (d, *J* = 8.4 Hz 1H), 7.04-7.11 (m, 4H), 7.19-7.23 (m, 4H), 7.66 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.3, 75.2, 91.1, 121.3, 124.5, 128.8, 128.9, 130.8, 132.4, 134.6, 136.0, 157.3, 170.7; HRMS (FAB+) calcd for $C_{18}H_{15}{}^{35}ClNO_4$, $(M+H)^+$: 344.0690, found: 344.0692. ^1H NMR analysis of

the crude products indicated that *syn*:*anti* ratio was 10:90. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-H column ; flow rate 1 mL/min; hexane : EtOH = 50 : 1; (5*S*, 1'*R*) t_R = 12.7 min, (5*R*, 1'*S*) t_R = 14.1 min). Absolute configuration was assigned by analogy with compound **3ah** (Table 3-2, entry 7).

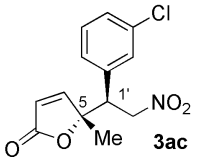
Synthesis of compound **3ab** according to the procedure I (Table 3-2, Entry 1).



3ab

Reaction (reaction time, 0.5 h) gave compound **3ab** in 104 mg (0.37 mmol, 74%) as a colorless solid: mp 81-82 °C; $[\alpha]_D^{23}$ −96.5 (*c* 0.15, $CHCl_3$), IR (nujol) 1752, 1553, 820, 719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.29 (s, 3H), 3.92 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.70 (dd, *J* = 8.4, 5.7 Hz, 2H), 6.02 (d, *J* = 5.7 Hz, 1H), 7.30-7.52 (m, 4H), 7.67-7.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 50.0, 75.6, 88.4, 121.9, 129.5, 130.6, 133.1, 134.9, 159.0, 171.2; HRMS (FAB+) calcd for $C_{13}H_{13}{}^{35}ClNO_4$, $(M+H)^+$: 282.0533, found: 282.0535. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 6:94. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AD-H column; flow rate 1.0 mL/min; hexane : EtOH = 45 : 1; (5*R*, 1'*S*) t_R = 39.7 min, (5*S*, 1'*R*) t_R = 52.9 min). Absolute configuration was assigned by analogy with compound **3ah.**

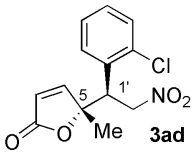
Synthesis of compound **3ac** according to the procedure I (Table 3-2, Entry 2)



3ac

Reaction (reaction time, 0.5 h) gave 115 mg (0.41 mmol, 82%) of compound **3ac** as oil; $[\alpha]_D^{23}$ −82.0 (*c* 0.29, $CHCl_3$); IR (nujol) 1762, 1559, 794, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.23 (s, 3H), 3.73 (t, *J* = 7.5 Hz, 1H), 4.55-4.57 (m, 2H), 6.09 (d, *J* = 5.4 Hz, 1H), 7.31-7.45 (m, 4H), 7.35 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 49.8, 75.4, 88.0, 121.9, 127.5, 129.2, 129.4, 130.5, 135.1, 135.1, 136.7, 159.0, 171.2; HRMS (FAB+) calcd for $C_{13}H_{13}{}^{35}ClNO_4$: $(M+H)^+$: 282.0533, found: 282.0539; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 10:90. The enantiomeric excess (96% ee) was determined through chiral HPLC analysis (Daicel AD-H column; flow rate 1.0 mL/min; hexane : EtOH = 54 : 1; (5*R*, 1'*S*) t_R = 19.6 min, (5*S*, 1'*R*) t_R = 33.5 min. Absolute configuration was assigned by analogy with compound **3ah**.

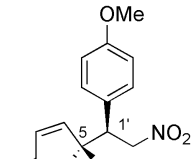
Synthesis of compound **3ad** according to the procedure I (Table 3-2, Entry 3)



3ad

Reaction (reaction time, 0.5 h) gave 115 mg (0.41 mmol, 82%) of compound **3ad** as an oil; $[\alpha]_D^{23}$ −96.5 (*c* 0.4, $CHCl_3$); IR (nujol) 1768, 1556, 822, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.26 (s, 3H), , 4.51 (d, *J* = 8.1 Hz, 1H), 4.54 (d, *J* = 6.0, 1H), 4.64 (dd, *J* = 8.1, 6.0 Hz, 1H), 6.08 (d, *J* = 5.7 Hz, 1H), 7.23-7.30 (m, 2H), 7.37-7.42 (m, 2H), 7.48 (dd, *J* = 7.5, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 44.2, 75.1, 88.7, 121.7, 127.9, 129.5, 129.9, 130.2, 132.7, 135.2, 159.3, 171.4; HRMS (FAB+) calcd for $C_{13}H_{13}{}^{35}ClNO_4$: M^+: 282.0533, found: 282.0534; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 4:96. The enantiomeric excess (98% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : EtOH = 36 : 1; (5*R*,1'*S*) t_R = 11.7 min, (5*S*,1'*R*) t_R = 19.9 min). Absolute configuration was assigned by analogy with compound **3ah**.

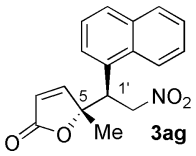
Synthesis of compound **3ae** according to the procedure I (Table 3-2, Entry 4)



3ae

Reaction (reaction time, 0.5 h) gave compound **3ae** in 108 mg (0.39 mmol, 78%) as an oil; $[\alpha]_D^{23}$ −88.2 (*c* 0.1, $CHCl_3$), IR (nujol) 1752, 1161, 1559, 1257cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.32 (s, 3H), 3.81 (s, 3H), 4.65 (d, *J* = 7.5 Hz, 2H), 6.12 (d, *J* = 5.7 Hz, 1H), 6.90 (d, *J* = 8.7, 2H), 7.23-7.27 (m, 3H), 7.39 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 49.7, 55.4, 75.8, 88.9, 114.6, 121.6, 126.2, 130.3, 159.5, 159.9, 171.5; HRMS (FAB+) calcd for $C_{14}H_{16}NO_5$, $(M+H)^+$: 278.1028, found: 278.1030; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 4:96. The enantiomeric excess (94% ee) was determined through chiral HPLC analysis (Daicel AD-H column; flow rate 1.0 mL/min; hexane : EtOH = 25 : 1; (5*R*, 1'*S*) t_R = 40.4 min), (5*S*, 1'*R*) t_R = 57.8 min,. Absolute configuration was assigned by analogy with compound **3ah**.

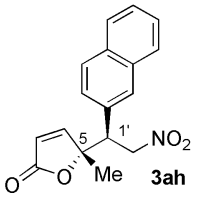
Synthesis of compound **3ag** according to the procedure I (Table 3-2, Entry 6)



3ag

Reaction (reaction time, 2 h) gave 101 mg (0.34 mmol, 68%) of compound **3ag** as a colorless solid; mp 112-114 °C; $[\alpha]_D^{23}$ −13.7 (*c* 0.1, $CHCl_3$), IR (nujol) 1747, 1554, 1459, 1375, 956 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.26 (s, 3H), 4.68-4.85 (m, 3H), 6.06 (d, *J* = 5.7 Hz, 1H), 7.26 (d, *J* = 5.7 Hz, 1H), 7.43-7.58 (m, 3H), 7.75-7.86 (m, 1H), 7.90-7.86 (m, 2H), 8.01 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 42.9, 75.9, 89.1, 120.0, 121.3, 122.5, 125.5, 126.2, 126.4, 127.2, 129.4, 129.5, 130.8, 134.1, 159.7, 171.6; HRMS (FAB+) calcd for $C_{17}H_{16}NO_4$, $(M+H)^+$: 298.1079, found 298.1077. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 5:95. The enantiomeric excess (98% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : *i*-PrOH = 18 : 1; (5*R*,1'*S*) t_R = 37.5 min, (5*S*,1'R*S*) t_R = 68.8 min). Absolute configuration was assigned by analogy with compound **3ah**.

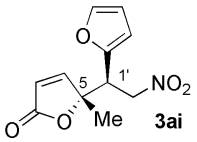
Synthesis of compound **3ah** according to the procedure I (Table 3-2, Entry 7)



3ah

Reaction (reaction time, 2 h) gave 92 mg (0.31 mmol, 62%) of compound **3ah** as a colorless solid: mp 137-140 °C; $[\alpha]_D^{23}$ −105.1 (*c* 0.1, $CHCl_3$), IR (nujol) 1751, 1552, 1375, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.29 (s, 3H), 3.92 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.70 (dd, *J* = 8.4, 5.7 Hz, 2H), 6.00 (d, *J* = 5.7 Hz, 1H), 7.30 -7.52 (m, 4H), 7.67-7.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 50.5, 75.7, 88.8, 121.7, 126.3, 126.8, 127.8, 128.1, 128.8, 129.2, 132.0, 133.2, 133.3, 159.4, 171.5; HRMS (FAB+) calcd for $C_{17}H_{16}NO_4$, $(M+H)^+$: 298.1079, found: 298.1077. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 7:93. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 40 : 1; (5*R*, 1'*S*) t_R = 14.4 min, (5*S*, 1'*R*) t_R = 25.1 min. Absolute configuration was determined by X-ray crystallographic analysis.

Synthesis of compound **3ai** according to the procedure I (Table 3-2, Entry 8)

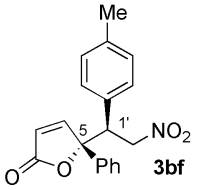


3ai

Reaction (reaction time, 2 h) gave 76 mg (0.32 mmol, 63%) of compound **3ai** as a colorless solid: mp 106-108 °C; $[\alpha]_D^{23}$ +24.6 (*c* 0.1, $CHCl_3$), IR (nujol) 1761, 1559, 1458 1376,

cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.35 (s, 3H), 3.86 (dd, *J* = 8.7, 6.0 Hz, 1H), 4.73 (d, *J* = 1.2 Hz, 1H), 4.75 (d, *J* = 4.2 Hz, 1H), 6.06 (d, *J* = 5.7 Hz, 1H), 6.26 (d, *J* = 3.3 Hz, 1H), 6.32 (dd, *J* = 3.3, 2.1 Hz, 1H), 7.32 (d, *J* = 5.7 Hz, 1H), 7.36 (m, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 22.8, 49.7, 75.5, 88.4, 121.9, 129.5, 130.6, 133.1, 134.9, 159.0, 171.2; HRMS (FAB+) calcd for $C_{11}H_{12}NO_5$ $(M+H)^+$: 238.0715 found: 238.0713; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 6:94. The enantiomeric excess (99% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 50 : 1; (5*R*, 1'*S*) t_R = 27.1 min. Absolute configuration was assigned by analogy with compounds **3ah.**

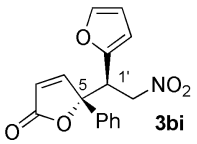
Synthesis of compound **3bf** according to the procedure II (Table 3-2, Entry 10)



3bf

Reaction (reaction time, 12 h) gave 120 mg (0.37 mmol, 74%) of compound **3bf** as a colorless solid; mp 182-185 °C; $[\alpha]_D^{25}$ −103.3 (*c* 0.2, $CHCl_3$), IR (nujol) 1758, 1563, 1457, 1377, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 2.20 (s, 3H), 4.07 (dd, *J* = 8.7, 6.0 Hz, 1H), 4.55 (dd, *J* = 14.1, 8.7 Hz, 1H), 4.76 (dd, *J* = 14.1, 6.0 Hz, 1H), 6.08 (d, *J* = 4.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 7.8 Hz, 2H), 7.02-7.13 (m, 2H), 7.18-7.25 (m. 3H), 7.64 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 51.9, 75.5, 91.4, 121.1, 125.8, 128.7, 128.8, 130.4, 136.0, 138.5, 157.7, 161.5, 170.9; HRMS (FAB+) calcd for $C_{19}H_{18}NO_4$ $(M+H)^+$: 324.1236, found: 324.1232. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 8:92. The enantiomeric excess (99% ee) was determined through chiral HPLC analysis (Daicel AD-3 column; flow rate 1.0 mL/min; hexane : EtOH = 9 : 1; (5*R*, 1'*S)* t_R = 19.0 min. Absolute configuration was assigned by analogy with compound **3ah**.

Synthesis of compound **3bi** according to the procedure II (Table 3-2, Entry 11)

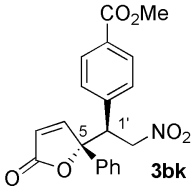


3bi

Reaction (reaction time 2 h) gave 45 mg (0.30 mmol, 60%) of compound **3bi** as a colorless solid; mp 46-48 °C; $[\alpha]_D^{23}$ −82.2 (*c* 0.13, $CHCl_3$), IR (nujol) 1766, 1558, 1459, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 4.23 (dd, *J* = 9.3, 5.1 Hz, 1H), 4.49 (dd, *J* = 13.8, 9.3 Hz, 1H), 4.73 (dd, *J* = 13.8, 5.1 Hz, 1H), 6.03 (d, *J* = 3.3 Hz, 1H), 6.10 (d, *J* = 5.7 Hz, 1H), 6.24 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.02-7.10 (m, 2H), 7.02-7.30 (m, 4H), 7.75 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 43.4, 73.5, 90.1, 110.4, 111.0, 118.1, 121.1, 125.6, 128.9,129.1, 143.0, 147.4, 157.2, 170.6; HRMS (FAB+) calcd for $C_{16}H_{14}NO_5$ $(M+H)^+$: 300.0872, found: 300.0875; ^{1}H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 5:95. The enantiomeric excess (84% ee) was determined through chiral HPLC analysis (Daicel AD-H column; flow rate 1.0 mL/min; hexane : EtOH = 18 : 1; (5*R*, 1'*S*) t_R = 14.9 min, (5*S*, 1'*R*) t_R = 22.1 min). Absolute configuration was assigned by analogy with compound **3ah**.

