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Recent Progress in Chiral Multinucleating System Utilizing Tartaric Acid Esters

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ABSTRACT: In order to develop a practical method for the construction of chiral molecules, we have designed a novel chiral reaction system possessing multi-metal centers utilizing tartaric acid ester as a chiral auxiliary. Based on this concept, we have developed an asymmetric 1,3-dipolar cycloaddition reaction of azomethine imines, an asymmetric hetero Diels-Alder reaction of nitroso compounds, an asymmetric Diels-Alder reaction of *o*-quinodimethanes. Furthermore, an asymmetric nucleophilic addition of alkynylzinc reagents, prepared *in situ* from dialkylzinc and 1-alkynes, to nitrones was achieved with high level of stereocontrol. In the last case, the addition of methylzinc salt of a product-like racemic hydroxylamine was found to be effective for unprecedented enhancement of enantioselectivity.

Key words: asymmetric synthesis, 1,3-dipolar cycloaddition, Diels-Alder reaction, nucleophilic addition, tartaric acid ester, azomethine imine, nitrone, enhancement of enantioselectivity

Introduction

The synthesis of chiral compounds has attracted considerable attention in the areas of synthetic organic chemistry.[1] The development of new chiral reaction systems is quite important and various types of enantioselective reactions were developed based on metal containing chiral reaction systems. Most of ever developed asymmetric reaction systems contain one metal center in a chiral coordination sphere and often have limit in terms of enantioselectivity and substrate generality. It is well known that superior reaction systems exist in nature involving the cooperation of two or more metal centers.[2] By learning from nature, the principle of multimetallic chiral reaction system could offer many advantages over the systems comprised of single metal center. Recently several reaction systems were

developed by organizing two or more metal centers.[3,4] We have already designed a novel chiral reaction system possessing two metal centers on a tartaric acid ester as follows:[5] If reactants A and B were bound to two different metal centers M^1, M^2 of the dialkoxide, which was derived from tartaric acid ester and might form a rigid 5/5-fused bicyclic dinucleating structure, both reactants might be ideally oriented and/or activated by the metals, and the subsequent reaction might proceed in an enantioselective manner to afford the corresponding optically active products (Figure 1). Furthermore, the third metal M^3 could be assembled by coordination of ester carbonyl and alkoxide oxygens, and reactant C bound to M^3 could take part in the reaction (Figure 2). Based on this hypothesis, we developed a series of asymmetric Simmons-Smith reaction, asymmetric 1,3-dipolar cycloaddition reactions, and asymmetric nucleophilic additions, and have reviewed early part of them.[6] Herein we will describe our recent advances in asymmetric cycloaddition reactions and nucleophilic addition reactions with brief summary of our previous results.

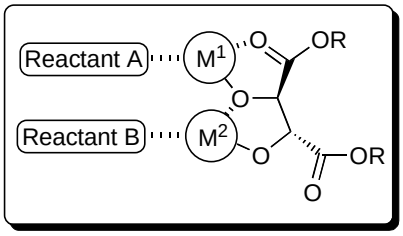


Figure 1

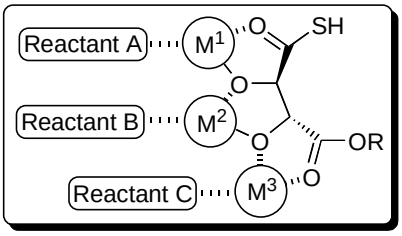
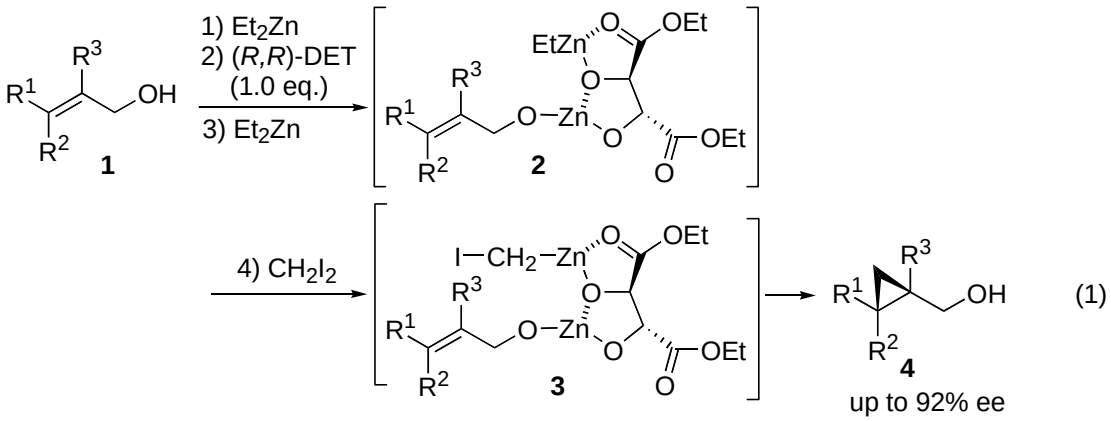


Figure 2

Asymmetric Simmons-Smith Reaction

The asymmetric Simmons-Smith reaction is a novel method for preparing optically active cyclopropanes and there had been no reports of enantioselective Simmons-Smith reactions when our project started.[7] Our proposal for a novel asymmetric Simmons-Smith reaction was based on the following analysis. When allylic alcohol **1** was treated successively with diethylzinc, (*R*,*R*)-tartaric acid ester, and second diethylzinc, the dinucleating intermediate **2** possessing an ethylzinc moiety might be generated. To the intermediate is added diiodomethane, ethylzinc moiety acts as a reductant resulting in the formation of the bis-zinc containing intermediate **3**, which has an iodomethyl zinc moiety. Ensuing Simmons-Smith reaction within this complex is expected to proceed enantioselectively (Eq. 1). Actually, by the use of diethyl (*R*,*R*)-tartrate [(*R*,*R*)-DET] as a chiral auxiliary, the corresponding cyclopropylmethyl alcohols **4** were obtained with the enantioselectivity up to 92% ee.[8]

