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Asymmetric catalysis of carbonyl–ene reactions and related carbon–carbon bond forming reactions

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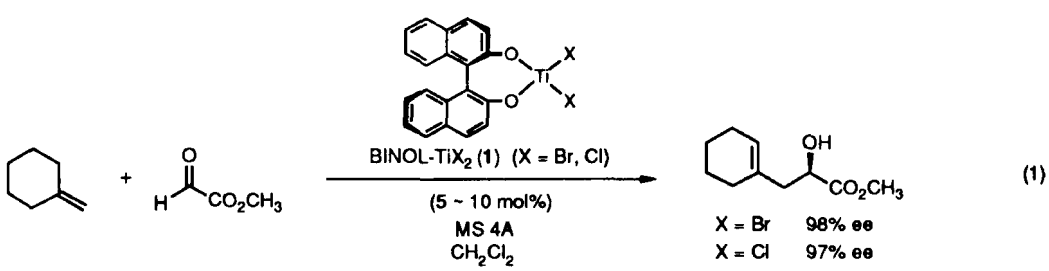
Abstract: The chiral titanium complexes (BINOL-TiX_2), prepared in situ from (i-$PrO)_2TiX_2$ (X=Br or Cl) and an optically pure binaphthol (BINOL) in the presence of molecular sieves 4A (MS 4A), serve as efficient enantioselective catalysts for glyoxylate-ene reactions to afford the α-hydroxy esters in high % ee's. The specific role of MS 4A and the structure of actual catalytic species are discussed. The most striking is the observation of positive non-linear effect (asymmetric amplification) that the catalyst derived from BINOL of ca. 40% ee affords the product of >90% ee. The BINOL-derived titanium catalysts work well for other carbon-carbon bond forming reactions such as the Mukaiyama aldol reactions, the (hetero) Diels-Alder reactions, and allylmetal-carbonyl addition reactions.

Recently, asymmetric catalysis has evolved into a rapidly growing, forefront area of chemical research.[1] Of particular importance is to develop asymmetric catalysts particularly for carbon-carbon (C-C) bond forming reactions.[2] Most promising candidates for such enantioselective catalysts are metal complexes bearing a chiral organic ligand.

Glyoxylate-Ene Reaction The ene reaction involving a carbonyl compound as the enophile, which we refer to as "carbonyl-ene reaction",[3] constitutes a useful synthetic method for carbon skeleton construction. In fact, the carbonyl-ene reaction, particularly promoted by a stoichiometric to catalytic amount of Lewis acid, has currently emerged as a useful method for the asymmetric syntheses of acyclic molecules (acyclic stereocontrol).[4]



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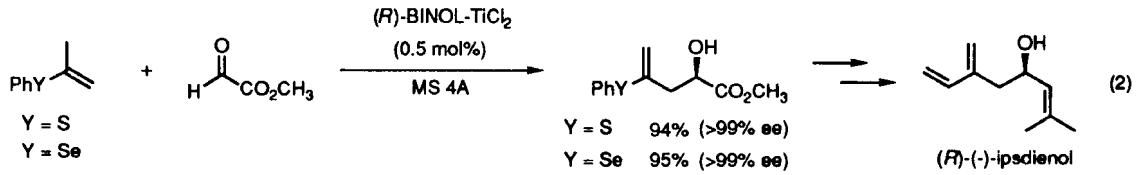
Of special synthetic value among many carbonyl-ene variants is the glyoxylate-ene reaction which provides the α-hydroxy esters of biological and synthetic importance (eq. 1). Before 1986,[5] no asymmetric catalyst had been reported particularly for this ene reaction and we had been engaged in diastereocontrol in the glyoxylate-ene reactions promoted by a substoichiometric amount of various Lewis acid.[6] Based on the experiences and in view of the lengths of metal-oxygen bonds, we decided to employ an early transition metal, titanium, as the central metal for the asymmetric catalyst and a chiral diol for the ligand. We screened various chiral titanium catalysts, prepared in situ from (i-$PrO)_2TiCl_2$ and various chiral diols in the presence of molecular sieves 4A (MS 4A) in the ene reaction of isopropyl glyoxylate with methylenecyclohexane.[7] The best result was obtained with the catalyst derived from an optically pure 1,1'-bi-2,2'-naphthol (BINOL) which is commercially available in either (R) and (S) form. The remarkable levels of enantioselection and rate acceleration observed with the BINOL-derived titanium catalyst stem from the favorable influence of the inherent C_2 symmetry and the higher acidity of BINOL compared to those of aliphatic diols. Particularly notable is that the use of methyl glyoxylate instead of isopropyl glyoxylate provides an enhanced enantioselectivity (97% ee) (eq. 1). The BINOL-derived titanium complexes **1** (BINOL-TiX_2) are thus most conveniently prepared in situ from the reaction of diisopropoxytitanium dihalides ((i-$PrO)_2TiX_2$: X=Br[8] or Cl[9])) with BINOL in the presence of MS 4A.