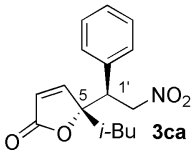
Synthesis of compound **3bk** according to the procedure II (Table 3-2, Entry 12)



3bk

Reaction (reaction time, 12 h) gave 150 mg (0.41 mmol, 82%) of compound **3bk** as a colorless solid; mp 192-194 °C; $[\alpha]_D^{23}$ −124.2 (*c* 0.2, $CHCl_3$), IR (nujol) 1763, 1719, 1554, 1459, 1377, 1283 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 3.81 (s, 3H), 4.22 (dd, *J* = 8.1, 5.7 Hz, 1H), 5.60 (d, *J* = 14.1, 8.1 Hz, 1H), 4.77 (dd, *J* = 14.1, 6.01 Hz, 1H), 6.11 (d, *J* = 5.0 Hz, 1H), 7.07- 7.43 (m, 4H), 7.15-7.20 (m, 3H), 7.67 (d, *J* = 5.0 Hz, 1H), 7.76-7.90 (m, 2H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 51.7, 52.3, 75.0, 91.0, 121.1, 125.4, 129.0, 129.6, 129.8, 130.3, 136.0, 138.9, 157.3, 166.5, 170.7; HRMS (FAB+) calcd for $C_{20}H_{18}NO_6$ $(M+H)^+$: 368.1134, found: 368.1132; ^{1}H NMR analysis of the crude products indicated *syn*:*anti* ratio was 10:90. The enantiomeric excess (88% ee) was determined through chiral HPLC analysis (Daicel AD-H column; flow rate 0.5 mL/min; hexane : EtOH = 45 : 1; (5*R*, 1'*S*) t_R = 30.0 min, (5*S*, 1'*R*) t_R = 33.8 min). Absolute configuration was assigned by analogy with compound **3ah**.

Synthesis of compound **3ca** according to the procedure I (Table 3-2, Entry 13)

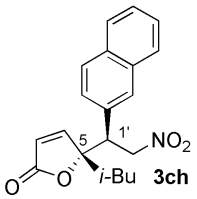


3ca

Reaction (reaction time, 12 h) gave 101 mg (0.35 mmol, 70%) of compound **3ca** as a colorless solid; mp 92-94 °C; $[\alpha]_D^{23}$ −65.5 (*c* 0.1, $CHCl_3$), IR (nujol) 1743, 1552, 1457, 1377, 1260 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 0.71 (dd, *J* = 6.3, 3.9 Hz, 6H), 1.29-1.36 (m, 1H), 1.43-1.57 (m, 2H), 1.50 (d, *J* = 12.3 Hz, 1H), 1.53 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 7.2 Hz, 2H), 6.25 (d, *J* = 5.7 Hz, 1H), 7.20-7.33 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 23.8, 24.7, 43.6, 50.7, 75.8, 91.5, 122.7, 128.8, 129.2, 129.4, 134.7, 158.2, 171.7; HRMS (FAB+) calcd for $C_{16}H_{20}NO_4$ $(M+H)^+$: 290.1392, found: 290.1395. ^{1}H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 8:92. The enantiomeric excess (94% ee) was

determined through chiral HPLC analysis (Daicel AD-H column; flow rate 0.5 mL/min; hexane : EtOH = 63 : 1; (5*R*, 1'*S*) t_R = 12.6 min. Absolute configuration was assigned by analogy with compound **3ah**.

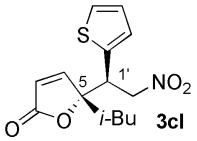
Synthesis of compound **3ch** according to the procedure I (Table 3-2, Entry 14)



3ch

Reaction (reaction time; 12 h) gave 102mg (0.30 mmol, 60%) of compound **3ch** as a colorless solid; mp 121-124 °C; $[\alpha]_D^{26}$ −83.7 (*c* 0.15, $CHCl_3$), IR (nujol) 1747, 1552, 1455, 1375 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.69 (dd, *J* = 6.6, 4.8 Hz, 6H), 1.90 (m, 1H), 1.48 (s, 2H), 3.93 (t, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 8.1 Hz, 2H), 6.16(d, *J* = 5.7 Hz, 1H), 7.30-7.50 (m, 3H), 7.70 (br s, 1H), 7.76-7.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 23.8, 24.7, 43.7, 50.8, 75.8, 91.7, 122.7, 126.5, 126.8, 126.9, 127.8, 128.0, 128.1, 129.0, 129.2, 132.2, 133.2, 133.3, 158.2, 171.8; HRMS (FAB+) calcd for $C_{20}H_{22}NO_4$, $(M+H)^+$: 340.1549, found: 340.1547; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 10:90. The enantiomeric excess (98% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : EtOH = 54 : 1; (5*R*, 1'*S*) t_R = 15.2 min, (5*S*, 1'*R*) t_R = 22.5 min). Absolute configuration was assigned by analogy with compound **3ah**.

Synthesis of compound **3cl** according to the procedure (I) (Table 3-2, Entry 15)



3cl

Reaction conditions (II) (reaction time: 12 h) gave 89 mg (0.30 mmol, 60%) of compound **3cl** as a colorless solid; mp 100-102 °C; $[\alpha]_D^{26}$ −84.7 (*c* 0.1, $CHCl_3$), IR (nujol) 1748, 1557, 1459, 1377, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.76 (dd, *J* = 6.6, 4.8 Hz, 6H), 1.33-1.42 (m, 1H), 1.58 (dd, *J* = 14.7, 6.6 Hz, 1H), 1.68 (dd, *J* = 14.7, 5.4 Hz, 1H), 4.08 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.49 (dd, *J* = 13.5, 8.1 Hz, 1H), 4.59 (dd, *J* = 13.5, 6.0 Hz, 1H), 6.13(d, *J* = 5.7 Hz, 1H), 6.92-6.99 (m, 2H), 7.24-7.26 (m, 1H), 7,33 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6,23.8, 224.6, 43.1, 46.4, 76.4, 91.1, 122.8, 126.6, 127.3, 128.5, 136.1, 157.7, 171.4; HRMS (FAB+) calcd for $C_{14}H_{18}NO_4S$, $(M+H)^+$: 296.0957, found: 296.0953; ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was 12:88. The enantiomeric excess (99% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : EtOH = 72 : 1; (5*R*,1'*S*) t_R = 26.8 min. Absolute configuration was

assigned by analogy with compound **3ah**.

3.5.4 Computational data

(a) Optimized Structure of (2*R*)-nitroammonium **9** (B3LYP/6-31G(d)) (Fig. 3-1)

DFT THRESHOLD =.493E-08

TOTAL ENERGY = -1512.0382547300

COORDINATES OF ALL ATOMS ARE (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	-0.2902039495	-1.2571441307	0.3286294643
N	7.0	-1.8391817450	-1.3137673912	0.0783503322
C	6.0	-2.1131269657	-1.8607542989	-1.3245032474
C	6.0	0.2630791650	-2.7089316759	0.2966349472
C	6.0	-1.3142868009	-3.1574750188	-1.5743683531
C	6.0	-0.7857822932	-3.6887980404	-0.2362126455
C	6.0	-2.4149500307	-2.3225619739	1.0800936203
C	6.0	-1.9484675130	-3.7568011210	0.7584094831
C	6.0	-2.5990071972	0.4957063353	1.7702841837
C	6.0	0.4123341549	-0.2143155530	-0.5991631378
C	6.0	1.8253634227	-0.5744083893	-1.0412049685
C	6.0	2.0526750567	-0.7821662302	-2.3872639136
C	6.0	3.3465451590	-1.1306828016	-2.8497859055
N	7.0	4.3829585237	-1.2756810657	-2.0513037848
C	6.0	4.1961607840	-1.0675464602	-0.7167074583
C	6.0	2.9322857777	-0.6988439241	-0.1414839254
C	6.0	2.8433530090	-0.4944922762	1.2566785739
C	6.0	3.9553111559	-0.6732805144	2.0609614633
C	6.0	5.2038602827	-1.0486473327	1.4970681089
C	6.0	5.3173390490	-1.2302811180	0.1403911956
O	8.0	3.7999752730	-0.4742112813	3.3955939760
C	6.0	0.2735233481	3.4277643047	-0.2575296128
C	6.0	0.4947685407	4.1831385484	0.8972514480
C	6.0	-0.6105123661	3.9141516900	-1.2297765001
C	6.0	-0.1528560869	5.4048913343	1.0824733785
C	6.0	-1.2599862936	5.1358225092	-1.0509676336
C	6.0	-1.0321382919	5.8804647260	0.1090278453
C	6.0	1.0257618387	2.1440659786	-0.4801694193

O	8.0	0.3118392743	1.0217215800	0.1116707340
C	6.0	-2.4771468876	0.0977348002	0.2950183462
C	6.0	-3.7902997431	0.3368446206	-0.4744701121
N	7.0	-4.9732074591	-0.4329770964	0.0610961600
O	8.0	-5.5668665548	0.0503207108	1.0152387707
H	1.0	-0.2151937411	-0.8570481892	1.3394843045
H	1.0	-1.8670109749	-1.0826097078	-2.0460491209
H	1.0	-3.1867444997	-2.0447081472	-1.3660384129
H	1.0	0.5770436929	-2.9971720780	1.3055898838
H	1.0	1.1549714422	-2.7423313909	-0.3311960641
H	1.0	-0.4853904324	-2.9789152824	-2.2658632463
H	1.0	-1.9731368457	-3.8916881434	-2.0471850268
H	1.0	-0.3383557282	-4.6754564368	-0.3725865357
H	1.0	-3.4977028540	-2.2379841101	1.0335685518
H	1.0	-2.0777160580	-1.9930278678	2.0607303880
H	1.0	-2.7767861668	-4.3417817884	0.3470451607
H	1.0	-1.6353981487	-4.2431825851	1.6866608170
H	1.0	-2.9201357349	1.5419026255	1.7979514643
H	1.0	-1.6367850136	0.4550488114	2.2901410651
H	1.0	-3.3407528429	-0.0844621491	2.3235032737
H	1.0	-0.1582844417	-0.1252286367	-1.5359721473
H	1.0	1.2488204724	-0.6699057674	-3.1120263377
H	1.0	3.5146383685	-1.2919242436	-3.9135306118
H	1.0	1.9219486303	-0.1580139170	1.7193063900
H	1.0	6.0706531093	-1.1839139475	2.1440160674
H	1.0	6.2626224466	-1.5042114221	-0.3150629014
H	1.0	4.6506466178	-0.5801141913	3.8512549876
H	1.0	1.2024925498	3.8236036139	1.6438903037
H	1.0	-0.7619712736	3.3516248477	-2.1513409501
H	1.0	0.0502147304	5.9982031004	1.9709879513
H	1.0	-1.9177374712	5.5201705834	-1.8261747479
H	1.0	-1.5288646709	6.8374909594	0.2446920045
H	1.0	2.0134550603	2.1835813253	-0.0064849171
H	1.0	1.1701965766	1.9627289494	-1.5509800561
H	1.0	-1.7600329977	0.7832422493	-0.1574848445
H	1.0	-4.0441417907	1.3883473562	-0.3407889075
H	1.0	-3.7184928464	0.1094107170	-1.5358621135

O	8.0	-5.2309542219	-1.5131298080	-0.4747616405

(b) *re*-face adduct **7** (B3LYP/6-31G(d)) (Fig. 3-1)
DFT THRESHOLD = 0.501E-08
TOTAL ENERGY = -1512.6505028092
COORDINATES OF ALL ATOMS ARE (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	1.3218165354	-1.3626542579	-0.4918792809
N	7.0	0.5768976785	-2.6261941010	-0.2625915288
C	6.0	0.2988843645	-3.3363864665	-1.5272802305
C	6.0	2.7133659957	-1.6677702917	-1.1519502670
C	6.0	1.5940478964	-3.5324495705	-2.3754064876
C	6.0	2.7948332604	-3.1737696876	-1.4743878616
C	6.0	1.4174976534	-3.4969032048	0.5869206182
C	6.0	2.6926315856	-3.9868514386	-0.1681747494
H	1.0	3.5892205353	-3.8472494737	0.4487891643
C	6.0	-2.6650783937	-2.7464479680	0.9092413620
C	6.0	0.5236766021	-0.3406532484	-1.3365368798
C	6.0	1.2694466939	0.9829152274	-1.5271403560
C	6.0	1.7307619512	1.3000424423	-2.7918564126
C	6.0	2.4687030511	2.4821682823	-3.0152463901
N	7.0	2.7574343299	3.3470854534	-2.0648542450
C	6.0	2.3013278871	3.0806333037	-0.8093889507
C	6.0	1.5313468774	1.9137053285	-0.4668520352
C	6.0	1.0868228961	1.7596704655	0.8769153222
C	6.0	1.4247970081	2.6932414863	1.8431630262
C	6.0	2.1976772969	3.8367964160	1.4980542352
C	6.0	2.6145970268	4.0247496297	0.2073946872
O	8.0	1.0663720668	2.6123127585	3.1458178828
C	6.0	-3.0203926363	0.7180879872	-1.0998706978
C	6.0	-3.2116191457	1.4316531903	0.0939770280
C	6.0	-4.1397839928	0.2359741952	-1.7855763714
C	6.0	-4.4986585163	1.6574460216	0.5818267433
C	6.0	-5.4305026398	0.4719905280	-1.3061327290
C	6.0	-5.6117564166	1.1863067715	-0.1208263778
H	1.0	-2.3471107698	1.8242142098	0.6256042782

H	1.0	-6.6143958146	1.3869850322	0.2476448186
H	1.0	-4.0002813776	-0.3177271655	-2.7135289966
H	1.0	1.4736782397	-0.9289356781	0.4998140396
H	1.0	-0.1323936789	-4.3083804914	-1.2569442854
H	1.0	-0.4770575334	-2.7946858089	-2.0790783162
H	1.0	3.5290575449	-1.3674593270	-0.4844182910
H	1.0	2.8420012309	-1.0929374530	-2.0756924069
H	1.0	1.6689958392	-4.5652870445	-2.7413629119
H	1.0	1.5914743347	-2.8807774760	-3.2589852963
H	1.0	3.7394686859	-3.3888708831	-1.9891072402
H	1.0	0.8031942535	-4.3430585450	0.9222167692
H	1.0	1.6844804490	-2.9237695132	1.4820307737
H	1.0	2.6285319175	-5.0570677764	-0.4024733200
H	1.0	-3.6176420892	-2.9975918206	1.3988755659
H	1.0	-2.3372698820	-3.6215316505	0.3426285283
H	1.0	-2.8444484160	-1.9223491541	0.2142297682
H	1.0	0.4008548591	-0.7745747323	-2.3416297422
H	1.0	1.5379844702	0.6292913819	-3.6244560894
H	1.0	2.8343186306	2.7114748622	-4.0154853728
H	1.0	0.4592164888	0.9164093177	1.1376910933
H	1.0	2.4387361432	4.5440618597	2.2850391664
H	1.0	3.1939846992	4.8968376848	-0.0834771243
H	1.0	0.5754212674	1.7872952661	3.3379880450
H	1.0	-4.6377846064	2.2194119287	1.5026830293
H	1.0	-6.2894503377	0.1039422886	-1.8600558742
C	6.0	-1.6408769655	0.5389681789	-1.6852876603
O	8.0	-0.7798740936	-0.1563266354	-0.7795775584
H	1.0	-1.7107790262	-0.0234609756	-2.6297673524
H	1.0	-1.2131082591	1.5223446092	-1.9246806942
C	6.0	-1.6492058171	-2.3634283978	1.9394973704
C	6.0	-1.5708625906	-1.1337176762	2.4563611171
H	1.0	-0.9661929866	-3.1200614653	2.3166256191
N	7.0	-0.5743349792	-0.7904885817	3.4379010382
H	1.0	-2.1690012258	-0.2818239918	2.1687604593
O	8.0	0.2121998584	-1.6372410351	3.8564860182
O	8.0	-0.5750165862	0.4010667301	3.8101946536