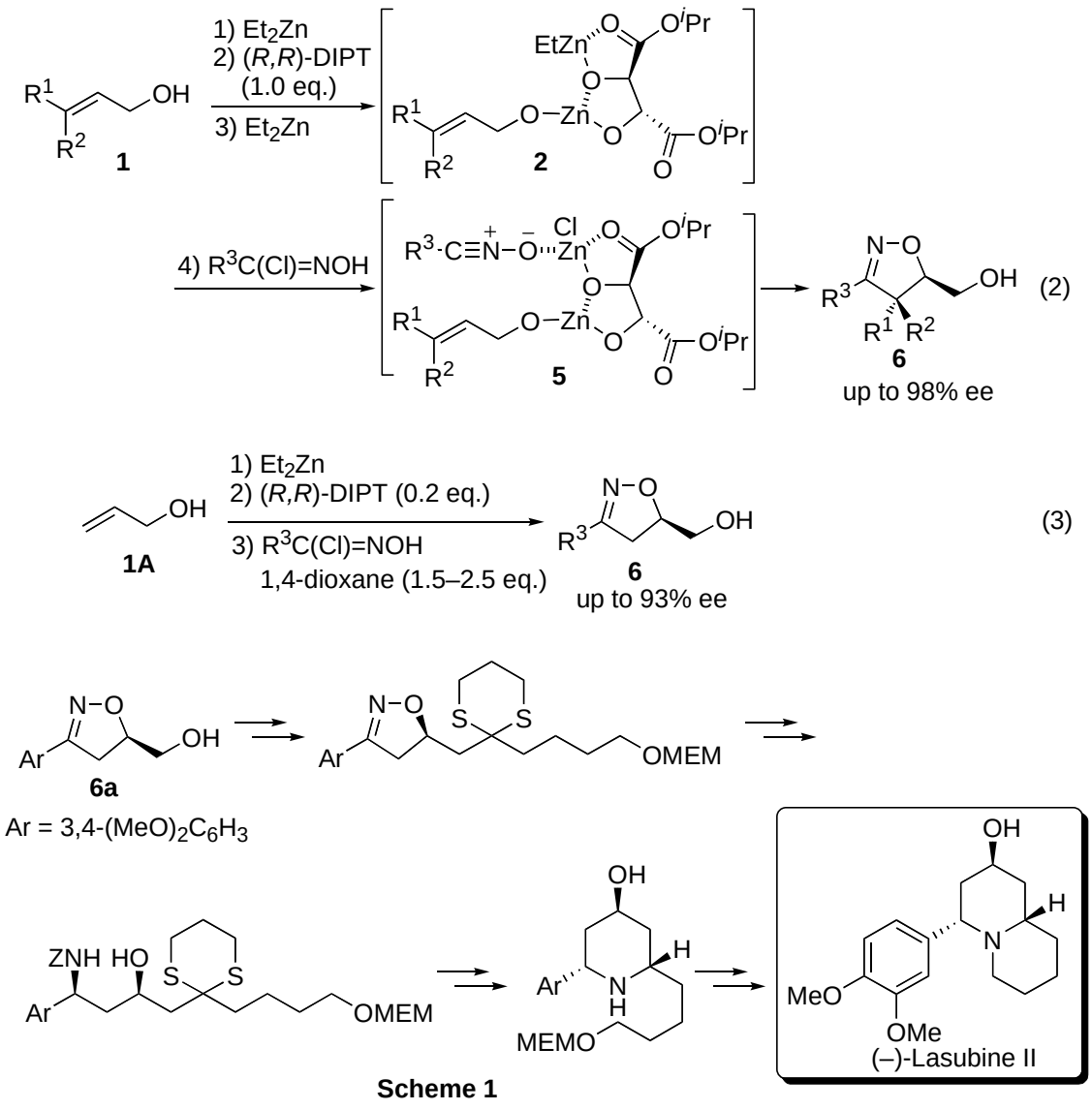


(1)

Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides and Nitrones

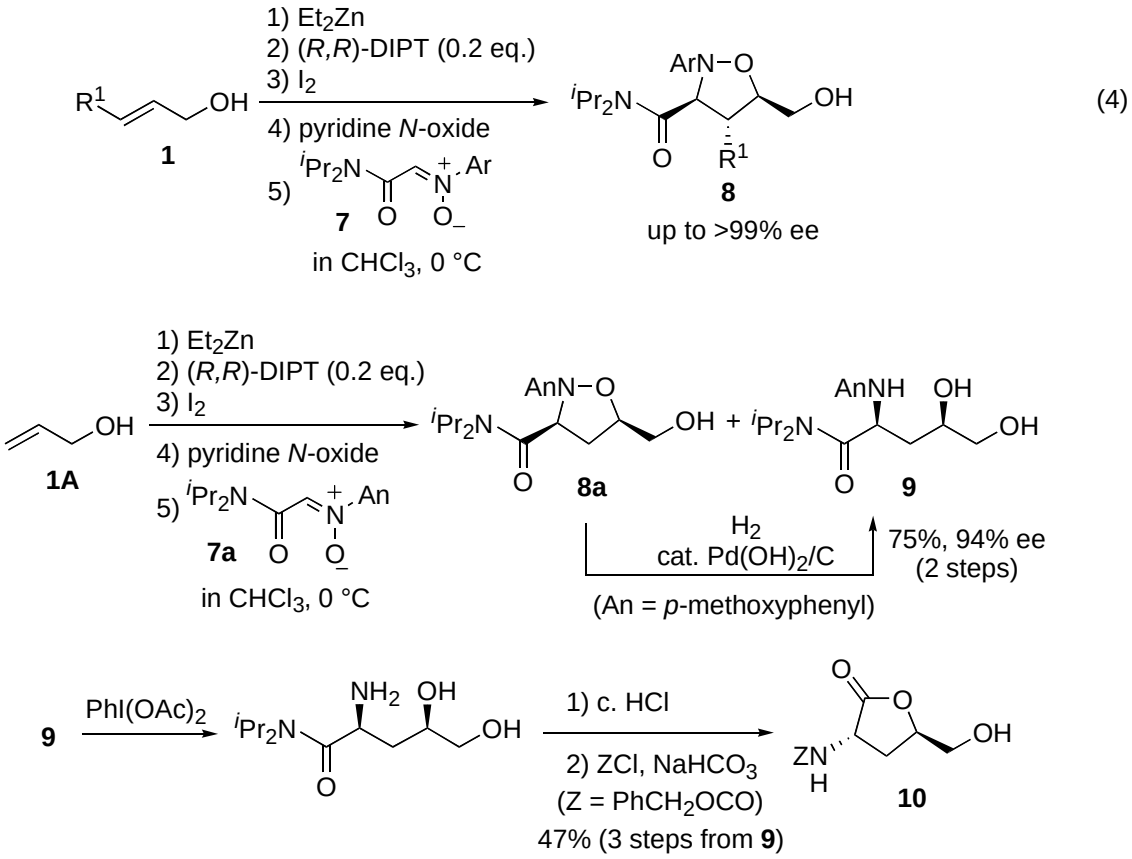
Cycloadditions have been the focus of considerable attention in synthetic organic chemistry, since it can create contiguous carbon stereocenters.[9] Although, among [4π+2π] cycloadditions, the asymmetric Diels-Alder reaction using chiral Lewis acids stands as a landmark achievement, the enantioselective 1,3-dipolar cycloaddition, which is one of the most important methods for the construction of heterocyclic 5-membered rings in organic chemistry,[10] had yet to meet with success when the present research project started. The current challenge for 1,3-dipolar cycloaddition is to control the absolute configuration because the multiple chiral centers can be formed in a single step.[11]

A novel chiral multinucleating system utilizing tartaric acid ester as a chiral auxiliary was found to be promising for the Simmons-Smith reaction as described above. This result prompted us to firstly apply the strategy to the asymmetric 1,3-dipolar cycloaddition of nitrile oxides. Our idea was presented as follows: when allylic alcohol **1** (R^3 = H) was treated successively with diethylzinc, (*R,R*)-tartaric acid ester, and second diethylzinc, the dinucleating intermediate **2** possessing an ethylzinc moiety might be generated as in the case of asymmetric Simmons-Smith reaction. When hydroximoyl chloride is added to the intermediate, ethylzinc moiety acts as a base to generate the nitrile oxide *in situ* as depicted as **5** in Eq. 2, and the subsequent 1,3-dipolar cycloaddition is anticipated to proceed in a stereoselective manner to give the corresponding 2-isoxazoline **6** in an optically active form. In accordance with this hypothesis, the asymmetric 1,3-dipolar cycloaddition of nitrile oxides to allylic alcohols was realized to afford the corresponding 2-isoxazolines **6** with excellent enantioselectivity. Even when a catalytic amount (0.2 eq.) of (*R,R*)-DIPT was employed, the 2-isoxazolines **6** were obtained with the selectivity of up to 93% ee by the addition of a small amount of 1,4-dioxane (Eq. 3). This method was the first catalytic enantioselective 1,3-dipolar cycloaddition of nitrile oxides with alkenes. The method was efficiently applied to the total synthesis of (–)-Lasubine II (Scheme 1).[12,13]