The present asymmetric catalysis is applicable to a variety of 1,1-disubstituted olefins to provide the ene products in extremely high % ee by the judicious choice of the dibromo or dichloro catalyst. In the reactions with mono- and 1,2-disubstituted olefins, however, no ene product was obtained. The limitation has been overcome by the use of vinylic sulfide and selenide instead of mono- and 1,2-disubstituted olefins to afford the ene products with virtually complete enantioselectivity along with high diastereoselectivity.[10] The synthetic advantage of the vinylic sulfide and selenide approach is exemplified by the enantio-pure synthesis of (R)-(-)-ipsdienol (eq. 2).



Specific Role of Molecular Sieves (Zeolite) The significant feature of our asymmetric catalysis is the specific role of molecular sieves.[5] When the catalyst solution was prepared in the absence of MS 4A, the catalytic ene reaction does proceed but provides a quite low optical yield. However, the use of the catalyst solution prepared in the presence of MS 4A and then via removal of the MS 4A by filtration was found to provide an equally high level of enantioselectivity to that obtained in the reaction in the presence of MS 4A. These results clearly indicate that MS does not play an important role in the ene reaction.

We next turned our attention to the role of MS in the formation of the chiral titanium complex. When BINOL was mixed with $(i\text{-PrO})_2TiCl_2$ in the absence of MS, almost no change was observed on the hydroxy-carbon signal of BINOL in the ^{13}C NMR spectrum. However, addition of MS to the solution of BINOL and $(i\text{-PrO})_2TiCl_2$ brought about a down field shift of the hydroxy-carbon signal, indicating the formation of the BINOL-attached chiral complex. It thus appears likely that MS (zeolite) serves as a certain acid and/or base catalyst[11] and significantly facilitates the alkoxy-ligand exchange in the in situ preparation step of the chiral catalyst, BINOL-$TiCl_2$.

Positive Non-Linear Effect (Asymmetric Amplification) Much interest has currently been focused on the so-called non-linear effect (NLE) in asymmetric catalytic processes, which are of practical and mechanistic importance.[1,12] We have observed a remarkable level of the positive non-linear effect ((+)-NLE)[13] (asymmetric amplification) in the present catalytic ene reaction. The glyoxylate-ene reaction with α-methylstyrene catalyzed by the chiral titanium complex derived from a partially-resolved BINOL of ca. 40% ee, for instance, provides the ene product with >90% ee in >90% chemical yield (Figure 1). Thus, the use of 35-40% ee of BINOL is good enough to provide an equally high (>90% ee) level of % ee to that (94.6% ee) obtained with enantio-pure BINOL. Furthermore, the degree of asymmetric amplification significantly increases with decreasing the concentration (molar ratio) of the BINOL-derived titanium catalyst with a given enantio-purity of BINOL (31.0% ee), on going from 74.9% ee, (170 mM, 100 mol% of BINOL-$TiCl_2$) to 87.6% ee (1.7 mM, 1 mol% of BINOL-$TiCl_2$).