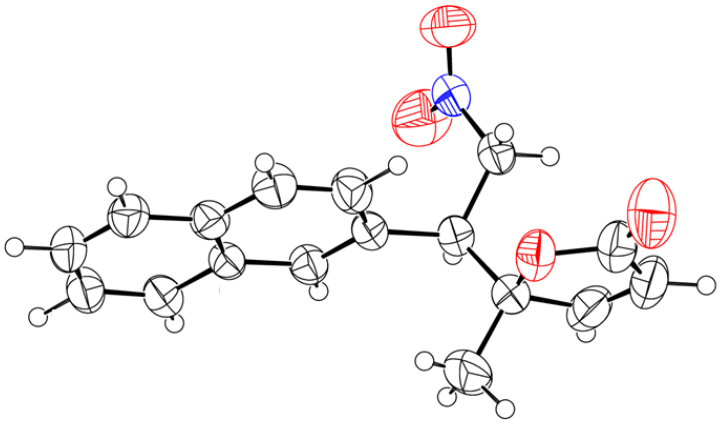
(c) *si*-face adduct **8** (B3LYP/6-31G(d)) (Fig. 3-1)
DFT THRESHOLD = 0.493E-08
TOTAL ENERGY = -1511.046059668

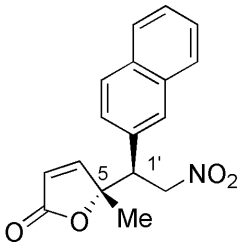
COORDINATES OF ALL ATOMS (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	0.3620581348	-1.6150717460	-0.1319885439
H	1.0	-4.2512443500	-1.2364814182	0.9220906897
N	7.0	-1.0216726278	-2.3455542952	0.0777931199
H	1.0	-3.7688856784	-2.9232231254	0.7510125820
C	6.0	-1.4853738411	-2.8512966311	-1.2897036309
H	1.0	-2.0484537915	-2.2473447034	2.8154870029
H	1.0	0.7561313015	-5.0943678695	0.9094647603
C	6.0	1.4111325951	-2.7142078753	-0.4694023800
H	1.0	-3.7797724747	-1.8253848392	-0.6534133836
C	6.0	-0.3483171975	-3.6199951853	-2.0022715386
C	6.0	0.7266430270	-3.9954997759	-0.9717102881
C	6.0	-3.5519781441	-1.9049460391	0.4110955521
C	6.0	-0.7734907391	-3.5755695114	0.9635102342
C	6.0	0.0269146014	-4.6610846437	0.2180186504
C	6.0	0.3450070920	-0.4796090374	-1.2084437949
C	6.0	1.7294731538	0.1520932725	-1.3628153389
C	6.0	2.4098292415	-0.0214629730	-2.5541555808
C	6.0	3.7188538521	0.4928860474	-2.7058985765
N	7.0	4.3596975960	1.1343707478	-1.7500952027
C	6.0	3.7120295636	1.3450905636	-0.5741135948
C	6.0	2.3659491766	0.9006252268	-0.3237596819
C	6.0	1.7583789179	1.2229917796	0.9144673278
C	6.0	2.4678865317	1.8942872219	1.8949828412
C	6.0	3.8086015211	2.3103907258	1.6610460795
C	6.0	4.4034907929	2.0474369884	0.4527293482
O	8.0	1.9364664079	2.1967088031	3.1035355204
C	6.0	-2.1151722865	2.2882413730	-1.3316892368
C	6.0	-2.1524001178	2.9986314797	-0.1216025088
C	6.0	-3.2637446328	2.2456275448	-2.1317859077
C	6.0	-3.3194599699	3.6475011265	0.2794503734

C	6.0	-4.4298399092	2.9044085543	-1.7372724695
C	6.0	-4.4594448008	3.6037370828	-0.5294712904
H	1.0	-1.2638575266	3.0464304836	0.5040671521
H	1.0	-5.3634338234	4.1205488629	-0.2215631521
H	1.0	-3.2427112121	1.7070611393	-3.0774786370
H	1.0	0.5897368456	-1.1712123333	0.8328763074
H	1.0	-2.3365986744	-3.5028493033	-1.0997526430
H	1.0	-1.8305504581	-1.9856341985	-1.8563063096
H	1.0	2.0137405803	-2.9317327588	0.4185592608
H	1.0	2.0970915019	-2.3254226343	-1.2234481452
H	1.0	-0.7700974445	-4.5184810514	-2.4629727623
H	1.0	0.0851452595	-3.0196397271	-2.8081446996
H	1.0	1.4637618047	-4.6692370159	-1.4170205268
H	1.0	-1.7543158462	-3.9399880782	1.2778958999
H	1.0	-0.2350697927	-3.2111390999	1.8378858115
H	1.0	-0.6268934917	-5.4746099470	-0.1147956303
H	1.0	0.0966989742	-0.9205583822	-2.1854695512
H	1.0	1.9538662863	-0.5581901606	-3.3830883741
H	1.0	4.2488798148	0.3550941457	-3.6483821988
H	1.0	0.7123830467	0.9978605819	1.0746721054
H	1.0	4.3307555224	2.8421969186	2.4488352151
H	1.0	5.4205057578	2.3672857891	0.2415115118
H	1.0	1.0557650866	1.7880445208	3.1796140059
H	1.0	-3.3373753319	4.1958712976	1.2178823430
H	1.0	-5.3095939006	2.8743166112	-2.3751752520
C	6.0	-0.8631774183	1.5635283630	-1.7509334614
O	8.0	-0.6759323518	0.4426019661	-0.8501231732
H	1.0	-0.9532058562	1.1868573769	-2.7789738063
H	1.0	0.0218022263	2.2067731211	-1.6979012367
C	6.0	-2.1234145403	-1.4367468438	0.7372166751
C	6.0	-2.0330059869	-1.3017116836	2.2741289476
H	1.0	-1.9614507096	-0.4587500049	0.2875502403
N	7.0	-0.8322419906	-0.5457410739	2.7925750878
H	1.0	-2.8831264892	-0.6931804652	2.5821000589
O	8.0	-0.9151608589	0.6799142516	2.8114676137
O	8.0	0.1441646213	-1.1961715455	3.1539237266

3.5.5 X-ray structure of (5*R*, 1'*S*)-3ah





(5*R*, 1'*S*)-3ah

3.5.6 References

(1) Mandel, T.; Zhao, C. -G. *Angew. Chem., Int. Ed*. **2008**, *47*, 7714.

(2) He, P.; Liu, X.; Shi, J.; Lin, L.; Feng, X. *Org. Lett*. **2011**, *13*, 936.

(3) (a) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829.; (b) Xia, X. -Z.; Shu, K.; Ji, Y. -F.; Yang, A.; Shaukat, X. -Y.; Liang, Y. -M. *J. Org. Chem*. **2010**, *75*, 2893.; (c) Bassas, O.; Huuskonen, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem*. **2009**, 1340.

(4) Marshall, J. A.; Wolf, M. A.; Wallence, E. M. *J. Org. Chem*., **1997**, *62*, 367.

(5) Yang, Y.; Li, Z.; Xiong, T. ; Zhao, J. ; Meng, Q. *Synlett* **2014**, *25*, 2155.

(6) Liang, M.; Li, Z.; Du, J.; Gao, Z. *Eur. J. Org. Chem*., **2010**, 6525.

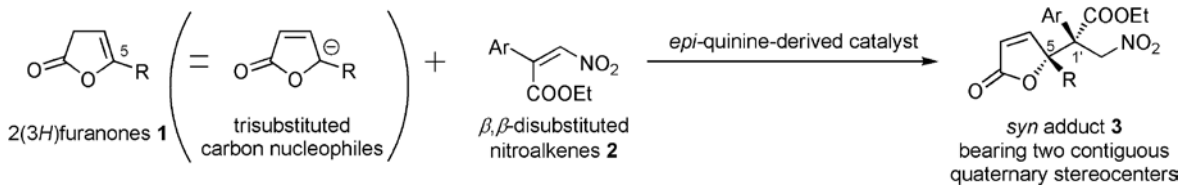
Chapter 4

Syn-Selective Nitro-Michael Addition of Furanones to β,β-Disubstituted Nitroalkenes Catalyzed by *Epi*-Quinine Derivatives

4.1 Introduction

Quaternary carbon stereogenic centers exist widely in natural products and biologically active compounds.[1] Catalytic enantioselective construction of all-*carbon* quaternary stereogenic center is one of the most important subjects in organic synthesis.[2] Among the various strategies for constructing the enantiomerically enriched quaternary carbon centers, the catalytic asymmetric Michael addition of carbon nucleophiles to *β,β*-disubstituted nitroalkenes is a most simple and straightforward method for constructing an all-*carbon* quaternary stereogenic center. However, only a handful studies are available dealing this reaction.[3] The significant steric repulsion between incoming carbon nucleophiles and *β,β*-disubstituted nitroalkenes seems to be the reason for the difficulty of the nitro-Michael reaction of *β,β*-disubstituted nitroalkenes.

The author describes herein the *epi*-quinine catalyzed asymmetric Michael addition of 5-substituted 2(3*H*)-furanones **1** to *β,β*-disubstituted nitroalkenes **2**; this reaction is highly effective in constructing the sterically congested all-*carbon* quaternary stereogenic centers adjacent to oxygen-containing quaternary stereogenic center (Scheme 4-1).[4] To the best of the author's knowledge, catalytic asymmetric conjugate addition of trisubstituted carbon nucleophiles to *β,β*-disubstituted nitroalkene is very rare.



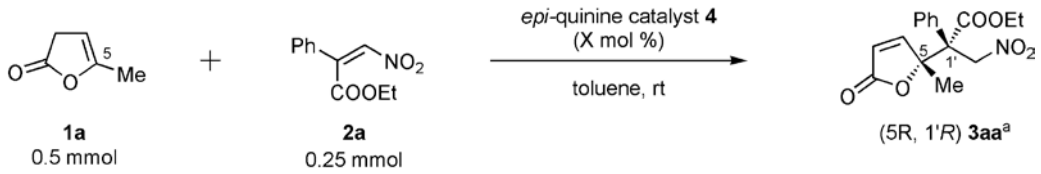
Scheme 4-1. Asymmetric nitro-Michael addition of furanones to *β,β*-disubstituted nitroalkenes

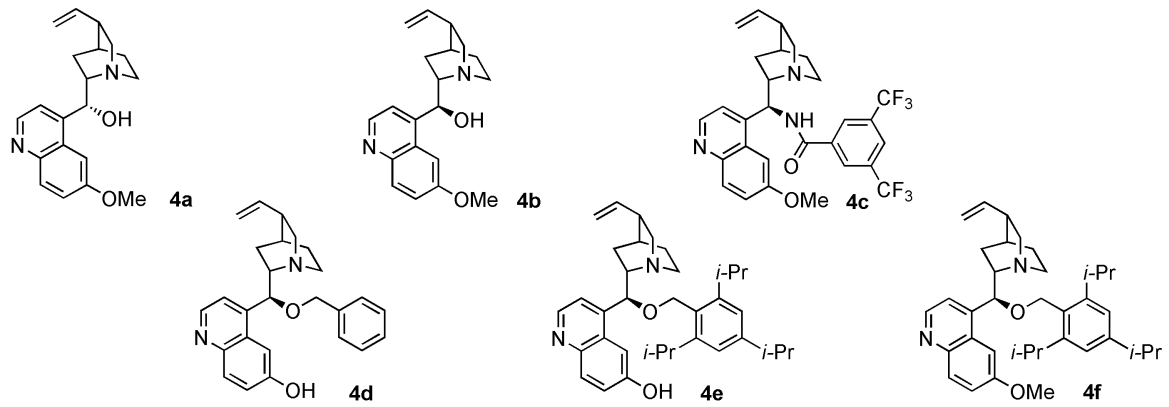
4.2 Results and Discussion

4.2.1 Catalyst scope

With the purpose of evaluating the catalytic activity of a series of *epi*-quinine derivatives, the catalytic asymmetric Michael addition of angelica lactone **1a** to (*Z*)-1-phenyl-2-nitroacrylate **2a** was examined at 10 mol % loading of *epi*-quinines at room temperature. Solvent screening indicated that toluene is the solvent of choice. As shown in Table 4-1, *epi*-quinine-derived catalysts **4** are capable of promoting the Michael addition of angelica lactone **1a** to 1-phenyl-2-nitroacrylate **2a**, affording the Michael adduct **3aa** with *syn*-selectivity. For example, with a 10 mol % loading of quinine **4a**, the corresponding Michael adduct **3aa** was obtained in moderate yield (67% yield), while diastereo- and enantioselectivity was very low (76:24 dr, *syn* major; 27% ee (*syn*)) (entry 1). Catalyst **4b**[5] showed no improvement of the catalytic activity (entry 2). To our surprise, amide catalyst **4c**[4a]

Table 4-1. Catalytic asymmetric nitro-Michael reaction of **1a** to **2a** [a, b]





entry	catalyst	X [mol %]	Time [h]	Yield [%][c]	*syn*/*anti*[d]	ee [%][e]
1	4a	10	17	67	76/24	27
2	4b	10	24	68	83/17	-11
3	4c	10	30	65	51/47	24
4	4d	10	17	65	>98/2	90
5	4e	10	16	88	>98/2	91
6	4f	10	17	57	95/5	16
7 [f]	4e	5	24	93	>98/2	98

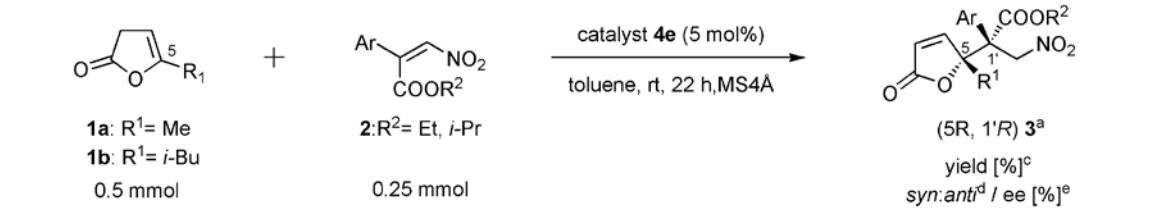
[a] Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3). [b] Reaction of **1a** (0.5 mmol) with **2a** (0.25 mmol) was conducted with 10 mol % loading of **4** at room temperature otherwise noted. [c] Isolated yield. [d] Diastereoselectivity was determined by ^{1}H NMR analysis of the crude product. [e] Obtained by chiral HPLC analysis. [f] Reaction was conducted in the presence of MS 4 Å (50 mg).