Scheme 1

The asymmetric 1,3-dipolar cycloaddition of nitrones instead of nitrile oxides was also realized: The nitrones **7** possessing an amide moiety were reacted with allylic alcohols **1** (R^2, R^3 = H) by the use of a catalytic amount of (*R*,*R*)-DIPT as a chiral auxiliary to afford the corresponding 3,5-*cis*-isoxazolidines **8** with high regio-, diastereo-, and enantioselectivity up to over 99% ee (Eq. 4). This asymmetric 1,3-dipolar cycloaddition was applied to the synthesis for the (2*S*,4*R*)-4,5-dihydroxynorvaline derivative **10**, which is a key component of Polyoxin E, via amino alcohol intermediate **9** (Scheme 2).[14,15]



Scheme 2

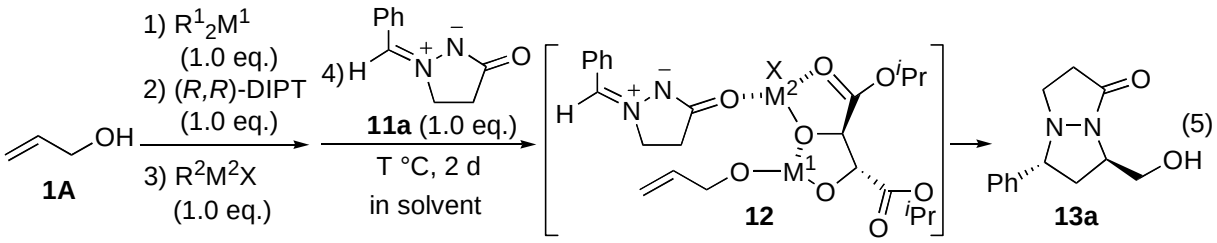
Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Imines

Although a lot of cycloadditions of nitrone possessing nitrogen and oxygen atoms have been developed, the cycloaddition of 1,3-dipoles with two nitrogen atoms were still limited. We turned our attention to develop the enantioselective 1,3-dipolar cycloaddition of azomethine imines.[16]

First the 1,3-dipolar cycloaddition of 1-benzylidene-3-oxopyrazolidin-1-ium-2-ide (**11a**) was examined in CH_2Cl_2 at room temperature. When 2-propen-1-ol (**1A**) was treated with 1.0 eq. of diethylzinc, (*R,R*)-DIPT, and ethylzinc halide, zinc bridging intermediate **12** (M^1 = M^2 = Zn) would be formed and the subsequent asymmetric 1,3-dipolar cycloaddition was anticipated to proceed (Eq. 5). In this case, however, such 1,3-dipolar cycloaddition did not occur (Table 1, Entry 1). It was found that a magnesium-mediated system instead of the zinc-mediated system was effective to realize the 1,3-dipolar cycloaddition; i.e., **1A** was successively treated with dibutylmagnesium, (*R,R*)-DIPT, butylmagnesium bromide, and **11a** to give the corresponding *trans*-pyrazolidine **13a** in 23% yield with enantioselectivity of 79% ee (Entry 3) with complete regio- and diastereoselectivities. A magnesium-zinc mixed system was less effective (Entry 2). The effect of solvent was examined. In halogenated

solvents, enantioselectivities were not altered much (Entries 3-5). Nitriles were found to be the solvent of choice to realize excellent enantioselectivities (Entries 6 and 8). When the reaction temperature was raised to accelerate the cycloaddition, the chemical yields were improved without remarkable decrease of enantioselectivities (Entries 6-10). In CH_3CN, the cycloadduct was obtained in 66% yield with the enantioselectivity of 88% ee.

Table 1. The asymmetric 1,3-dipolar cycloaddition of azomethine imine **11a** to allyl alcohol (**1A**).

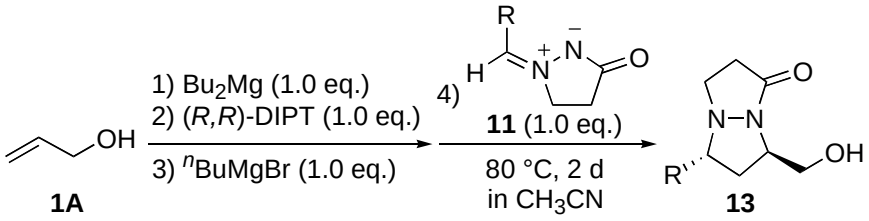


Entry	$R^1_2M^1$	R^2M^2X	Solvent	T/°C	Yield of **13a**/%	ee/%
1	Et_2Zn	EtZnCl	CH_2Cl_2	25	--	--
2	Et_2Zn	^{n}BuMgBr	CH_2Cl_2	25[a]	3	61
3	Bu_2Mg	^{n}BuMgBr	CH_2Cl_2	25	23	79
4	Bu_2Mg	^{n}BuMgBr	$CHCl_3$	25	20	84
5	Bu_2Mg	^{n}BuMgBr	$Cl(CH_2)_2Cl$	25	28	77
6	Bu_2Mg	^{n}BuMgBr	CH_3CN	25	15	90
7				80	66	88
8	Bu_2Mg	^{n}BuMgBr	C_2H_5CN	25	23	92
9				80	64	88
10				97	53	90

a) The reaction time was 3 d.

The asymmetric cycloaddition of several azomethine imines **11** to allyl alcohol (**1A**) was performed in CH_3CN at 80 °C as shown in Table 2. Aryl-substituted azomethine imines **11a**–**11f** realized high enantioselectivities (Entries 1–6). The cycloaddition of pentyl- and cyclohexyl-substituted azomethine imines **11g**, **11h** proceeded in moderate stereoselective manners (Entries 7 and 8), while *t*-butyl-substituted azomethine imine **11i** resulted in high enantioselectivity (Entry 9).

Table 2. The asymmetric 1,3-dipolar cycloaddition of azomethine imines **11**.