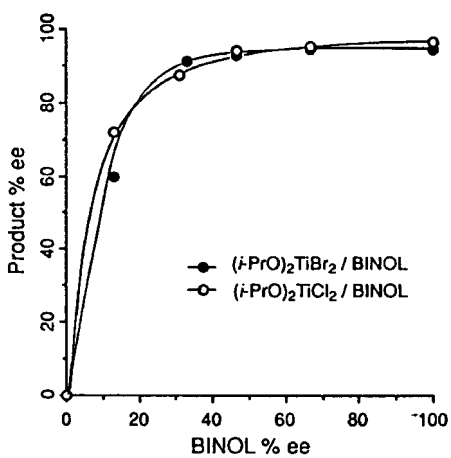


Figure 1. Glyoxylate-ene reaction with α-methylstyrene catalyzed by BINOL-TiX_2 (1.0 mol%).

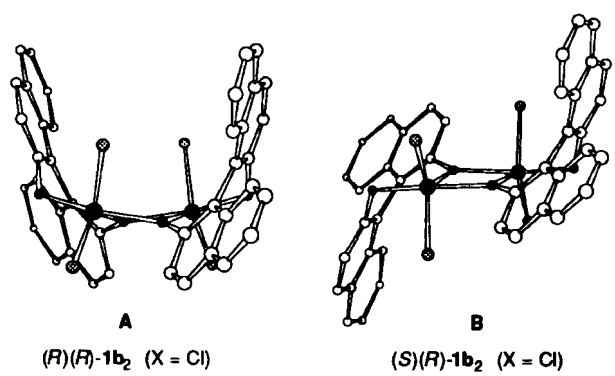


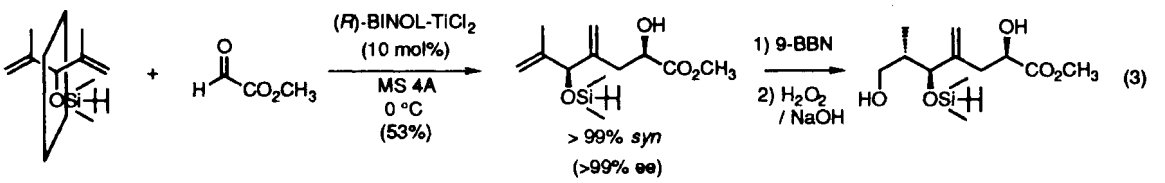
Figure 2. 3-D representation of (*R*)(*R*)-**1b**$_2$ (X = Cl) and (*S*)(*R*)-**1b**$_2$ (X = Cl).

In view of the dinuclear chelate structure determined by X-ray crystal analysis of diphenoxytitanium dichloride,[14] it appears likely that the remarkable NLE is a result of a marked difference in catalytic activity between the diastereomeric dimers, namely, homochiral dimer (R)(R)-**1b**$_2$ (A) and heterochiral dimer