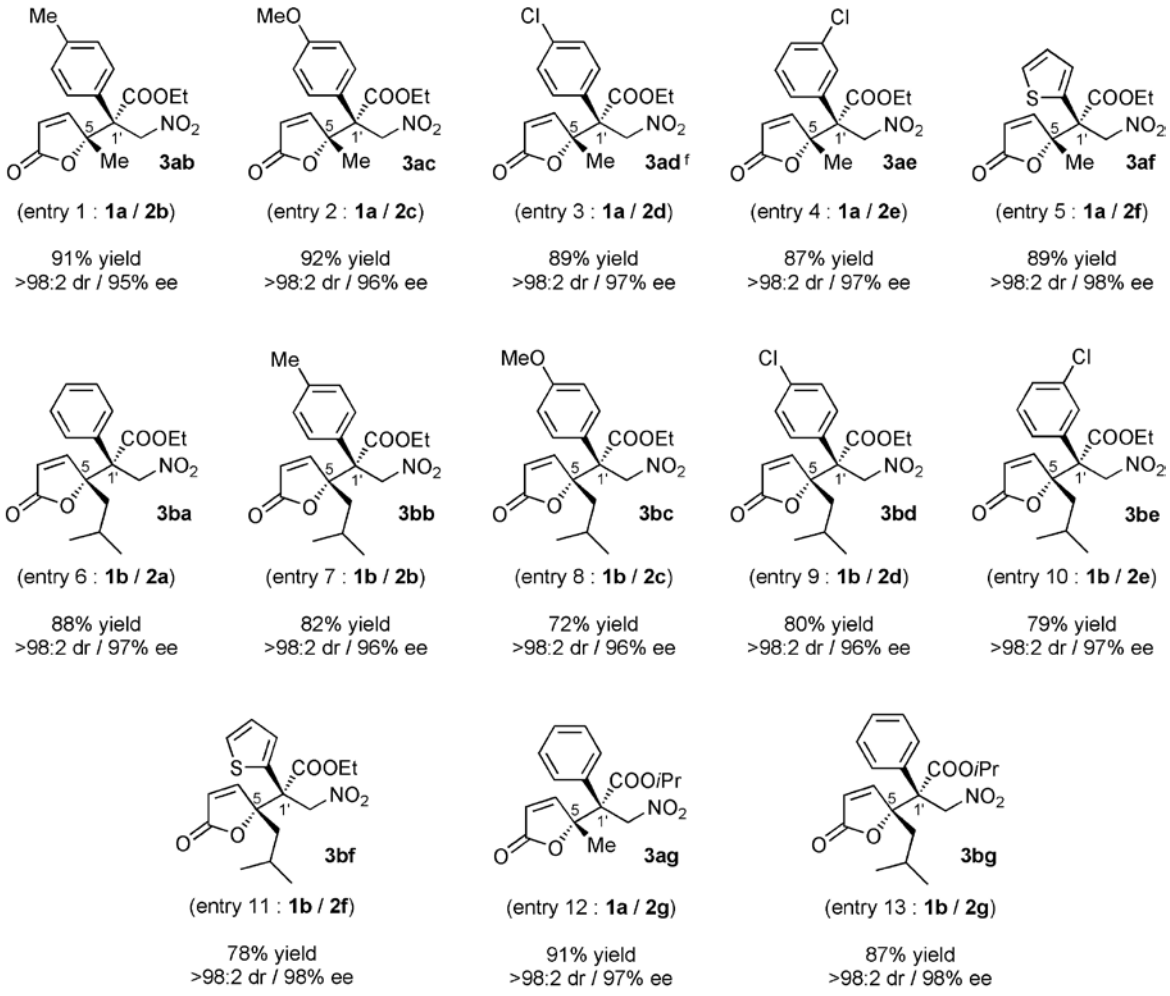
exhibited very low diastereoselectivity (53:47 dr) (entry 3), although the nitro-Michael addition of furanones to *β*-nitrostyrene catalyzed by **4c** gave the Michael adduct with extremely high *syn*-selectivity (> 98:2 dr).[4a] A significant improvement of the diastereo- and enantioselectivity has been attained upon the employment of *epi*-quinine derivatives **4d** and **4e** (entries 4 and 5). A 10 mol % loading of **4e** successfully catalyzed the Michael addition of **1a** to **2a**, affording the Michael adduct **3aa** in 88% yield with high diastereo- and enantioselectivity (> 98:2 dr; *syn* major; 91% ee) (entry 5). In contrast, the replacement of 6'-OH of **4e** with 6'-OMe (**4f**) profoundly depresses the effectiveness of the catalyst (95:5 dr, *syn* major; 16% ee) (entry 6). These results conclusively revealed that 6'-OH of *epi*-quinine derivatives **4d** and **4e** are essential for the high asymmetric induction. To the author's delight,

the addition of MS 4Å to the reaction mixture considerably reduced the catalyst loading as low as 5 mol % without affecting the high diastereo- and enantioselectivity (> 98:2 dr, *syn* major; 98% ee) (entry 7).

4.2.2 Substrate scope

Table 4-2. Catalytic asymmetric nitro-Michael addition of furanones **1** to *β*,*β*-disubstituted nitroalkenes **2**[a, b]





[a] Absolute configuration was assigned by analogy with compound **3ad** (entry 3). [b] Reaction of **1** (0.5 mmol) with **2** (0.25 mmol) was conducted with 5 mol % loading of **4e** at room temperature for 22 h otherwise noted. [c] Isolated yield. [d] Diastereoselectivity was determined by ^{1}H NMR analysis of the crude product. [e] Obtained by chiral HPLC analysis. [f] Absolute configuration of **3ad** was determined by X-ray crystallographic analysis.

The author then turned out our attention to the substrate scope of the *syn*-selective nitro-Michael reaction catalyzed by **4e** (Table 4-2). Table 4-2 shows that 5 mol % loading of catalyst **4e** allowed complete conversion of the *β,β*–disubstituted nitroalkenes **2** in toluene at room temperature, giving the corresponding Michael adducts **3** in good yields (72-93%) with the extremely high diastereo- and enantioselectivities (> 98:2 dr, *syn* major; 96-99% ee) (entries 1 to 14). The absolute configuration of **3ad** was unambiguously determined by X-ray crystallographic analysis to be (5*R*, 1'*R*) (Figure 4-1).[6] The configuration of other Michael adducts **3** was assigned by analogy. (*Z*)-1-Aryl-2-nitroacrylate **2** bearing electron-withdrawing

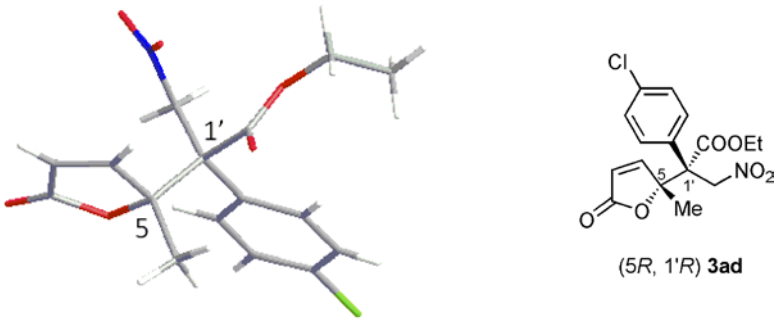
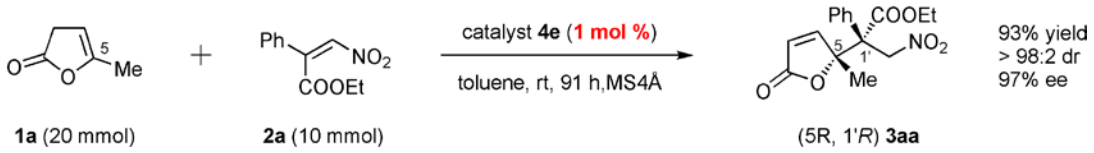


Figure 4-1. X-ray structure of compound **3ad**

and electron-releasing substituents on the aromatic ring smoothly reacted with angelica lactone **1a**, affording **3ab** (91% yield; 95% ee), **3ac** (92% yield; 96% ee), **3ad** (89% yield; 97% ee), and **3ae** (87% yield; 97% ee) (entries 1 to 4). Thus, electronic properties of substituents on the aromatic ring of Michael acceptors **2** have no effect on the reaction. Substitution pattern in the aromatic rings had no deleterious effect on the diastereo- and enantioselectivity (entries 3, 4, 9 and 10). Furthermore, the Michael additions of sterically demanding 5-isobutylfuranone **1b** to 1-aryl-2-nitroacrylates **2a**, **2b**, **2c**, **2d**, and **2e** smoothly proceeded, giving the *syn*-adducts **3ba** (97% ee), **3bb** (99% ee) , **3bc** (96% ee), **3bd** (96% ee) and **3be** (98% ee) in high yields (79-82%) (entries 6 to 10). The reaction of the heteroaryl substituted Michael acceptor **2f** with the Michael donor **1a** and **1b** also successfully took place to furnish the corresponding adducts **3af** (98% ee) and **3bf** (98% ee) in good yields (entries 5 and 11). Furthermore, the nitroalkene **2g** bearing sterically demanding COO-*i*-Pr substituent also smoothly underwent the **4e**-catalyzed Michael reaction with furanone **1a** and **1b**, furnishing the corresponding Michael adduct **3ag** and **3bg** in high yields (91% and 87% yield, respectively) with very high diastereo- and enantioselectivities (> 98:2 dr, *syn* major; 97% ee and 98% ee, respectively) (entries 12 and 13). These results displayed that steric bulk of the Michael donor **1** and Michael acceptor **2** had no effect on the yield as well as the diastereo- and enantioselectivity. We examined the large scale reaction to establish the practical reaction conditions. When the reaction of **1a** (20 mmol) and **2a** (10 mmol) was

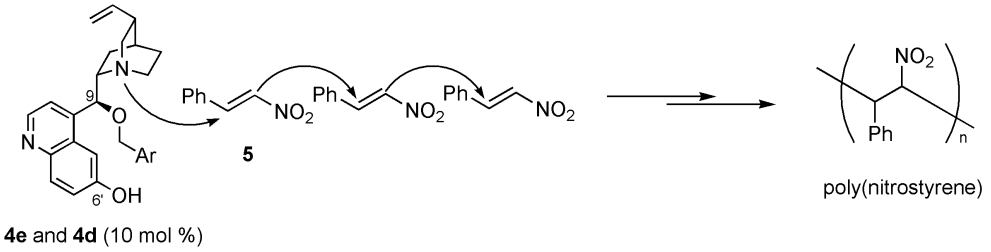
conducted at room temperature, it has been found that the catalyst loading could be reduced to only 1 mol % without affecting the high diastereo- and enantioselectivity as well as the high yield of the Michael adduct **3aa** (> 98:2 dr; 97% ee; 93% yield; TON = 93) (Scheme 4-2). Thus, the present method is especially useful for constructing the sterically congested all-*carbon* quaternary stereogenic centers adjacent to oxygen-containing quaternary stereogenic centers with extremely high diastereo- and enantioselectivity.



Scheme 4-2. Large scale reaction of **1a** to **2a**

4.2.3 Discussion of the mechanism

Organocatalytic asymmetric C-C bond forming reactions that afford acyclic compounds with all-*carbon* quaternary stereogenic center continues to be developing.[1] The present method is potentially promising for constructing other types of vicinal quaternary stereogenic centers involving quaternary all-*carbon* stereogenic centers. It is noteworthy that with a 10 mol % loading of **4d** and **4e**, the polymerization of (*E*)-*β*-nitrostyrene **5** proceeded in toluene at room temperature (Scheme 4-3). The reaction furnished poly(nitrostyrene) as an insoluble material, whose structure was determined by elementary analysis. In contrast, catalytic amount of **4a**, **4b**, **4c** and **4f** failed to promote the polymerization of nitrostyrene **5**, suggesting that the 6'-OH of **4e** and **4d** plays an important role in activating the nitroalkenes.

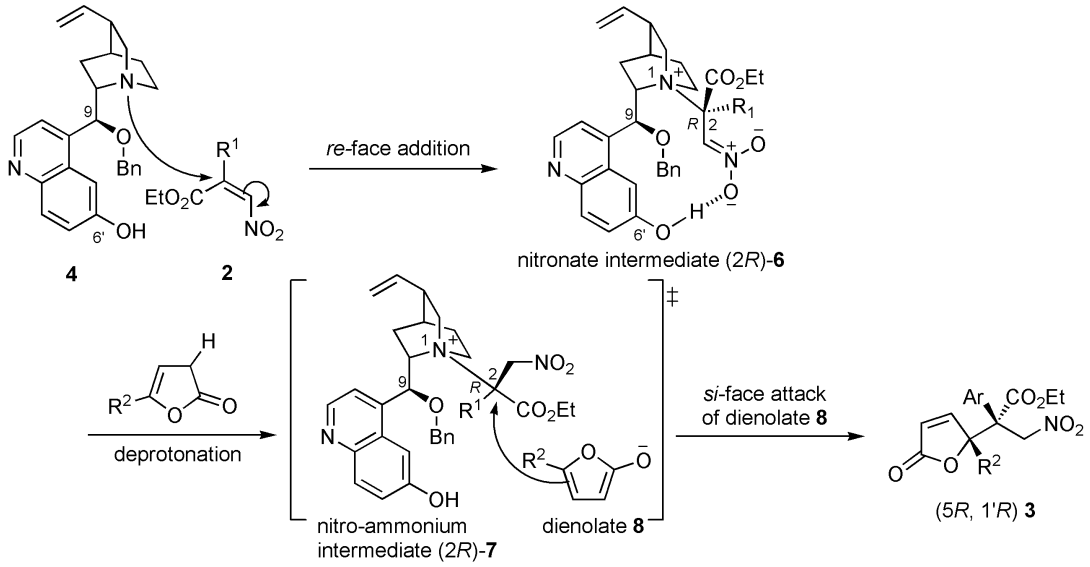


Scheme 4-3. Polymerization of *β*-nitrostyrene **5** promoted by **4e** and **4d**.