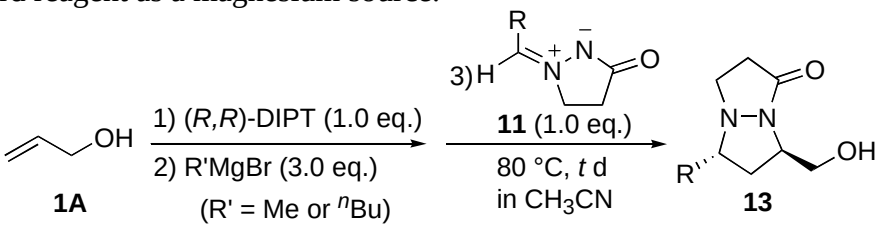


(6)

Entry	R	**11**	Yield of **13**/%	ee/%
1	Ph	**a**	66	88
2	$^{p}EtC_6H_4$	**b**	57	92
3	$^{p}MeOC_6H_4$	**c**	49	92
4	$^{p}ClC_6H_4$	**d**	67	91
5	$^{p}O_2NC_6H_4$	**e**	53	88
6	2-Furyl	**f**	42	82
7	^{n}Pen	**g**	7	72
8	^{c}Hex	**h**	17	54
9	^{t}Bu	**i**	36	89

Next, in order to make the procedure simpler, only Grignard reagent was used as a magnesium source instead of dibutylmagnesium. It is well known that dibutylmagnesium could be generated from 2.0 eq. of butylmagnesium bromide accompanied with generation of $MgBr_2$. To a mixture of allyl alcohol (**1A**) and (*R*,*R*)-DIPT were added 3.0 eq. of butylmagnesium bromide and azomethine imine **11a** successively (Eq. 7). Surprisingly, the pyrazolidine **13a** was obtained in an enhanced chemical yield with the excellent enantioselectivity (Table 3, Entry 1). The 1,3-dipolar cycloaddition of several other azomethine imines **11** also realized excellent enantioselectivities as listed in Table 3, even in the case of pentyl- and cyclohexyl-substituted ones **11g**, **11h** (Entries 7 and 8).[17]

Table 3. The asymmetric 1,3-dipolar cycloaddition of azomethine imines **11** by the use of only Grignard reagent as a magnesium source.



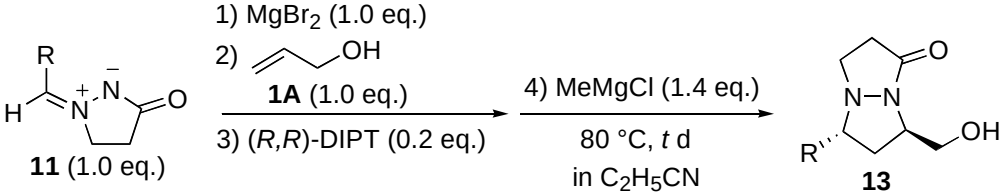
(7)

Entry	R	**9**	*t*/d	Yield of **13**/%	ee/%
1	Ph	**a**	4	81	94
2	$^{p}EtC_6H_4$	**b**	4	57	96
3	$^{p}MeOC_6H_4$	**c**	2	75	94
4	$^{p}ClC_6H_4$	**d**	2	75	94
5	$^{p}O_2NC_6H_4$	**e**	4	66	94
6	2-Furyl	**f**	2	60	88
7	^{n}Pen	**g**	3	51	96
8	^{c}Hex	**h**	4	78	94
9	^{t}Bu	**i**	4	50	96

Toward improvement of this method, we paid efforts to establish the catalytic reaction system. The reaction was carried out by an alternative procedure: Azomethine imines **11** were treated with $MgBr_2$ in C_2H_5CN to get a clear solution, followed by subsequent addition of allyl alcohol (**1A**), a catalytic amount of (*R*,*R*)-DIPT, and Grignard reagent as shown in Eq. 8. The reproducible higher enantioselectivity was realized when the 1,3-dipolar cycloaddition was performed in the presence of an equimolar amount of $MgBr_2$ in C_2H_5CN. Furthermore, the use of alkylmagnesium chloride as a Grignard reagent to generate

magnesium alkoxides improved the enantioselectivity. The catalytic asymmetric cycloaddition of several azomethine imines **11** to allyl alcohol (**1A**) was performed in the presence of $MgBr_2$ as shown in Table 4. Aryl-substituted azomethine imines **11c** and **11d** realized high enantioselectivities (Entries 2 and 3). The cycloaddition of pentyl- and cyclohexyl-substituted azomethine imines **11g** and **11h** also proceeded in an enantioselective manner (Entries 4 and 5). *t*-Butyl-substituted azomethine imine **11i** resulted in the highest enantioselectivity of 93% ee (Entry 6).[18]

Table 4. The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine imines **11**.



(8)

Entry	R	**11**	*t*/d	Yield of **13**/%	ee/%
1	Ph	**a**	2	70	87
2	$^{p}MeOC_6H_4$	**c**	2	63	89
3	$^{p}ClC_6H_4$	**d**	2	74	84
4	^{n}Pen	**g**	2	54	81
5	^{c}Hex	**h**	4	71	84
6	^{t}Bu	**i**	4	65	93

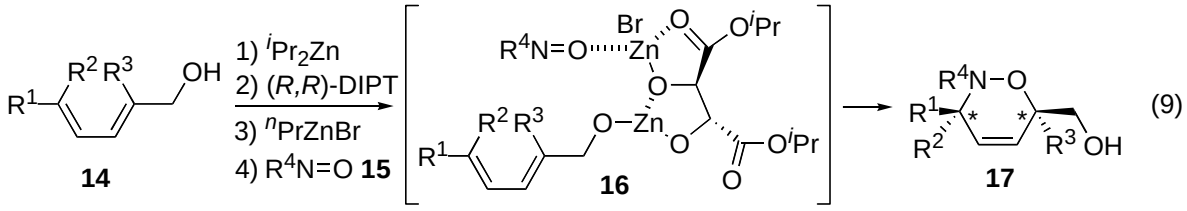
Asymmetric Diels-Alder Reactions

We anticipated that tartaric acid ester based chiral multi-nucleating system described above would also serve as important stereochemical control elements in asymmetric hetero Diels-Alder reaction of nitroso compound and the asymmetric Diels-Alder reaction of *o*-quinodimethanes.

The hetero Diels-Alder reaction provides a very convenient approach to the synthesis of six-membered partially saturated heterocycles, a class of compounds that have been found extensive use as starting materials for total syntheses of natural products.[19] A wide range of nitroso compounds have been proven to be useful dienophiles for the hetero Diels-Alder reaction to afford dihydro-1,2-oxazine derivatives, which are key intermediates for the synthesis of biologically active nitrogen-containing chemicals.[20] Development of asymmetric hetero Diels-Alder reaction of nitroso compounds was for a long time restricted to only diastereoselective reactions using chiral dienes or chiral nitroso compounds in spite of

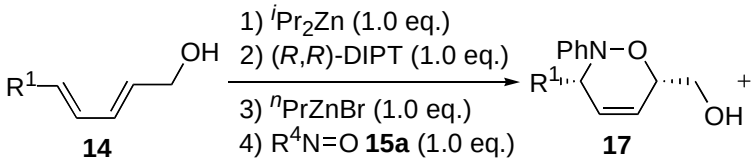
the great potential of the synthetic methodology. Recently catalytic hetero Diels-Alder reactions of nitroso compounds catalyzed by chiral metal complexes were reported.[21]

When dienol **14** is successively treated with diisopropylzinc, (*R*,*R*)-DIPT, and propylzinc bromide, a zinc-bridging intermediate shown in **16** would be presumably formed. To the intermediate is added a nitroso compound **15**, it can be activated and well oriented to allow the subsequent hetero Diels-Alder reaction in an enantioselective manner and the corresponding optically active dihydro-1,2-oxazine derivatives **17** is expected to be produced (Eq. 9). Based upon this hypothesis, the hetero Diels-Alder reaction was examined.