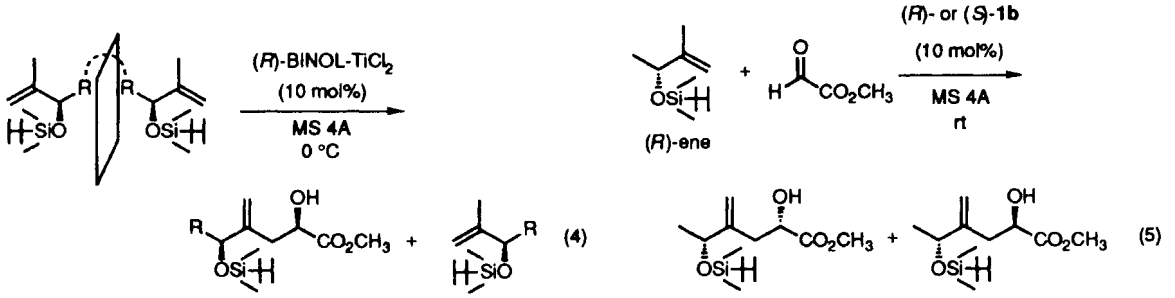
(S)(R)-**1b**$_2$ (**B**) (Figure 2). In fact, simple kinetic studies reveal that the catalytic activity of the titanium complex derived from 100% ee of BINOL is 35 times greater than that of the complex derived from 0% ee of BINOL (10 mol% catalytic scale in 17 mM concentration of BINOL-$TiCl_2$). It thus appears that the complex formed from racemic BINOL is not a racemic mixture of the homochiral (R)(R)- and (S)(S)-enantiomers which should exhibit the same level of catalytic activity, but the meso dimer (R)(S) which is less active. The enantio-pure BINOL would afford the dinuclear chelate complex (**A**) with C_2 symmetry and the distorted Ti_2O_2 four-membered ring. In contrast, racemic BINOL would generate the meso type (C_i symmetric) dinuclear complex (**B**) possessing the coplanar Ti_2O_2 four-membered ring.

The dimeric nature of the BINOL-derived titanium complex was proven by the vapor pressure osmometric molecular weight (MW) measurement in dichloromethane. However, the MW of the (R)(R)-dimer prepared from enantio-pure (R)-BINOL is concentration-dependent ranging from 864 in a 37 mM solution to 762 in a dilute (9.2 mM) solution, thus suggesting that the homochiral dimer dissociates into a monomeric form in a dilute solution. In sharp contrast, the MW of the heterochiral dimer (R)(S) is not concentration-dependent, 872 in 37 mM and 874 in 9.2 mM, clearly indicating that the heterochiral dimer does not dissociate. The observed concentration effect on the MW of the homochiral dimers accounts for the higher degree of asymmetric amplification in lower concentration of the titanium complex. In other words, the dissociated monomer is the actual catalytic species, which is responsible for the equally high % ee to that obtained with enantio-pure BINOL.

Asymmetric Desymmetrization Desymmetrization of an achiral, symmetrical molecule through a catalytic process is a potentially powerful but relatively unexplored concept for asymmetric synthesis. While the ability of enzymes to differentiate between enantiotopic functional groups is well known, little has been explored on a similar ability of non-enzymatic catalysts, particularly for C-C bond forming processes. The desymmetrization by the enantiofacial selective glyoxylate-ene reaction of prochiral ene substrates with the planar symmetry provides an efficient access to remote and internal asymmetric induction which is otherwise difficult to attain (eq. 3).[15] The (2R,5S)-syn-product is obtained in >99% ee along with more than 99% diastereoselectivity. The product once desymmetrized can be transformed to a more functionalized compound in a regioselective and diastereoselective manner.



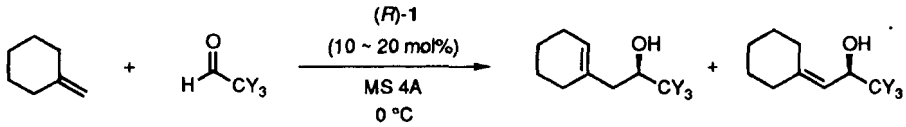
Kinetic Optical Resolution On the basis of the desymmetrization concept, the kinetic optical resolution of a racemic substrate[16] might be recognized as an intermolecular desymmetrization. The kinetic resolution of a racemic allylic ether by the glyoxylate-ene reaction also provides an efficient access to remote but relative asymmetric induction. The reaction of allylic ethers catalyzed by the (R)-BINOL-derived complex provides the 2R,5S-syn-products with >99% diastereoselectivity along with > 95% ee (eq. 4).