Based on this result, the author has made an assumption that the quinuclidine nitrogen N(1) of *epi*-quinine-derived catalysts **4e** and **4d** would undergo the conjugate addition to the *re*-face of *β,β*-disubstituted nitroalkenes **2**, giving nitronate intermediate (2*R*)-**6** (Scheme 4-4). Protonation of **6** with furanone **1** affords nitro-ammonium intermediate (2*R*)-**7**. Subsequently, nucleophilic attack of dienolate **8** to intermediate (2*R*)-**7** takes place from the *si*-face of **8** to furnish the Michael adduct (5*R*, 1'*R*)-**3**. Thus, the extremely high diastereo- and enantioselectivity of the nitro-Michael reaction catalyzed by **4e** would result from the

addition-elimination mechanism depicted in Scheme 4-4. However the ^{13}C NMR spectra of the mixture of **4e** and 1-phenyl-2-nitroacrylate **2a** (**4e** : **2a** = 1 : 2, in C_6D_6) indicated that δ (^{13}C) of the β-carbon of **2a** did not shift upon the addition of **4e**, indicating the very weak interaction between the quinuclidine N(1) of **4e** and nitrostyrene **2a**.

In order to reveal the role of 6'-OH group of *epi*-quinine-derived catalysts **4d** and **4e**, the author carried out theoretical calculations (Figure 4-2). The simplified structure of nitronate intermediate (2*R*)-**6** was optimized at B3LYP/6-31G(d). The results of the calculations are wholly surprising. The structure of optimized intermediate (2*R*)-**6** discloses the very weak interaction between the quinuclidine N(1) and nitroalkene as indicated by the very long N(1)-C(2) bond length (3.47 Å), but an intramolecular hydrogen-bonding between 6'-OH and nitronate oxygen seems to stabilize the intermediate (2*R*)-**6**, supporting the essential role of 6'-OH in promoting the conjugate addition of N(1) to the *re*-face of nitroalkene. The long N(1)-C(2) bond length would be ascribed to the strong electrostatic repulsion between the



Scheme 4-4. Plausible reaction mechanism of the nitro-Michael reaction catalyzed by **4e** and **4d**

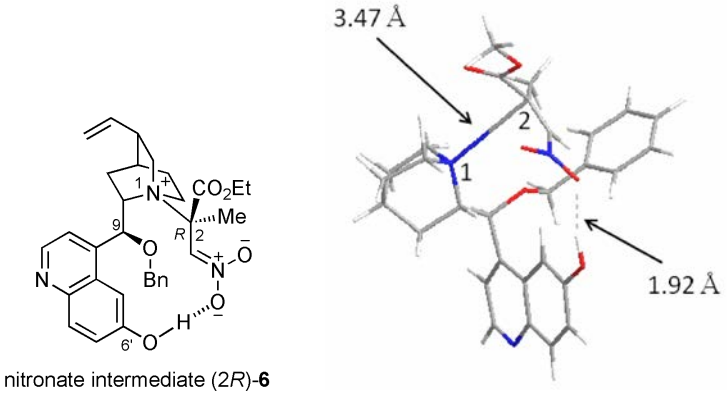


Figure 4-2. Simplified structure of (2*R*)-nitronate intermediate **6** optimized at B3LYP/6-31G(d)

nitrate moiety and N(1), which bears a considerable negative charge (−0.391: Mulliken charge). The formal positive charge on N(1) would be neutralized by electron releasing from five neighboring hydrogen atoms in germinal positions relative to N(1). The electrostatic repulsion between N(1) and C(2) of the (2*R*)-**6** can be reduced by protonation of (2*R*)-**6** (Figure 4-2). Resulting nitroammonium intermediate (2*R*)-**7** is considered thermodynamically stable; the N(1)-C(2) bond length of 1.56 Å is normal as a N-C covalent bond length.

A large number of the nitro-Michael addition of aldehydes to *β*-monosubstituted nitroalkenes catalyzed by enamine catalysts and bifunctional hydrogen-bonding catalysts have been reported.[7] The very high diastereoselectivity of these reaction is explained by the transition state model proposed by Seebach, in which donor atoms and acceptor atoms are close to each other.[8] It is interesting to note that despite the large difference in the reaction mechanism, the addition-elimination mechanism of the present reaction leads to an almost perfect diastereo- and enantioselectivity.

More noteworthy is the extremely high catalytic activity of *epi*-quinine derived **4e**, which can promote the carbon-carbon bond formation between the sterically congested Michael donors such as compound **1b** and sterically demanding *β*,*β*-disubstituted nitroalkenes **2**, in spite of unfavorable steric repulsion.[9] The nitro-Michael reactions catalyzed by bifunctional hydrogen-bonding catalysts such as thiourea derivatives and secondary amine catalysts proceed with a weak non-covalent H-bonding activation of nitroalkenes.[10d,h] In view of the weak activation of nitroalkenes in the reactions catalyzed by these catalysts, it is likely that the bifunctional hydrogen-bonding catalysts as well as the secondary amine catalysts hardly promote the nitro-Michael addition of the sterically demanding Michael donors to *β*,*β*-disubstituted nitroalkenes **2.** As for the **4e**-catalyzed reaction, strong activation of nitroalkenes by a covalent bond eanbles the carbon-carbon bond formation containing highly sterically congested reaction centers.[9] Thus, the potential of the **4e** and similar catalysts for the other asymmetric Michael reactions containing sterically congested reaction centers seems to be very promising.

4.3 Summary

In summary, the author has developed the highly diastereo- and enantioselective nitro-Michael addition of furanones to *β*,*β*-disubstituted nitroalkenes catalyzed by *epi*-quinine-derived catalyst **4e**. Present reaction offers an effective and reliable method for constructing all-*carbon* quaternary stereogenic center adjacent oxygen-containing quaternary stereogenic center.

4.4 References

(1) Liu, Y.; Han, S. -J.; Liu,W. -B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48,* 740.

(2) (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369.; (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed*. **1998**, *37*, 388.; (c) Bella, M.; Gasperi, T.; *Synthesis* **2009**, 1583.

(3) (a) Kastle, R.; Wennemers, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7228.; (b) Chen, L. –A.; Xiaojuan, T.; Jianwet, X.; Weici, X.; Lei, G.; Meggers, E. *Angew. Chem. Int. Ed.* **2013**, *52*, 14021.; (c) Wang, J. -Q.; Deng, Q. -M.; Wu, L.; Xu, K.; Wu, H.; Liu, R. -R.; Gao, J. -R. *Org. Lett.* **2014**, *16*, 776.

(4) Recently, we have reported the asymmetric nitro-Michael addition of furanones promoted by alkaloid catalyst. (a) Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2015**, *17*, 3026.; (b) Manna, M. S.; Kumar, V.; Mukherjee, S. *Chem. Commun.* **2012**, *48*, 5193.; (c) Terada, M; Ando, K. *Org. Lett.* **2011**, *13*, 2026.

(5) Wang, Y.; Li, Z.; Xiong, T.; Zhao, J.; Meng, Q. *Synlett* **2014**, 2155.

(6) CCDC 1443401 (**3ad**) contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(7) For selected recent review of organocatalytic asymmetric nitro-Michael reactions and the application to organic synthesis, see: (a) Somanatham, R.; Chávez, D.; Servin, F. A.; Romero, J. A.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; de Parrod, C. A.; González, J. S. *Curr. Org. Chem.* **2012**, *16*, 2440.; (b) Chauhan, P.; Chimni, S. S. *RSC. Adv*, **2012**, *2*, 737. (c) Raimondi, W.; Bonne, D.; Rodriguez, J. *Angew. Chem., Int. Ed*. **2012**, *51*, 40.; (d) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051.; (e) Xi, Y.; Shii, X. *Chem. Commun*. **2013**, *49*, 8583.; (f) Roux, C.; Bressy, C. In *Comprehensive Enantioselective Organocatalysis*; Dalco P., Ed.; Wiley-VCH: Weinheim, 2013, Vol. 3, pp. 1013-1042.; (g) Rios, R.; Moyano, A. In *Catalytic Asymmetric Conjugate Reaction*; Cordóva, A.; Ed.; Wiley-VCH: Weinheim, 2010; pp. 191-218.

(8) (a) Seebach, D.; Goliński, J. *Helv. Chim. Acta* **1981**, *64*, 1413.; (b) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 8822.; (c) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 71.; (d) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc*. **2012**, *134*, 6741.; (e) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439–4449.

(9) Compounds **3** are highly sterically congested. The ^{1}H NMR spectra of compounds **3ba**, **3bb**, **3bc**, **3bd**, **3be**, **3bf**, and **3bg** displyed that two terminal methyl groups involved in *iso*-butyl groups are not chemical shift equivalent because of rotational hindrance of *iso*-butyl groups in sterically-congested environment. Two methyl groups of COO-*i*-Pr in compound **3ag** and **3bg** also are not chemical shift equivalent.

4.5 Experimental Section

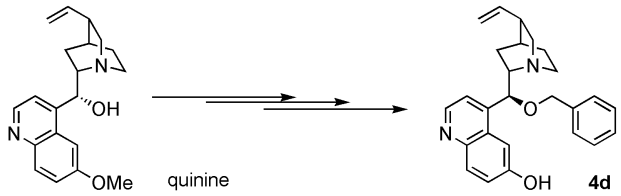
4.5.1 Materials and methods

General Methods: All manipulations were carried out under nitrogen atmosphere using Schlenk tube technique. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a BRUKER-300 spectrometer. Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ (7.26 ppm) for ^{1}H NMR, and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as internal standards respectively. Infrared spectra were measured on a JASCO FT/IR-230 in Nujol mulls. All the melting points were measured by using Yanagimoto micro melting point apparatus under inert atmosphere and are uncorrected. Toluene was purified by distillation from benzophenone ketyl under nitrogen; dichloromethane and chloroform by distillation from calcium hydride. Optical rotation was measured on RUDOLPH AUTOPOL IV digital polarimeter. Analytical HPLC was performed on a Shodex Model RI-72 instrument using Daicel CHIRALPACK AS-H (4.6 × 150 mm), and Daicel CHIRALPACK AD-H (4.6 × 150 mm). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Facility of Osaka City University.

Materials: *Epi*-quinine derivative **4b** was prepared according to the literature procedure.[1] Angelica lactone **1a** was obtained from Aldrich. (8a, 9S)-6'-methoxy-9-hydroxycinchonan was obtained from Fluka. Nitroalkenes **2a-2g** were prepared according to the literature procedure.[2] 5-Substituted-2(3*H*)-furanones **1b** and **1c** were prepared according to the literature procedure.[3]

4.5.2 Preparation of catalysts

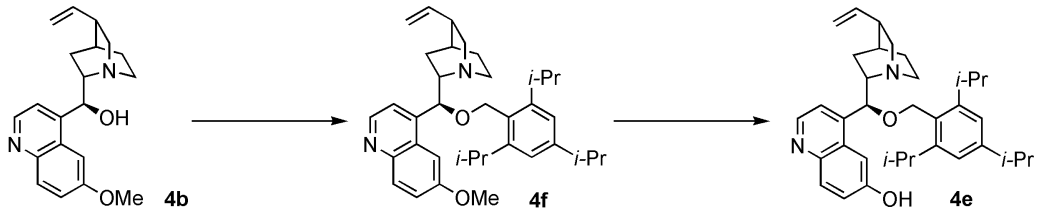
Preparation of catalyst **4d**



To a solution of quinine (3.1 g, 9.25 mmol) in THF (60 mL) was added triethylamine (2.96 mL) and methanesulfonyl chloride (2.0 g, 17.6 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was washed with saturated $NaHCO_3$ and brine. The aqueous phase was extracted with CH_2Cl_2 (2 ×10 mL). Combined CH_2Cl_2 layer was dried over $MgSO_4$, and concentrated under reduced pressure. Obtained crude material was subjected to next step without purification. To a solution of the clued product in water (54 mL) was added D-tartaric acid (1.37 g, 9.12 mmol). The resulting reaction mixture was refluxed for 1 h. Powder of $NaHCO_3$ was added slowly. After ceasing of gas evolution, the reaction mixture was extracted by CH_2Cl_2 (3 × 10 mL) and combined organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure gave (8a,

9*S*)-6'-methoxy-9-hydroxycinchonan, which was used for next step after the short column purification. To a DMF solution (10 mL) of NaH (100 mg) and crude (8a, 9*S*)-6'-methoxy-9-hydroxycinchonan (0.97 g, 3.08 mmol) was added benzylchloride (0.43 g. 3.39 mmol). The resulting reaction mixture was stirred at room temperature for 12 h. The reaction mixture was poured into the mixture of brine (20 mL) and ethylacetate (20 mL), then washed with 1N HCl. The organic layer was washed with sat. $NaHCO_3$. Subsequently, organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded (8a, 9*S*)-6'-methoxy-9-(benzyl)cinchonan, which was used next step without isolation. To a DMF solution (3 mL) of crude (8a, 9*S*)-6'-methoxy-9-(benzyl)chonan (440 mg, 1.1 mmol) and potassium *tert*-butoxide (280 mg, 2.1 mmol) was added dodecanethiol (0.85 g, 4.25 mmol). The reaction mixture was stirred at room temperature for 2 h, and then heated to 110 °C for 12 h. The reaction mixture was poured into the mixture of ethylacetate (20 mL) and 1N HCl (10 mL), and extracted by CH_2Cl_2 (3 ×10 mL). The combined organic layer was dried over $MgSO_4$, and condensed under reduced pressure, giving the crude product. Obtained crude material was purified by silica-gel column chromatography (CH_2Cl_2 : MeOH = 9 : 1), to give 360 mg (0.90 mmol) of compound **4d**. as a colorless solid: mp 153-156 °C; $[\alpha]_D^{23}$ −74.2 (*c* 0.36, $CHCl_3$), IR (nujol), 4334, 1615, 1456, 1376, 1243, 1089 cm^{-1}; ^1H NMR (300 Mz, $CDCl_3$); δ 0.61 (dd, *J* = 13.5, 8.1 Hz, 1 H), 1.04-1.30 (m, 1H), 1.31-1.62 (m, 2H), 1.15 (s, 1H), 2.25 (br s, 1H), 2.55-2.80 (m, 2H), 2.88 (m, 1H), 3.34 (dd, *J* = 13.2, 10.2 Hz, 1H), 3.80 (br s, 1H), 3.93 (d, *J* = 12.3 Hz, 1H), 4.45 (d, *J* = 12.3 Hz, 1 H), 4.77 (d, *J* = 10.2 Hz, 1 H), 4.84 (d, *J* = 17.1 Hz, 1 H), 5.50-5.70 (m, 1H), 6.84 (br s, 1H), 8.17 (s, 2H), 7.03-7.25 (m, 5H), 7.40 (dd, *J* = 9.3, 1.8 Hz, 1 H), 8.01 (d, *J* = 9.0 Hz, 1 H), 8.54 (d, *J* = 4.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.16, 25.4, 27.4, 27.5, 39.9, 49.8, 56.0, 70.4, 76.7, 94.7, 115.6 , 123.3, 128.1, 128.4, 128.6, 129.4, 132.0, 134.8, 137.0, 140.9, 144.5, 156.9; HRMS (FAB+) calcd for $C_{26}H_{29}N_2O_2$, $(M+H)^+$: 401.2229, found: 401.2227.