(9)

First, the enantioselective hetero Diels-Alder reaction between nitrosobenzene (**15a**) and (*E*)-2,4-pentadien-1-ol (**14A**, R^1 = H) was examined (Eq. 10). The corresponding dihydro-1,2-oxazine derivative was obtained as a mixture of regioisomers with different N-O orientation in favor of **17Aa**, in which oxygen of the nitroso group oriented toward the diene carbon bearing CH_2OH moiety. The enantioselectivity of the major product **17Aa** was 33% ee. The hetero Diels-Alder reaction to (*E*,*E*)-2,4-hexadien-1-ol (**14B**, R^1 = Me) was also examined to give **17Ba** with the enantioselectivity of 55% ee along with the regioisomer (Eq. 10). This modest enantioselectivity encouraged us to further investigate the reaction for a sterically locked dienol.

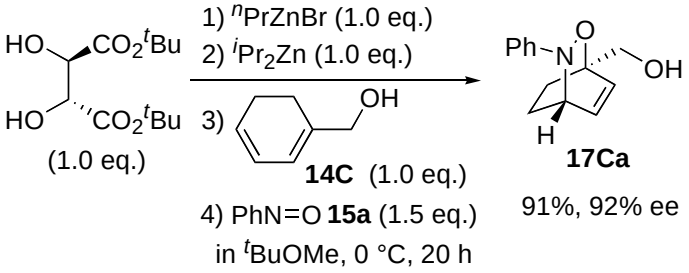


Aa; R^1 = H, 37%, 33% ee 13% yield
Ba; R^1 = Me, 57%, 55% ee 28% yield

(10)

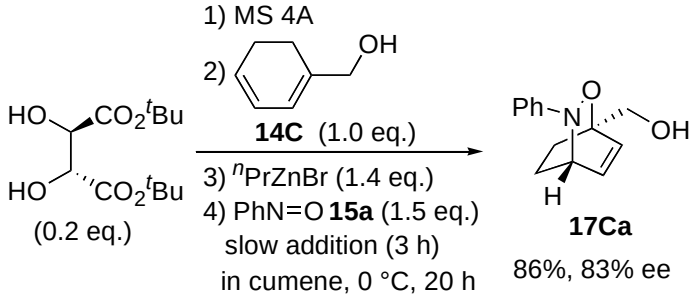
When cyclohexa-1,3-dienylmethanol (**14C**) was used as a diene component, we were pleased to find that the reaction proceeded in complete regioselective manner. An alternative procedure was tried by successively treating tartaric acid ester with propylzinc bromide and diisopropylzinc, followed by addition of the dienol **14C** and nitrosobenzene (**15a**). The effects of solvent and chiral auxiliary were also examined. Finally, the

corresponding bicyclic dihydro-1,2-oxazine **17Ca** was obtained with high enantioselectivity of 92% ee by utilizing bulky di(*t*-butyl) (*R,R*)-tartrate [(*R,R*)-DTBT] as a chiral auxiliary (Eq. 11). To our surprise, the sense of enantiofacial discrimination of **14C** was opposite to that in the case of **14A**, that is, nitrosobenzene (**15a**) attacked from *re*-face at the C1 position of **14C**, while the reaction occurred from *si*-face at the C2 position of **14A**.[22]



(11)

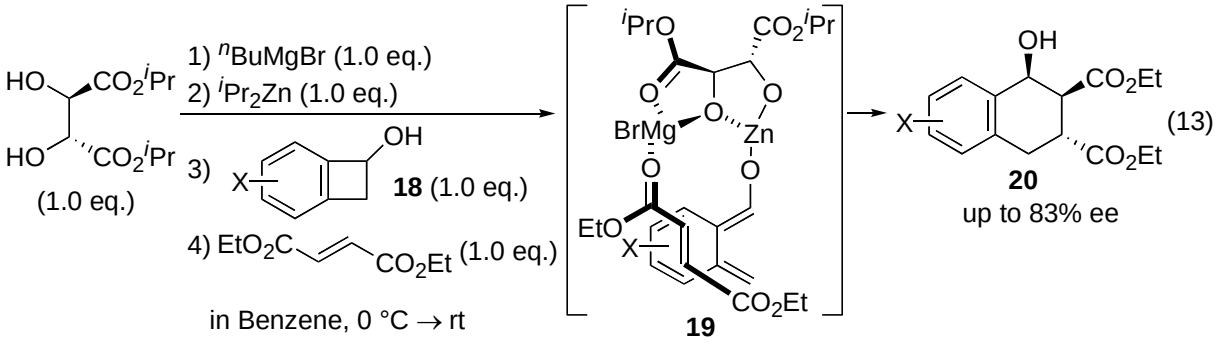
A catalytic version of the asymmetric hetero Diels-Alder reaction of the nitroso compound **15a** with the dienol **14C** was also achieved to afford the corresponding optically active cycloadduct **17Ca** with 83% ee. The addition of MS 4A was crucial to realize reproducible high enantioselectivity (Eq. 12).[22b]



(12)

Next, we investigated an asymmetric Diels-Alder reaction of *o*-quinodimethanes generated *in situ* from benzocyclobutenols utilizing a tartaric acid ester as a chiral auxiliary. The Diels-Alder reaction of *o*-quinodimethane with olefins is a useful method to construct the corresponding tetrahydronaphthalene frameworks bearing up to four stereocenters, which are key intermediates for the synthesis of polycyclic compounds in one step.[23] Especially the Diels-Alder reaction of *α*-hydroxy *o*-quinodimethane is useful to afford oxygen-functionalized tetrahydronaphthalenes. Although several diastereoselective Diels-Alder reactions of *o*-quinodimethanes were reported for the synthesis of optically active tetrahydronaphthalenes, enantioselective ones were scarcely reported,[24] despite of recent development of asymmetric Diels-Alder reactions catalyzed by chiral Lewis acid.

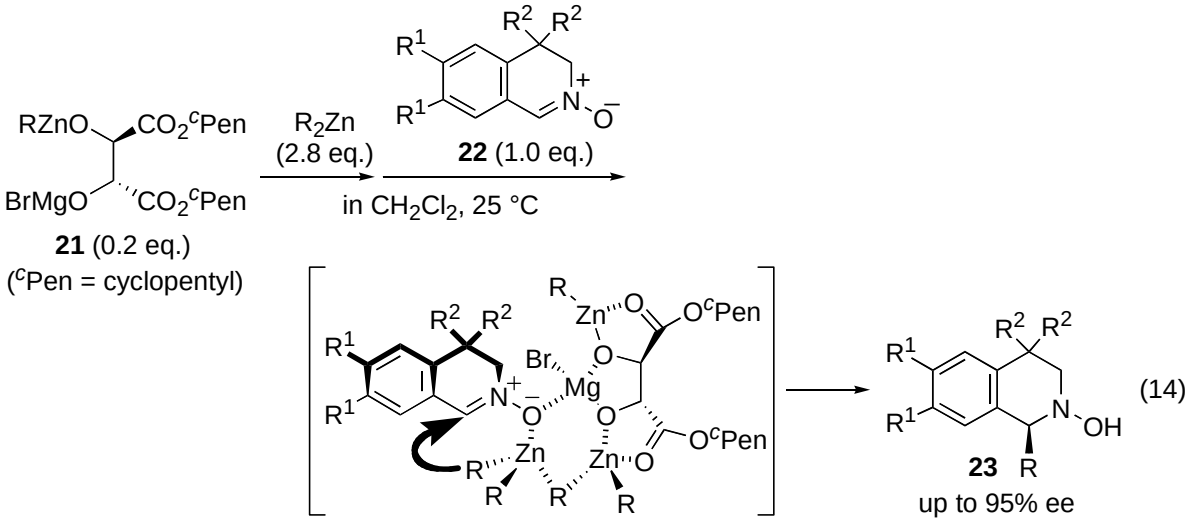
When (*R*,*R*)-DIPT is successively treated with butylmagnesium bromide, diisopropylzinc, and benzocyclobutenols **18**, magnesium and zinc bridging intermediate might be formed. After addition of fumaric acid ester, which is anticipated to coordinate to the more Lewis acidic magnesium of the intermediate, the intermediary complex **19** containing the *o*-quinodimethane generated by electrocyclic ring-opening reaction might be formed, followed by Diels-Alder reaction to afford the corresponding optically active tetrahydronaphthalenes **20**. When benzene was used as a solvent, the corresponding 1,2-*cis*-tetrahydronapthalene **20** was produced in up to 83% ee (Eq. 13).[25]