R = *i*-Pr	34%	>99% *syn* (99.5% ee)	54% (59.4% ee)	(*S*)-**1b**	>99	: <1	(71%)
R = Me	20%	>99% *syn* (96.2% ee)	59% (22.0% ee)	(*R*)-**1b**	50	: 50	(33%)

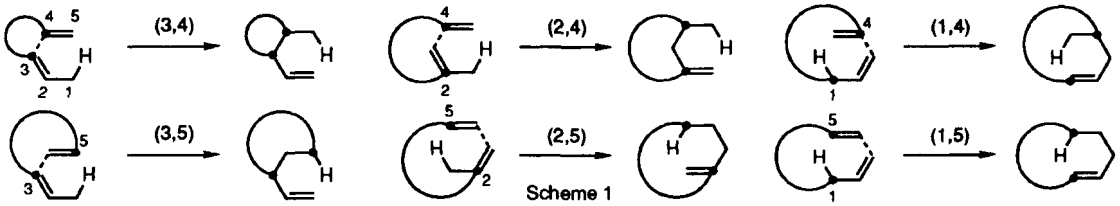
The high diastereoselectivity, coupled with the high % ee, strongly suggests that the catalyst/glyoxylate complex efficiently discriminates between the two enantiomeric substrates to accomplish the effective kinetic resolution. In fact, the relative rates between the reactions of the ether enantiomers, calculated by the equation $(\ln[(1-c)(1-ee_{recov})]/\ln[(1-c)(1+ee_{recov})]$, $c=ee_{recov}/(ee_{recov}+ee_{prod})$, $0<c$, $ee<1$ where c is the fraction of consumption), were ca. 700 for R = i-Pr and 65 for R = Me. As expected, the double asymmetric induction[17] in the reaction of (R)-ene component using the catalyst (S)-**1b** ("matched" catalytic system) leads to the complete (>99%) 1,4-syn-diastereoselectivity in high chemical yield, whereas the reaction of (R)-ene using (R)-**1b** ("mis-matched" catalytic system) produces a diastereomeric mixture in quite low yield (eq. 5).

Other Types of Carbonyl Enophiles It is highly desirable to develop other types of carbonyl enophiles, which eventually provide enantio-enriched molecules with different functionality. For example, we have recently developed the asymmetric catalytic fluoral-ene reaction,[18] which provides an efficient approach for the asymmetric synthesis of fluorine containing substrates of biological and synthetic importance. The fluoral-ene reaction proceeds smoothly by the catalysis of BINOL-$TiBr_2$ or -$TiCl_2$ to provide the corresponding homoallylic alcohol in >95% ee, but together with the formation of the allylic alcohol as byproducts (eq. 6). Interestingly, much lower ee's were observed and more allylic alcohols were formed when chloral was used as the enophile. Thus, the ene reactivity of trihaloacetaldehydes including chloral has been analyzed in terms of the balance of LUMO energy level with the electron density on the carbonyl-carbon on the basis of the MNDO, PM3, and 6-31G** levels.[18a]



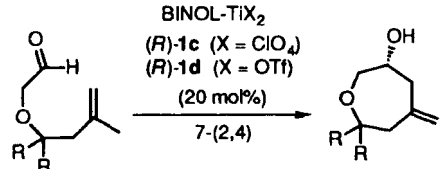
Y = F	X = Br (1a)	79 (>95% ee)	:	21 (>95% ee)	(95%)
	X = Cl (1b)	76 (>95% ee)	:	24 (>95% ee)	(93%)
Y = Cl	X = Br (1a)	48 (45% ee)	:	52 (80% ee)	(40%)
	X = Cl (1b)	52 (34% ee)	:	48 (66% ee)	(49%)

Carbonyl-Ene Cyclization Conceptually, intramolecular ene reactions (ene cyclization) can be classified into six different modes of cyclizations (Scheme 1).[3,19] In the ene cyclizations, the carbon numbers where the tether connects the [1,5]-hydrogen shift system, are expressed in (m,n) fashion. A numerical prefix (l-) stands for the forming ring size.