Preparation of catalysts **4e** and **4f**



Preparation of **4f**

The solution of **4b** (2.1 g, 6.5 mmol), and NaH (0.39 g, 16.2 mmol) in DMF (21 mL) was stirred for 2 h at room temperature. The reaction proceeded with the evolution of hydrogen gas. A solution of 5-tri(isopropyl)benzylchloride (3.27 g, 13.0 mmol) in DMF (10 mL) was added dropwise to the reaction mixture at 0 °C. After stirring at room temperature for 12 h,

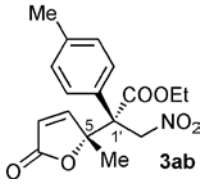
the reaction mixture was poured into the mixture of Et_2O (30 mL) and aq. HCI (1N, 30 mL). The aqueous phase was extracted with Et_2O (10 mL) for three times. Combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, giving solid material. Purification of the crude material by silica gel column chromatography (AcOEt : MeOH = 10 : 1) gave **4f** (3.25 g, 6.02 mmol, 93%) as a colorless solid.: mp 48-50 °C; $[\alpha]_D^{23}$ 107.6 (*c* 1.0, $CHCl_3$), IR (nujol), 1621, 1507, 1457, 1378, 1240 cm^{-1}; ^1H NMR(300 Mz, $CDCl_3$); δ 0.80-1.03 (m, 6H), 1.03-1.20 (m, 12H),1.45-1.53 (m, 3H), 2.07-2.20 (m, 1H), 2.41-2.84 (m, 4H), 2.84-3.38 (m, 5H), 3.65-3.38 (m, 1H), 3.85 (br s, 3H), 4.11-4.38 (m, 2H), 4.38-4.73 (m, 1H), 4.42-4.73 (m, 2H), 4.42-5.27 (m, 1H), 5.66 (br s, 1H), 6.84 (s, 2H), 7.34 (dd, *J* = 9.3, 2.4 Hz, 1H), 7.38-7.67 (m, 1H), 8.01 (d, *J* = 9.3 Hz, 1H), 8.72 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 24.4 27.8, 28.3, 28.9, 29.1, 34.4, 39.8, 45.0, 55.7, 56.2, 64.2, 114.2, 120.9, 128.6, 131.9, 141.9, 148.6, 148.9, 157.7; HRMS (FAB+) calcd. for $C_{36}H_{49}N_2O_2$, $(M+H)^+$: 541.3794, found: 527.3635.

Preparation of **4e**

The solution of potassium *t*-butoxide (1.87 g, 16.6 mmol) and 1-dodecanethiol (5.3 mL, 22 mmol) in DMF (23 mL) was stirred for 2 h at room temperature. To this solution, a solution of **4f** (3.08 g, 5.7 mmol) in DMF (20 mL) was added dropwise and heated to 110 °C for 12 h. After cooling of the reaction mixture, the solution was treated with 1N HCl (15 mL) and extracted with Et_2O (4 ×10 mL). After the treatment of organic phase with sat. NH_4OH (20 mL), aqueous phase was extracted with Et_2O (10 mL) for four times. Combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, giving a solid product. Purification by column chromatography (Et_2O : MeOH = 10 : 1) gave **4e** (1.26 g, 2.39 mmol, 42%) as a colorless solid.: mp 127-129 °C; $[\alpha]_D^{25}$ 157.4 (*c* 0.11, $CHCl_3$), IR (nujol), 4327, 2910, 1617, 1462, 1240, 1054 cm^{-1}; ^1H NMR(300 Mz, $CDCl_3$); δ 0.99 (d, *J* = 6.6 Hz, 7H), 1.06-1.16 (m, 1H),1.60-1.40 (m, 3H), 2.19 (br s, 1H), 2.63-2.77 (m, 3H), 2.95-3.14 (m, 3H), 3.26 (m, 1H), 3.41 (q, *J* = 7.2 Hz, 1H), 33.57 (q, *J* = 7.2 Hz, 1H), 4.68 (q, *J* = 10.2 Hz, 1 H), 4.81-4.90 (m, 3 H), 5.60 (q, *J* = 7.8 Hz, 1H), 6.84 (s, 2H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.44 (br s, 2H), 7.70 (m, 1H); 7.92 (d, *J* = 9.9 Hz, 7H), 8.63 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 15.3, 22.7, 24.0, 24.0, 24.2, 24.6, 27.7, 27.8, 29.2, 31.6, 34.3, 39.5, 56.0, 64.3, 65.9, 114.7, 120.9,122.5, 128.4, 130.8, 141.3, 143.0, 146.0, 148.6, 149.0, 156.7; HRMS (FAB+) calcd. for $C_{35}H_{47}N_2O_2$, $(M+H)^+$: 527.3638, found: 527.3635.

4.5.3 Preparation of substrates

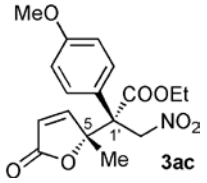
Experimental procedure for the Michael addition of furanone **1a** to nitroalkene **2b** (Table 4-2, entry 1)



3ab

To a solution of nitroalkene **2b** (59 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (50 mg) in toluene (0.25 mL) was added angelica lactone **1a** (50 mg, 0.50 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (THF : hexane = 1 : 3), giving 76 mg (0.23 mmol, 91%) of compound **3ab** as a colorless solid.: mp 108-110 °C; $[\alpha]_D^{23}$ −79.0 (*c* 1.05, $CHCl_3$), IR (nujol) 1758, 1732, 1556, 1231 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.20 (d, *J* = 7.2 Hz, 3H), 1.29 (s, *J* = 7.2 Hz, 3H), 2.29 (s, 3H), 4.24-4.26 (m, 2H), 4.92 (d, *J* = 15.6 Hz, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 5.85 (d, *J* = 5.7 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.77 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 21.1, 23.9, 59.0, 62.3, 76.3, 89.6, 119.7, 127.9, 129.6, 131.5, 139.0, 160.7, 170.0, 171.5; HRMS (FAB+) calcd for $C_{17}H_{20}NO_6$, $(M+H)^+$: 334.1291, found: 334.1293 ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (95% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : *i*-PrOH = 36 : 1; (5*R*, 1'*R*) t_R = 5.5 min, (5*S*, 1'*S*) t_R = 18.3 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

Experimental procedure for the Michael addition of angelica lactone **1a** to nitroalkene **2c** (Table 4-2, entry 2)

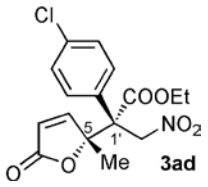


3ac

To a solution of nitroalkene **2c** (63 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4 Å (50 mg) in toluene (0.25 mL) was added angelica lactone **1a** (98 mg, 0.5 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (THF : hexane = 1 : 3) to give 91 mg (0.23 mmol, 92%) of compound **3ac** as a colorless solid.: mp 132-133 °C; $[\alpha]_D^{23}$ −86.9 (*c* 0.6, $CHCl_3$), IR (nujol) 1765, 1731, 1557, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 3.76 (s, 3H), 4.20-4.35 (m, 2H), 4.91 (d, *J* = 15.3 Hz, 1H), 5.09 (d, *J* = 15.3 Hz, 1H), 5.85 (d, *J* = 5.7 Hz, 1H), 6.84 (d, *J* = 9.3 Hz, 2H), 7.09 (d, *J* = 9.3 Hz, 2H), 7.77 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 23.9, 55.5, 58.8, 62.4, 76.4, 89.8,

114.3, 119.7, 126.4, 129.4, 159.8, 160.7, 170.1, 171.5; HRMS (FAB+) calcd for $C_{17}H_{20}NO_7$ $(M+H)^+$: 350.1240, found: 350.1237. ^{1}H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (96% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : *i*-PrOH = 9 : 1; (5*R*, 1'*R*) t_R = 4.0 min, (5*S*, 1'*S*) t_R = 18.5 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

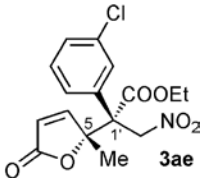
Experimental procedure for the Michael addition of furanone **1a** to nitroalkene **2d** (Table 4-2, entry 3)



3ad

To a solution of nitroalkene **2d** (64 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (100 mg) in toluene (1.0 mL) was added angelica lactone **1a** (50 mg, 0.5 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (THF : hexane = 1 : 3), to give 79 mg (0.22 mmol, 89%) of compound **3ad** as a colorless solid.: mp 100-102 °C; $[\alpha]_D^{23}$ −80.7 (*c* 1.07, $CHCl_3$), IR (nujol) 1765, 1732, 1558, 1224 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.30 (s, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.88 (d, *J* = 15.3 Hz, 1H), 5.07 (d, *J* = 15.3 Hz, 1H), 5.89 (d, *J* = 6.0 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 6.0Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 23.8, 58.9, 62.6, 76.1, 89.2, 120.2, 128.8, 129.6, 129.9, 135.3, 159.9, 169.5, 171.2; HRMS (FAB+) calcd for $C_{16}H_{17}{}^{35}ClNO_6$, $(M+H)^+$: 354.0744, found: 354.0743. ^{1}H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : EtOH = 36 : 1; (5*R*, 1'*R*) t_R = 17.2 min, (5*S*, 1'*S*) t_R = 32.6 min). The absolute configuration of **3ad** was determined by X-ray crystallographic analysis to be (5*R*, 1'*R*).

Experimental procedure for the Michael addition of furanone **1a** to nitroalkene **2e** (Table 4-2, entry 4)

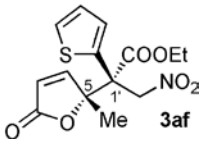


3ae

To a solution of nitroalkene **2e** (64 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS

4Å (50 mg) in toluene (1.0 mL) was added lactone **1a** (50 mg, 0.5 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (THF : hexane = 1 : 3), giving 77 mg (0.22 mmol, 87%) of compound **3ae** as a colorless liquid; $[\alpha]_D^{25}$ −72.4 (*c* 0.5, $CHCl_3$), IR (nujol) 1770, 1525, 1557, 1557, 1222 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.22 (t, *J* = 6.9 Hz, 3H), 1.32 (s, 3H), 4.29 (q, *J* = 6.9 Hz, 2H), 4.92 (d, *J* = 10.2 Hz 1H), 5.10 (d, *J* = 10.2 Hz 1H), 5.89 (d, *J* = 6.0 Hz, 1H), 7.10 (dt, *J* = 6.9, 1.2 Hz 1H), 7.16-7.22 (m, 1H), 7.24-7.35 (m, 2H), 7.76 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 13.8, 23.8, 59.1, 62.7, 76.0, 89.1, 120.0, 126.4, 128.4, 129.3, 130.1, 135.0, 136.4, 160.3, 169.3, 171.1; HRMS (FAB+) calcd for $C_{16}H_{17}{}^{35}ClNO_6$, $(M+H)^+$: 354.0744, found: 354.0746. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AS-H column ; flow rate 1 mL/min; hexane : *i*-PrOH = 36 : 1; (5 *R*, 1'*R*) t_R = 5.4 min, (5 *S*, 1'*S*) t_R = 20.5 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

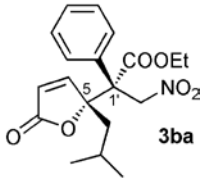
Experimental procedure for the Michael addition of furanone **1a** to nitroalkene **2f** (Table 4-2, entry 5)



3af

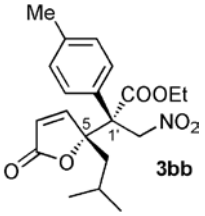
To a solution of nitroalkene **2f** (57 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4 Å (50 mg) in toluene (1.0 mL) was added lactone **1a** (50 mg, 0.5 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (THF : hexane = 1 : 3) to give 72 mg (0.22 mmol, 89%) of compound **3af** as a colorless solid.: mp. 96-98 °C; $[\alpha]_D^{25}$ +24.6 (*c* 1.2, $CHCl_3$), IR (nujol) 1771, 1741, 1554, 1376, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 5.05 (d, *J* = 15.3Hz, 1H), 5.26 (d, *J* = 15.3Hz, 1H), 5.98 (d, *J* = 5.7 Hz, 1H), 6.96 (dd, *J* = 5.4, 4.1 Hz 1H), 7.07 (d, *J* = 4.1 Hz 1H), 7.32 (d, *J* = 5.4 Hz 1H), 7.62 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.5, 58.0, 63.2, 76.7, 89.1, 120.1 126.5, 127.6, 127.8, 135.4, 158.6, 168.5, 170.7; HRMS (FAB+) calcd for $C_{14}H_{16}NO_6S$, $(M+H)^+$: 326.0698, found: 326.0695. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (98% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1 mL/min; hexane : *i*-PrOH = 18 : 1; (5 *R*, 1'*R*) t_R = 7.2 min, (5 *S*, 1'*S*) t_R = 15.9 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

Experimental procedure for the Michael addition of furanone **1b** to nitroalkene **2a** (Table 4-2, entry 6)