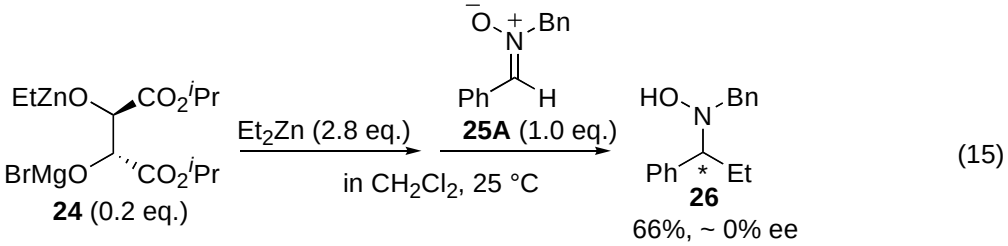
Asymmetric Nucleophilic Addition to Nitrones

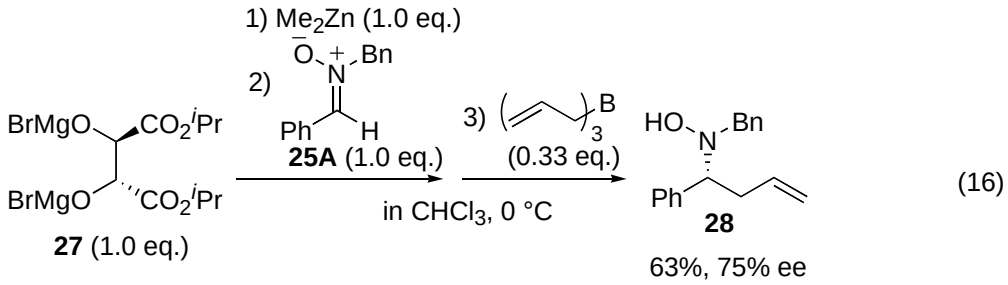
The asymmetric addition of organometallics to electron-deficient double bonds was one of the most useful ways to construct chiral carbons. The asymmetric C–C bond formation via nucleophilic addition of a *C*-nucleophile to imine functions provides one of the most important methods for synthesizing optically active amines, which are versatile building blocks for the optically active nitrogen-containing compounds.[26] Although various kinds of methods for enantioselective nucleophilic addition of organometallics to imine derivatives were recently reported, development of more efficient method in terms of enantioselectivity and the availability of chiral auxiliaries is still regarded as one of the challenging problems. Among the imine compounds, nitrone seems to be a promising candidate because it possesses an electronegative oxygen, which can activate C=N bond and strongly coordinate to metals. The multinucleating system provided by the tartaric acid esters was found to effectively control the stereochemical course not only of the cycloaddition described above but also of the nucleophilic addition reaction.

The catalytic asymmetric addition of dialkylzinc to a carbon-nitrogen double bond in 3,4-dihydroisoquinoline *N*-oxides **22** was achieved by utilizing a catalytic amount of 2-magnesium 3-zinc salt of dicyclopentyl (*R*,*R*)-tartrate **21** to afford (*S*)-1-alkyl-2-hydroxy-1,2,3,4-tetrahydroisoquinolines **23** (Eq. 14).[27]



However, this system did not work well for the nucleophilic addition to acyclic nitrones such as *N*-(benzylidene)benzylamine *N*-oxide (**25A**) (Eq. 15). When diallylzinc generated *in situ* from triallylborane and dimethylzinc was reacted with nitrone **25A**, an allylated product **28** was obtained in 75% ee (Eq. 16).[28]

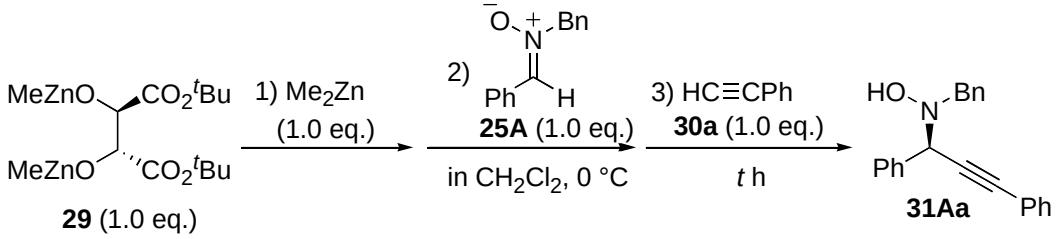




Recently we found that alkynylzinc reagent was a reagent of choice to give the corresponding optically active *N*-(propargylic)hydroxylamines **31**; *i.e.*, in the presence of 1.0 eq. of bis(methylzinc) salt of di(*t*-butyl) (*R,R*)-tartrate **29**, derived *in situ* from 1.0 eq. of di(*t*-butyl) (*R,R*)-tartrate [(*R,R*)-DTBT] and 2.0 eq. of dimethylzinc, the nitrone **25A** was treated with phenylacetylene (**30a**) and dimethylzinc. The corresponding (*R*)-*N*-(propargylic)hydroxylamines **31Aa** was obtained with the enantioselectivity of 82% ee. In order to confirm how the reaction proceeded, the time course of the reaction was observed

(Table 5). Surprisingly, enantioselectivity was increased remarkably after around 8 hours, suggesting that (*R*)-enantiomer was selectively produced after the induction time.

Table 5. The time-course of the production of **31Aa**.