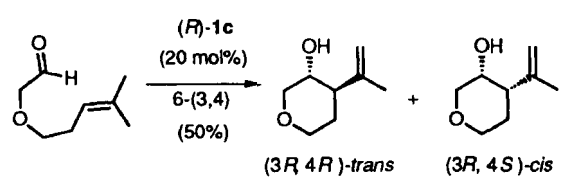


Scheme 1

We have reported the asymmetric catalysis of carbonyl-ene cyclization of both types (2,4) (eq. 7) and (3,4) (eq. 8) using the modified BINOL-Ti complexes (R)-BINOL-TiX_2 (X=ClO_4 or OTf).[19,20] The modified titanium complexes, BINOL-$Ti(ClO_4)_2$ or -$Ti(OTf)_2$, can easily be prepared by the addition of silver perchlorate or triflate (2 equiv) to the chloride **1b**. Thus, the catalytic 7-(2,4) carbonyl-ene cyclization gives the oxepane in a high % ee, where the gem-dimethyl groups are not required (eq. 7).



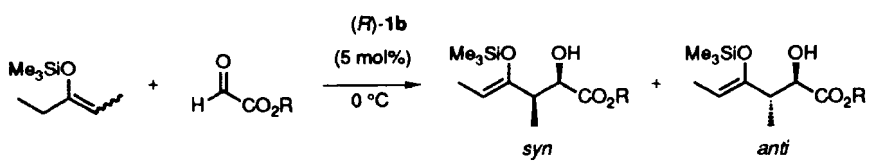
R = H	(R)-1c	91% ee	(43%)
	(R)-1d	92% ee	(40%)
R = Me	(R)-1c	82% ee	(40%)



(3*R*, 4*R*)-*trans* (3*R*, 4*S*)-*cis*

80 (84% ee) : 20 (74% ee)

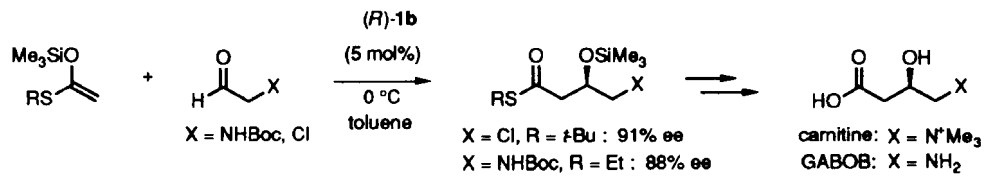
Mukaiyama Aldol Condensation Aldol reactions constitute one of the most fundamental bond construction processes in organic synthesis. Therefore, much attention has currently been focused on the asymmetric catalysis of aldol reactions and the detailed understanding of the reaction mechanisms. We have found that the BINOL-derived titanium complex also serves as an efficient catalyst for the "Mukaiyama-type aldol reaction" of ketone enol silyl ethers with control of absolute and relative stereochemistry (eq. 9).[21] Surprisingly, however, the aldol products were obtained as the enol silyl ether (ene product) form with high syn-diastereoselectivity from either geometrical isomer of the starting enol silyl ethers.



syn *anti*

86% *Z*	R = Me	(58%)	98 (94% *Z*, 99% ee)	:	2	
	R = *n*-Bu	(63%)	99 (99% *Z*, 99% ee)	:	1	
73% *E*	R = Me	(54%)	98 (96% *Z*, 99% ee)	:	2	