To a solution of nitroalkene **2a** (55 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (25 mg) in toluene (0.25 mL) was added lactone **1b** (70 mg, 0.5 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (purification with THF : hexane = 1 : 3 as an elution solvent, followed by further purification with CH_2Cl_2 as an elution solvent), giving 80 mg (0.22 mmol, 88%) of compound **3ba** as a colorless liquid.; $[\alpha]_D^{23}$ -53.8 (*c* 1.0, $CHCl_3$), IR (nujol) 1770, 1600, 1290, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.53 (d, *J* = 6.6 Hz, 3H) , 0.70 (d, *J* = 6.6 Hz, 3H), 0.98 (dd, *J* = 14.1, 5.7 Hz, 1H), 1.05-1.20 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 2.13 (dd, *J* = 14.1, 5.4 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.89 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 17.5 Hz, 1H), 5.95 (d, *J* = 5.7 Hz, 1H), 7.11-7.22 (m, 2H), 7.25-7.40 (m, 3H), 7.23 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 23.2, 23.8, 24.5, 42.9, 60.1, 62.4, 76.4, 92.1, 121.2, 128.3, 128.9, 128.9, 134.5, 159.0, 170.1, 171.9; HRMS (FAB+) calcd for $C_{19}H_{24}NO_6$, $(M+H)^+$: 362.1604, found: 362.1601. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : EtOH = 144 : 1; (5*R*, 1'*R*) t_R = 8.8 min, (5*S*, 1'*S*) t_R = 16.6 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

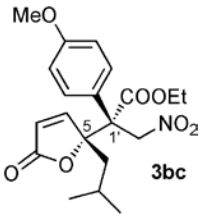
Experimental procedure for the Michael addition of furanone **1b** to nitroalkene **2b** (Table 4-2, entry 7)



To a solution of nitroalkene **2b** (59 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (25 mg) in toluene (0.25 mL) was added lactone **1b** (70.1 mg, 0.5 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (purification with THF: hexane = 1 : 3 as an elution solvent, followed by further purification with CH_2Cl_2 as an eluent solvent), giving 77

mg (0.21 mmol, 82%) of compound **3bb** as a colorless solid.: mp 109-110 °C; $[\alpha]_D^{23}$ −66.5 (*c* 1.1, $CHCl_3$), IR (nujol) 1765, 1735, 1560, 1376, 1207 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.53 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H), 1.03 (dd, *J* = 14.4, 6.0 Hz, 1H), 1.10-1.20 (m, 1H), 1.20 (t, *J* = 7.2 Hz, 3H), 2.10 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.29 (s, 3H), 4.27(q, *J* = 7.2 Hz, 2H), 4.86 (d, *J* = 15.3 Hz, 1H), 5.08 (d, *J* = 15.3 Hz, 1H), 5.93 (d, *J* = 5.7 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 21.1, 23.1, 23.8, 24.5, 42.9, 59.8, 62.3, 76.5, 92.3, 121.0, 128.1, 129.5, 131.4, 138.9, 159.0, 170.2, 171.9; HRMS (FAB+) calcd for $C_{20}H_{26}NO_6$, $(M+H)^+$: 376.1760, found: 376.1759. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (96% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane EtOH = 144 : 1; (5*R*, 1'*R*) t_R = 5.6 min, (5*S*, 1'*S*) t_R = 13.8 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

Experimental procedure for the Michael addition of furanone **1b** to nitroalkene **2c** (Table 4-2, entry 8)

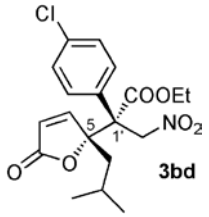


3bc

To a solution of nitroalkene **2b** (59 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (25 mg) in toluene (0.25 mL) was added lactone **1b** (70.1 mg, 0.5 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (purification with THF : hexane = 1 : 3 as an elution solvent, followed by further purification with CH_2Cl_2 as an elution solvent), giving 70 mg (0.18 mmol, 72%) of compound **3bc** as a colorless liquid.; $[\alpha]_D^{23}$ −55.4 (*c* 0.8, $CHCl_3$), IR (nujol) 1769, 1731, 1557, 1259, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.55 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H), 0.98 (dd, *J* = 14.4, 5.4 Hz, 1H), 1.05-1.20 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 2.09 (dd, *J* = 14.4, 5.4 Hz, 1H), 3.76 (s, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.85 (d, *J* = 15.3 Hz, 1H), 5.05 (d, *J* = 15.3 Hz, 1H), 5.93 (d, *J* = 5.7 Hz, 1H), 6.84 (d, *J* = 9.3 Hz, 2H), 7.08 (d, *J* = 9.3 Hz, 2H), 7.71 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 23.1, 23.9, 24.6, 42.9, 55.4, 59.5, 62.3, 76.6, 92.4, 114.1, 121.0, 126.2, 129.5, 159.0, 159.7, 170.3, 172.0; HRMS (FAB+) calcd for $C_{20}H_{26}NO_7$, $(M+H)^+$: 392.1709, found: 392.1706. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (96% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : *i*-PrOH = 72 : 1; (5*R*, 1'*R*) t_R = 7.7 min, (5*S*, 1'*S*) t_R = 27.3 min).

Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

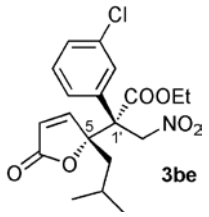
Experimental procedure for the Michael addition of furanone **1b** to nitroalkene **2d** (Table 4-2, entry 9)



3bd

To a solution of nitroalkene **2b** (64 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (100 mg) in toluene (1.0 mL) was added lactone **1b** (70.1 mg, 0.5mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (purification with THF : hexane = 1 : 3 as an elution solvent, followed by further purification with CH_2Cl_2 as an elution solvent), giving 79 mg (0.20 mmol, 80%) of compound **3bd** as a colorless liquid; $[\alpha]_D^{23}$ −64.9 (*c* 0.90, $CHCl_3$), IR (nujol) 1770, 1742, 1558, 1374, 1223 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.56 (d, *J* = 6.6 Hz, 3H), 0.71(d, *J* = 6.6 Hz, 3H), 1.02 (dd, *J* = 14.1, 6.3 Hz, 1H), 1.10-1.25 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 2.09 (dd, *J* = 14.5, 5.4 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.83 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 5.97 (d, *J* = 5.7 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 23.3, 23.8, 24.6, 42.9, 59.7, 62.6, 76.3, 91.9, 121.4, 129.1, 129.7, 133.0, 135.1, 158.6, 169.7, 171.6; HRMS (FAB+) calcd for $C_{19}H_{23}{}^{35}ClNO_6$, $(M+H)^+$: 396.1214, found: 396.1211. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (96% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : EtOH = 250 : 1; (5*R*, 1'*R*) t_R = 8.3 min, (5*S*, 1'*S*) t_R = 16.4 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

Experimental procedure for the Michael addition of furanone **1b** to nitroalkene **2e** (Table 4-2, entry 10)

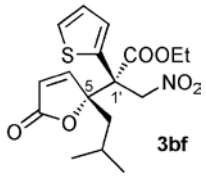


3be

To a solution of nitroalkene **2e** (128 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (25 mg) in toluene (0.25 mL) was added lactone **1b** (70.1 mg, 0.5 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was

purified by silica gel column chromatography (purification with THF : hexane = 1 : 3 as an elution solvent, followed by further purification with CH_2Cl_2 as an elution solvent), giving 79 mg (0.20 mmol, 79%) of compound **3be** as a colorless liquid.; $[\alpha]_D^{23}$ −47.5 (*c* 1.23, $CHCl_3$), IR (nujol) 1765, 1731, 1557, 792, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.57(d, *J* = 6.6 Hz 3H), 0.72 (d, *J* = 6.6 Hz, 3H), 1.05 (dd, *J* = 14.4, 6.0 Hz, 1H), 1.10-1.25 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 2.09 (dd, *J* = 14.4, 5.4 Hz, 1H), 4.25-4.35 (m, 2H), 4.85 (d, *J* = 15.3 Hz, 1H), 5.05 (d, *J* = 15.3 Hz, 1H), 5.97 (d, *J* = 6.0 Hz, 1H), 7.7 (ddd, *J* = 7.2, 3.0, 3.0 Hz, 1H), 7.16-7.23 (m, 1H), 7.24-7.34 (m, 2H) 7.69 (d, *J* = 6.0 Hz, 1H),; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 23.2, 23.8, 24.5, 43.0, 59.9, 62.7, 76.2, 91.8, 121.4, 126.6, 128.6, 129.2, 130.0, 134.9, 136.4, 158.6, 169.5, 171.6; HRMS (FAB+) calcd for $C_{19}H_{23}{}^{35}ClNO_6$, $(M+H)^+$: 396.1214, found: 396.1212. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AD-H column; flow rate 1.0 mL/min; hexane : EtOH = 180 : 1; (5*R*, 1'*R*) t_R = 7.9 min, (5*S*, 1'*S*,) t_R = 12.1 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

Experimental procedure for the Michael addition of furanone **1b** to nitroalkene **2f** (Table 4-2, entry 11)

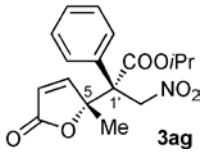


3bf

To a solution of nitroalkene **2b** (57 mg, 0.5 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (100 mg) in toluene (1.0 mL) was added lactone **1b** (70.1 mg, 0.50 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (purification with THF : hexane = 1 : 3 as an elution solvent, followed by further purification with CH_2Cl_2 as an elution solvent), giving 72 mg (0.20 mmol, 78%) of compound **3bf** as a colorless liquid.; $[\alpha]_D^{23}$ −18.1 (*c* 0.8, $CHCl_3$), IR (nujol) 1770, 1740, 1558, 1219, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.66 (d, *J* = 4.2 Hz, 3H), 0.69 (d, *J* = 4.2 Hz, 3H), 1.07-1.22 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.50 (dd, *J* = 14.1, 6.2 Hz, 1H), 1.57 (dd, *J* = 14.1, 6.0 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 5.01 (d, *J* = 15.3 Hz, 1H), 5.24 (d, *J* = 15.3 Hz, 1H), 6.07 (d, *J* = 6.0 Hz, 1H), 6.95 (dd, *J* = 5.4, 3.6 Hz, 1H), 7.06 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.32 (dd, *J* = 5.4, 1.2 Hz, 1H), 7.54 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 23.2, 24.0, 24.3, 41.6, 59.1, 63.3, 76.7, 91.7, 122.3, 126.4, 127.8, 128.0, 135.3, 157.2, 168.7, 171.1; HRMS (FAB+) calcd for $C_{17}H_{22}NO_6S$, $(M+H)^+$: 368.1168, found: 368.1170. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was

>98:2. The enantiomeric excess (98% ee) was determined through chiral HPLC analysis (Daicel AD-H column; flow rate 1.0 mL/min; hexane : EtOH = 180 : 1; (5*R*, 1'*R*) t_R = 16.5 min, (5*S*, 1'*S*) t_R = 24.9 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

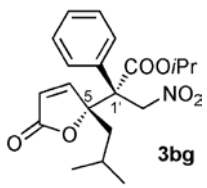
Experimental procedure for the Michael addition of furanone **1a** to nitroalkene **2g** (Table 4-2, entry 12)



3ag

To a solution of nitroalkene **2g** (59 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (100 mg) in toluene (1.0 mL) was added angelica lactone **1a** (50 mg, 0.50 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (THF : hexane = 3 : 1), giving 75 mg (0.23 mmol, 91%) of compound **3ag** as a colorless solid.: mp 58-60 °C; $[\alpha]_D^{23}$ −56.5 (*c* 1.0, $CHCl_3$), IR (nujol) 1769, 1731, 1560, 1256, 1376, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.77 (d, *J* = 6.3 Hz, 3H), 1.21(d, *J* = 6.3 Hz, 3H), 1.29 (s, 3H), 4.93 (d, *J* = 15.6 Hz, 1H), 5.13 (d, *J* = 15.6 Hz, 1H), 5.15-5.25 (m, 1H), 5.86 (d, *J* = 5.7 Hz, 1H), 7.14-7.25 (m, 2H), 7.27-7.38 (m, 3H), 7.80 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.5, 23.9, 59.2, 70.5, 76.3, 89.5, 119.6, 128.2, 128.8, 128.9, 134.7, 160.8, 169.2, 171.5; HRMS (FAB+) calcd for $C_{17}H_{20}NO_6$, $(M+H)^+$: 334.1291, found: 334.1294. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : *i*-PrOH = 36 : 1; (5*R*, 1'*R*) t_R = 6.1 min, (5*S*, 1'*S*) t_R = 20.5 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 2, entry 3).

Experimental procedure for the Michael addition of furanone **1b** to nitroalkene **2g** (Table 4-2, entry 13)

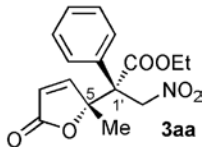


3bg

To a solution of nitroalkene **2b** (59 mg, 0.25 mmol), catalyst **4e** (6.6 mg, 0.013 mmol) and MS 4Å (25 mg) in toluene (0.25 mL) was added lactone **1b** (70.1 mg, 0.50 mmol) at room temperature. The resulting solution was stirred for 22 h. The reaction mixture was filtrated to

remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (purification with THF : hexane = 1 : 3 as an elution solvent, followed by further purification with CH_2Cl_2 as an elution solvent), giving 82 mg (0.22 mmol, 87%) of compound **3bg** as a colorless liquid.; $[\alpha]_D^{23}$ −45.8 (*c* 0.8, $CHCl_3$), IR (nujol) 1768, 1732, 1600, 1377, 1559 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.52 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H), 1.01 (dd, *J* = 14.4, 6.0 Hz, 1H), 1.05-1.20 (m, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 2.13 (dd, *J* = 14.4, 5.4 Hz, 1H), 4.87 (d, *J* = 15.3 Hz, 1H), 5.09 (d, *J* = 15.3 Hz, 1H), 5.20 (sept, *J* = 6.3 Hz, 1H), 5.95 (d, *J* = 5.8 Hz, 1H), 7.17-7.26 (m, 2H), 7.28-7.37 (m, 3H), 7.74 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 21.5, 23.2, 23.8, 24.6, 43.0, 60.0, 70.6, 76.5, 92.2, 121.0, 128.4, 128.8, 128.9, 134.6, 159.1, 169.5, 172.0; HRMS (FAB+) calcd for $C_{20}H_{26}NO_6$, $(M+H)^+$: 376.1760, found: 376.1758. ^1H NMR analysis of the crude products indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (98% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : EtOH = 144 : 1; (5*R*, 1'*R*) t_R = 6.5 min, (5*S*, 1'*S*) t_R = 12.5 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

Experimental procedure for the large scale Michael addition of furanone **1a** to nitroalkene **2a** (Scheme 4-2)



3aa

To a reaction mixture of nitroalkene **2a** (2.21 g, 10 mmol), catalyst **4e** (52 mg, 0.1 mmol) and MS 4Å (1.00 g) in toluene (50 mL) was added angelica lactone **1a** (1.96 g, 20 mmol) at room temperature. The resulting solution was stirred for 91 h. The reaction mixture was filtrated to remove MS 4Å. After removal of the solvent under reduced pressure, the crude material was purified by silica gel column chromatography (THF : hexane = 3 : 1), giving 2.97 g (9.3 mmol, 93%) of compound **3aa** as a colorless solid.: mp 83-85 °C; $[\alpha]_D^{23}$ −70.0 (*c* 1.0, $CHCl_3$), IR (nujol) 1764, 1732, 1558, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 4.24-4.33 (m, 2H), 4.94 (d, *J* = 15.6 Hz, 1H), 5.14 (d, *J* = 15.6 Hz, 1H), 5.86 (d, *J* = 5.7 Hz, 1H), 7.14-7.22 (m, 2H), 7.30-7.35 (m, 3H), 7.79 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 23.6, 58.8, 62.5, 76.0, 89.1, 119.9, 129.0, 129.5, 133.0, 135.0, 160.1, 169.4, 171.1; HRMS (FAB+) calcd for $C_{16}H_{18}NO_6$, $(M+H)^+$: 320.1134, found: 320.1136. ^1H NMR analysis of the crude material indicated that *syn*:*anti* ratio was >98:2. The enantiomeric excess (97% ee) was determined through chiral HPLC analysis (Daicel AS-H column; flow rate 1.0 mL/min; hexane : *i*-PrOH = 72 : 1; (5*R*, 1'*R*) t_R = 7.3 min, (5*S*, 1'*S*) t_R = 28.4 min). Absolute configuration was assigned by analogy with compound **3ad** (Table 4-2, entry 3).