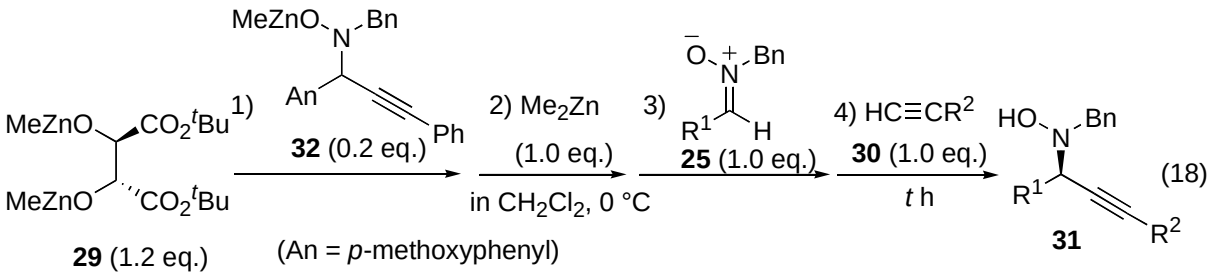


(17)

Entry	*t*/h	Yield of **31Aa**/%	ee/%
1	2	2	--
2	4	10	47
3	8	13	49
4	19	70	79
5	24	89	82

Based on this observation, it was expected that if the product at initial stage of the reaction was added into the original reaction mixture, the ee of the product could be enhanced without the induction time. In order to distinguish the reaction product and the additive, a product-like substrate was added to the reaction. Namely, a mixture of 1.2 eq. of bis(methylzinc) salt of (*R*,*R*)-DTBT **29** and 0.2 eq. of methylzinc salt of *racemic p*-methoxyphenyl-substituted product-like hydroxylamine **32**, generated *in situ* from 0.2 eq. of dimethylzinc and 0.2 eq. of the corresponding hydroxylamine **31Ba**, was treated with 1.0 eq. of dimethylzinc followed by addition of 1.0 eq. of the nitrone **25A** and phenylacetylene (**30a**). As expected, the enantioselectivity was enhanced from 82% ee to 94% ee (Table 6, Entry 1). The influence of the absolute configuration of the additive **32** was examined. To our surprise, the racemic additive was most effective and (*R*)-additive was not effective even though the absolute stereochemistry of the product was *R* (Entries 1–3). This indicated that the present peculiar phenomena might be different from auto catalyst.[29] The several asymmetric additions of zinc acetylides derived from acetylenes **30** to nitrones **25** were also carried out to furnish the corresponding *N*-(α-substituted propargylic)hydroxylamines **31** with excellent enantioselectivity (Entries 5–9). By comparison with the results of the reaction without the product-like additive **32** (shown in parentheses in Table 6), the dramatic enhancement of the enantioselectivity was observed.[30,31]

Table 6. The asymmetric addition of alkynylzinc reagents to nitrones **25** in the presence of product-like additive **32**.



Entry	R^1	**25**	R^2	**30**	*t*/h	**31**	Yield of **31**/%	ee/%	(Yield of **31**/%	ee/%)[a]
1	Ph	**A**	Ph	**a**	18	**Aa**	75	94	(89	82)
2[b]					18		80	80		
3[c]					18		70	85		
4[d]					21		93	93	(89	75)
5[e]	$^{p}MeOC_6H_4$	**B**	Ph	**a**	39	**Ba**	80	92	(70	74)
6	$^{p}BrC_6H_4$	**C**	Ph	**a**	18	**Ca**	92	91	(57	77)
7	$^{o}BrC_6H_4$	**D**	Ph	**a**	18	**Da**	67	95	(71	78)
8	Ph	**A**	$^{p}MeC_6H_4$	**b**	18	**Ab**	70	86	(58	76)
9[f]	Ph	**A**	^{n}Hex	**c**	18	**Ac**	62	79	(48	57)

a) Yields and enantioselectivities/% ee in parentheses were the results of the reaction carried out without the product-like additive under the same conditions as those in Table 5. b) (*R*)-Enantiomer of **32** was used as an additive. c) (*S*)-Enantiomer of **32** was used as an additive. d) Toluene was used as a solvent. e) The racemic methylzinc salt of **31Aa** was used as an additive instead of the racemic **32**. f) Step 2) was skipped and a mixed solution of 1.0 eq. of Me_2Zn and 1.0 eq. of acetylene **30c** in CH_2Cl_2 was added at room temperature on the step 4).

Next, the enantioselective addition using a catalytic amount of bis(methylzinc) salt of (*R*,*R*)-DTBT **29** was investigated. In the presence of 0.2 eq. of **29**, the nitrone **25A** was treated with phenylacetylene (**30a**) and dimethylzinc in CH_2Cl_2 at 0 °C. The reaction proceeded smoothly to give the corresponding (*R*)-*N*-(propargylic)hydroxylamine **31Aa** with the enantioselectivity of 68% ee (Eq. 19, Table 7, Entry 1). This result suggested that the zinc salt **29** can work as a catalyst. Then the effect of the product-like racemic additive **32** was also examined in the present catalytic reaction. The enantioselectivity was again enhanced from 68% ee to 83% ee (Table 7, Entry 2). The use of 0.2 or 0.3 eq. of **32** gave almost the same reproducible enantioselectivity. In order to confirm how the reaction proceeds, the time-courses of the reactions corresponding to Entries 1 and 2 in Table 7 were observed. In the catalytic reaction without the additive **32** (Figure 3a), enantioselectivity was lower at the initial stage of the reaction and it was slightly increased as the reaction proceeded. At later stage of the reaction, a part of the addition product cyclized to give the corresponding 4-isoxazoline **39Aa**, which will be discussed later. By the addition of a product-like racemic additive **32** (Figure 3b), induction time was not observed and the enantioselectivity was constantly high from the initial stage.

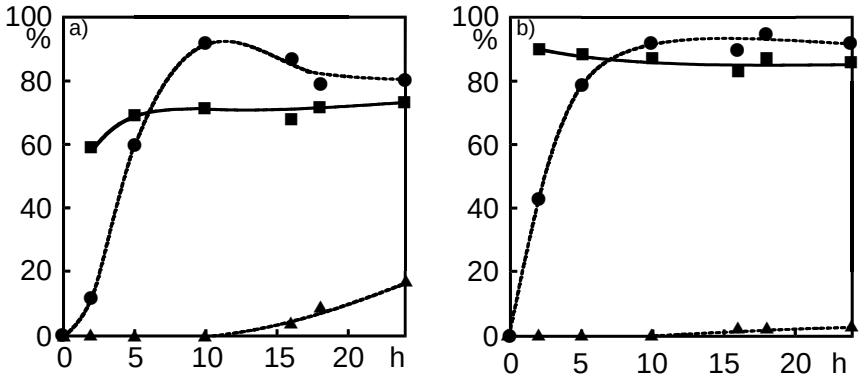
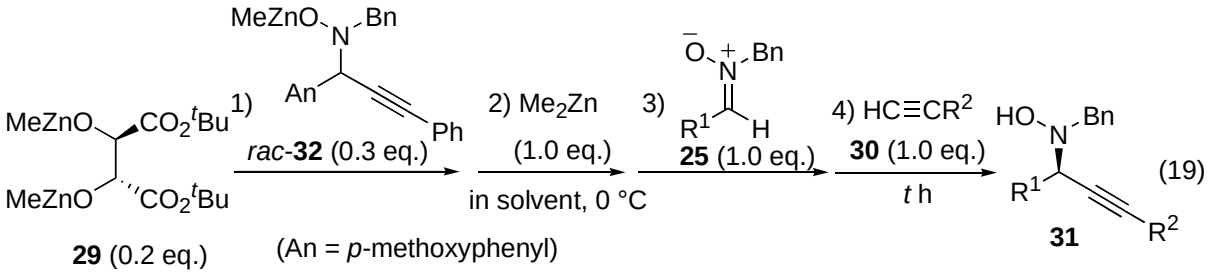


Figure 3. Yield of **31Aa**; ee of **31Aa**; Yield of **39Aa**

Next, the addition reactions were carried out in several solvents. The enantioselectivity was decreased in THF, but remarkably increased in aromatic solvents, toluene or ethylbenzene (Entries 5–7). The several other asymmetric additions of acetylides to nitrones **25** in the presence of *racemic*-**32** were also carried out to furnish the corresponding *N*-(propargylic)hydroxylamines **31** with excellent enantioselectivities (Entries 8–13).[32]

Table 7. The catalytic asymmetric addition of alkynylzinc reagents to nitrones **25** in the presence of a product-like racemic additive.