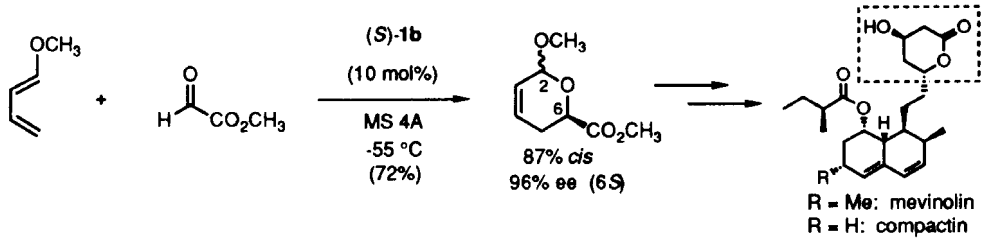
Furthermore, the silatropic ene pathway, in other words, direct silyl transfer from an enol silyl ether to an aldehyde, may be involved as a possible mechanism in the Mukaiyama aldol-type reaction. Recently, we have reported the possible intervention of silatropic ene pathway in the asymmetric catalytic aldol-type reaction with the enol silyl ethers of thioesters (eq. 10).[22] Chloro and amino compounds thus obtained are useful intermediates for the synthesis of carnitine and GABOB.



(10)

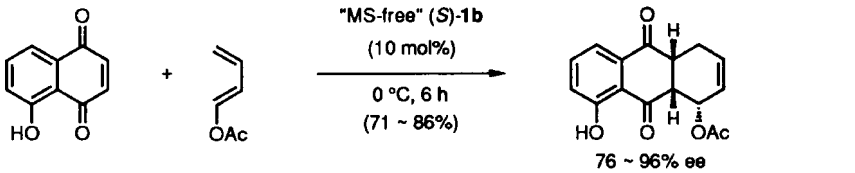
(Hetero) Diels-Alder Reaction The (hetero) Diels-Alder reactions are also one of the most efficient C-C bond forming processes in the construction of six-membered rings. In the course of the asymmetric catalytic glyoxylate-ene reactions, we have found that the use of isoprene as an ene component provides not only the carbonyl-ene product but also the D.-A. product in extremely high enantioselectivities.

The hetero D.-A. reaction with 1-methoxy-1,3-butadiene instead of isoprene proceeds smoothly by the catalysis of BINOL-$TiCl_2$ **1b** to give the cis-product in a high % ee (eq. 11).[11,23] The hetero D.-A. product can be transformed not only to monosaccaride[24] but also to the lactone portion of HMG-Co A inhibitors such as mevinolin or compactin[25] in short steps (eq. 11).



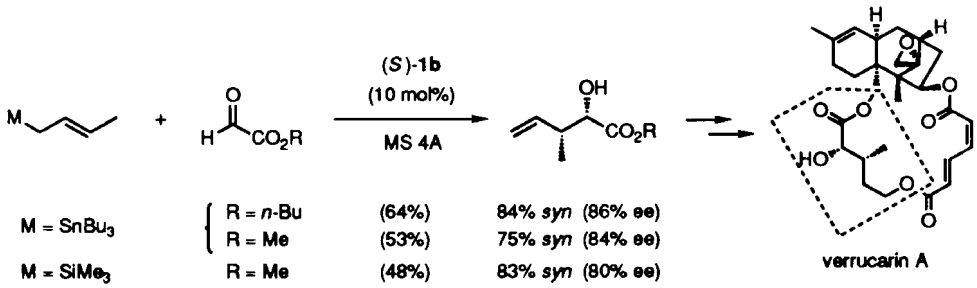
(11)

The D.-A. reaction of methacrolein with 1,3-dienol derivatives can also be catalyzed by the BINOL-derived titanium complex BINOL-$TiCl_2$ to give the endo-adduct in a high % ee.[11,26] The asymmetric catalytic D.-A. reaction of juglone provides, however, by the catalysis of a "MS-free"[11] BINOL-Ti complex, an entry to the asymmetric synthesis of tetra- and anthracyclinone[27] aglycones (eq.12).



(12)

Carbonyl Addition of Allylic Silanes and Stannanes Furthermore, the chiral titanium complex also catalyzes the carbonyl addition reaction of allylic silanes and stannanes. Thus, the reactions of glyoxylate with (E)-2-butenylsilane and -stannane proceed to afford the syn-product in a high % ee (eq.13).[21b,28] The syn-product can be readily converted to the lactone portion of verrucaline A.



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