4.5.4 Computational data

(a) Optimization of simplified structure of (2*R*)-nitronate intermediate **6** (B3LYP/6-31G(d)) (Fig. 4-2)

Dipole = (4.519187, -2.547876, -3.373031) 6.188058 Debye
Kinetic Energy = 1081938.0548 Kcal/Mol
Potential Energy = -2173429.9053 Kcal/Mol
Total Energy = -1091491.8506 Kcal/Mol

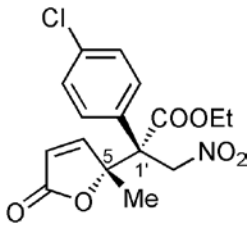
COORDINATES OF ALL ATOMS ARE (ANGS)

ATOM	CHARGE	X	Y	Z
C	6.0	0.0232070153	1.6979110744	-0.9242549317
N	7.0	1.4645534748	1.4223046859	-1.1226698466
C	6.0	1.8279816011	1.4180935046	-2.5498738896
C	6.0	-0.3573799032	3.1002857858	-1.5231107348
C	6.0	1.3724448445	2.7264641225	-3.2675519188
C	6.0	0.8927521335	3.7113356931	-2.1817972548
C	6.0	2.2412403136	2.4955405788	-0.4598878187
C	6.0	1.9942724864	3.8870902548	-1.1200508869
H	1.0	1.6869509170	4.6337678058	-0.3761648283
C	6.0	2.9034033199	-1.9647167463	-0.6228658908
C	6.0	-0.8985123194	0.5951454634	-1.5054108247
C	6.0	-2.3716610356	0.8720989357	-1.2052854380
C	6.0	-3.2250568223	1.1870920837	-2.2466474467
C	6.0	-4.5733696655	1.5292519126	-1.9913205575
N	7.0	-5.0946531735	1.5848968125	-0.7812137765
C	6.0	-4.2894436053	1.2500010260	0.2681123949
C	6.0	-2.9170073568	0.8505147957	0.1220156670
C	6.0	-2.1920130684	0.4593393270	1.2806601327
C	6.0	-2.7737057014	0.5178223120	2.5348914873
C	6.0	-4.1230684087	0.9461464587	2.6783309294
C	6.0	-4.8543011098	1.2940202376	1.5729224135
O	8.0	-2.1377218746	0.1794467175	3.6826352753
C	6.0	-0.7298470352	-3.1036387421	-1.2469678533
C	6.0	-0.9313698245	-3.4760994561	0.0912242188
C	6.0	-0.1689670585	-4.0351784562	-2.1285483939

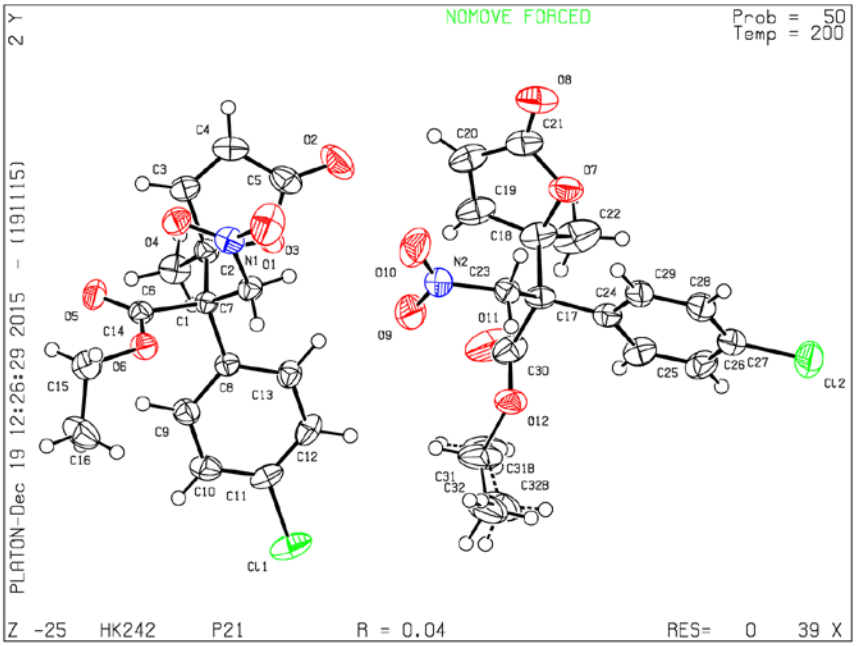
C	6.0	-0.5750213885	-4.7495391908	0.5329719173
C	6.0	0.1739198960	-5.3183717000	-1.6915863597
C	6.0	-0.0272995046	-5.6777509940	-0.3578651549
H	1.0	-1.3836649286	-2.7672028406	0.7834680328
H	1.0	0.2392541406	-6.6739915035	-0.0154751648
H	1.0	-0.0068600426	-3.7555691737	-3.1673733220
H	1.0	-0.1238844287	1.7200581585	0.1597845362
O	8.0	4.6794778693	0.3203483519	0.1852128321
H	1.0	1.3956759387	0.5294585938	-3.0239916899
H	1.0	-0.7490246138	3.7628112344	-0.7401627066
H	1.0	-1.1468137502	3.0052738929	-2.2789587880
H	1.0	2.1853531718	3.1596339983	-3.8639961858
H	1.0	0.5419942662	2.5207319960	-3.9567584394
H	1.0	0.6401188215	4.6759172251	-2.6337486398
H	1.0	3.2982465869	2.2151015355	-0.5143625918
H	1.0	1.9653579703	2.5033742370	0.6015791754
H	1.0	2.9119001018	4.2601606461	-1.5934912541
H	1.0	3.4115841479	-1.3939456325	-1.4056209200
H	1.0	1.8847323953	-2.1778517913	-0.9532017120
H	1.0	3.4346853185	-2.9164071151	-0.4913223026
H	1.0	-0.7894676644	0.6059765561	-2.6033788941
H	1.0	-2.8679474783	1.1859337198	-3.2737990633
H	1.0	-5.2355868778	1.7700833028	-2.8222043706
H	1.0	-1.1851771372	0.0731681850	1.1724268288
H	1.0	-4.5475497600	0.9737201498	3.6791758384
H	1.0	-5.8878664491	1.6150056550	1.6528009251
H	1.0	-1.2023970317	-0.0412111792	3.5064527572
H	1.0	-0.7356002067	-5.0244192729	1.5726041605
H	1.0	0.5978484484	-6.0295197627	-2.3938196750
C	6.0	-1.1659455569	-1.7476120754	-1.7480123475
O	8.0	-0.4919060109	-0.7007856162	-1.0424981288
H	1.0	-0.9562938272	-1.6597479436	-2.8256231718
H	1.0	-2.2523229443	-1.6383004396	-1.6253341826
C	6.0	2.8907497200	-1.1873541016	0.6680127506
C	6.0	1.7818104587	-1.2150546995	1.4193469941
C	6.0	4.1444475547	-0.4129201272	0.9922834777
N	7.0	1.5411238394	-0.4565625923	2.6239579575

H	1.0	0.9154358319	-1.7999721452	1.1486973366
O	8.0	2.2576080074	0.4902186318	2.9284024481
O	8.0	0.5430383747	-0.8166256602	3.2776997700
O	8.0	4.6271276423	-0.6828458623	2.2088239173
C	6.0	5.7507033208	0.1233277423	2.6247113909
H	1.0	5.5232193917	1.1850573856	2.5010019314
H	1.0	6.6369894453	-0.1272902609	2.0381165852
H	1.0	5.9098354638	-0.1162564556	3.6781630883
H	1.0	2.9168300657	1.3119878368	-2.5922643224

4.5.5 X-ray structure of (5*R*, 1'*R*)-3ad



(5*R*, 1'*R*) **3ad**



4.5.6 References

(1) Wang, Y.; Li, Z.; Xiong, T.; Meng, Q. *Synlett* **2014**, 2155.

(2) Kastl, R.; Wennemers, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7228.

(3) Marshall, J. A.; Wolf, M. A. ; Wallence, E. M. *J. Org. Chem.* **1997**, *62*, 367.

Conclusions

In this thesis, the investigations of the asymmetric vinylogous nitro-Michael reactions of 2(3*H*)-furanones to nitroalkenes catalyzed by cinchona alkaloid derivatives as hydrogen bonding catalysts are described. In Chapter 1, the present situation of the catalytic asymmetric nitro-Michael reaction is reviewed and the purpose of this doctoral thesis is described.

In Chapter 2, the highly *syn*-selective nitro-Michael reaction of 2(3*H*)-furanones has been described. With 0.1-5 mol % loading of *epi*-quinine derived catalysts, the reaction of 5-substituted 2(3*H*)-furanones with *β*-substituted nitroalkenes smoothly proceeded to give the *syn*-Michael adducts in good yields (up to 98% yield) with excellent diastereo- and enantioselectivities (up to > 98:2 dr, *syn* major; up to 97% ee). During the course of the investigation, the author has found that low reactive *β*-alkylsubstituted nitroalkenes can smoothly undergo the nitro-Michael reaction with 5-substituted 2(3*H*)-furanones. The DFT calculations revealed that the conformational flexibility of the catalyst-nitroalkene adducts play a critical role in the high asymmetric induction.

In Chapter 3, the catalyst-controlled switching of diastereoselectivity from the high *syn*-selectivity (> 98:2 dr, *syn* major) to the *anti*-selectivity (up to 97:3 dr, *anti* major) of the asymmetric nitro-Michael reaction of 2(3*H*)-furanones has been described. The *anti*-diastereoselectivity of the nitro-Michael reaction has been very rare. With 0.1-5 mol % loading of *epi*-quinine-derived catalyst, the reaction of 5-substituted 2(3*H*)-furanones with nitroalkenes smoothly proceeded to give the *anti*-Michael adducts in good yields (up to 95% yield) with excellent diastereo- and enantioselectivities (up to 97:3 dr, *anti* major; up to 99% ee). The DFT calculation suggested that the mechanism of the present reaction involves the conjugate addition of quinuclidine nitrogen to nitroalkenes, affording ammonium-nitronate intermediates. Subsequent nucleophilic substitution of the ammonium-nitronate intermediates with dienolate derived from furanones gave the expected *anti*-Michael adducts.

In Chapter 4, the asymmetric nitro-Michael reaction of 2(3*H*)-furanones to *β*,*β*-disubstituted nitroalkenes has been described. The products of this reaction have two contiguous quaternary stereogenic centers. With 1-5 mol % loading of *epi*-quinine-derived catalyst, the reaction of 5-substituted 2(3*H*)-furanones with *β*,*β*-disubstituted nitroalkenes smoothly proceeded to give the *syn*-Michael adducts in good yields (up to 93% yield) with excellent diastereo- and enantioselectivities (up to > 98:3 dr, *syn* major; up to 99% ee). This reaction provides an effective and straightforward method for constructing all-*carbon* quaternary stereogenic center adjacent to oxygen-containing quaternary stereogenic center.

The development of novel cinchona alkaloid-derived catalysts has effectively solved the inherent problems associated with the nitro-Michael reactions using organocatalysts.

List of Publications

1. Catalytic Activity of *Epi*-Quinine-Derived 3,5-Bis(trifluoromethyl)benzamide in Asymmetric Nitro-Michael Reaction of Furanones

T. Sekikawa, T. Kitaguchi, H. Kitaura, T. Minami, Y. Hatanaka, *Org. Lett.* ***2015***, *17*, 3026.

---------- Chapter 2

2. *Anti*-Selective Asymmetric Nitro-Michael Reaction of Furanones: Diastereocontrol by Catalyst

T. Sekikawa, T. Kitaguchi, H. Kitaura, T. Minami, Y. Hatanaka, *Org. Lett.* ***2016***, *18*, 646.

---------- Chapter 3

3. *Syn*-Selective Nitro-Michael Addition of Furanones to *β*,*β*-Disubstituted Nitroalkenes Catalyzed by *Epi*-Quinine Derivatives

T. Sekikawa, H. Kitaura, T. Kitaguchi, T. Minami, Y. Hatanaka, *Tetrahedron Lett.* ***2016***, *57*, 2985.

---------- Chapter 4

4. Chiral silicon Lewis acids having a pentacoordinate stereogenic silicon center: ^{29}Si NMR studies and application to asymmetric Diels-Alder reactions

Y. Sakaguchi, Y. Iwade, T. Sekikawa, T. Minami, Y. Hatanaka, *Chem. Commun.* **2013**, *49*, 11173.

---------- Chapter 2

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March, 2016

Tohru Sekikawa