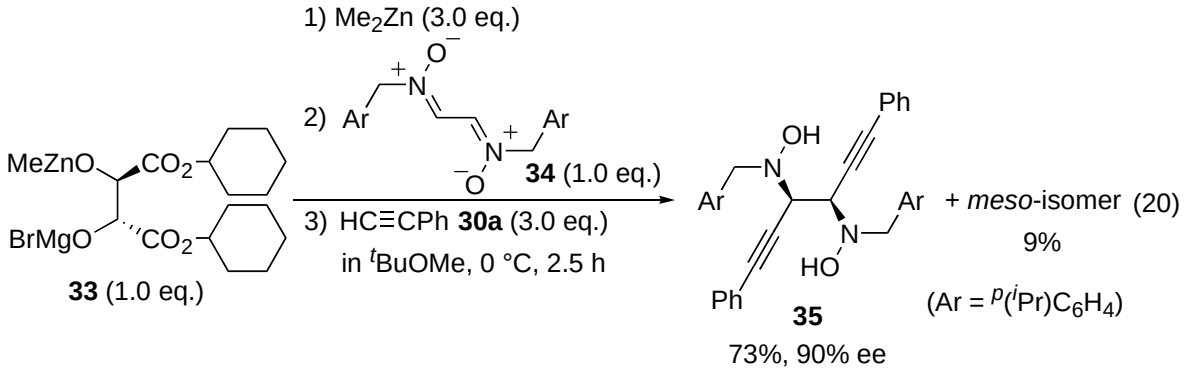


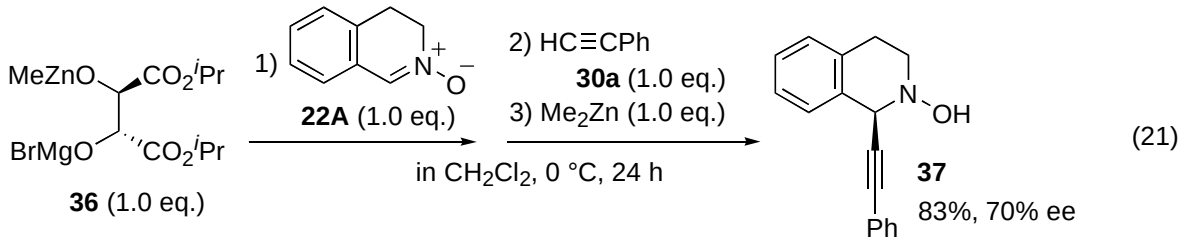
Entry	R^1	**23**	R^2	**28**	Solvent	*t*/h	**31**	Yield of **31**/%	ee/%
1[a)]	Ph	**A**	Ph	**a**	CH_2Cl_2	16	**Aa**	87	68
2					CH_2Cl_2	16		90	83
3[b)]					CH_2Cl_2	16		85	60
4[c)]					CH_2Cl_2	14		86	73
5					THF	20		62	75
6					toluene	14		92	91
7					ethylbenzene	14		84	95
8[d)]	$^{p}MeOC_6H_4$	**B**	Ph	**a**	ethylbenzene	13	**Ba**	87	90
9	$^{p}BrC_6H_4$	**C**	Ph	**a**	ethylbenzene	18	**Ca**	73	90
10	$^{o}BrC_6H_4$	**D**	Ph	**a**	ethylbenzene	19	**Da**	77	96
11	Ph	**A**	$^{p}MeC_6H_4$	**b**	ethylbenzene	18	**Ab**	86	93
12	Ph	**A**	^{n}Hex	**c**	ethylbenzene	18	**Ac**	75	88
13[e)]	Ph	**A**	$SiMe_3$	**d**	toluene	7	**Ad**	57	88

a) The reaction was carried out without an additive **32**. b) (*R*)-Enantiomer of **32** was used as an additive. c) (*S*)-Enantiomer of **32** was used as an additive. d) The racemic methylzinc salt of **31Aa** was used as an additive instead of the racemic **32**. e) The reaction was carried out at room temperature.

As described above, unprecedented enantiomeric enhancement by a racemic product-like additive was realized. If this enantiomeric enhancement is a general phenomenon in asymmetric reaction, it will be quite useful in enantioselective synthesis. Thus, we examined several addition reaction of alkynylzinc reagent to different types of nitrones. In the case of addition to dinitrones **34**, the corresponding dihydroxylamines **35** was obtained in the presence of magnesium zinc tartrate **33** (Eq. 20).[33] However, the enantiomeric enhancement by the addition of a product-like additive was not observed although the several

combination of metals and hydroxylamines were examined. The addition of alkynylzinc reagent to the nitrone **22A** possessing isoquinoline skeleton also gave the corresponding hydroxylamine **37** (Eq. 21). In this system, neither was the enantiomeric enhancement observed.



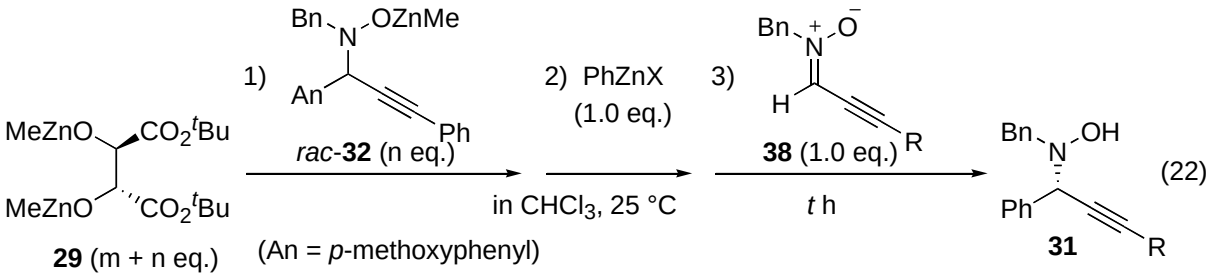


Finally, the enantiomeric enhancement by the addition of a product-like additive was again observed in an enantioselective addition of phenylzinc reagents to acyclic nitrones **38** bearing an alkynyl substituent on the carbon to produce the same *N*-(propargylic)hydroxylamines **31**.

By the addition of diphenylzinc to *N*-benzyl *C*-alkynyl nitrone **38a** (R = Ph) in the presence of a 1.0 eq. of bis(methylzinc) salt of (*R*,*R*)-DTBT **29** at 25 °C, the corresponding (*S*)-*N*-(propargylic)hydroxylamine **31Aa** was obtained in 70% yield with enantioselectivity of 64% ee (Eq. 22, Table 8, Entry 1, n = 0). The addition predominantly occurred from *si*-face of the nitrone **38a**, and the sense of the enantiofacial differentiation was same as that in the addition reaction of alkynylzinc reagents to *C*-(phenyl-substituted) nitrones **25A**. The effect of the addition of a product-like racemic additive **32** was also investigated in the present reaction (Eq. 22, n = 0.2). The enantioselectivity was remarkably enhanced to 88% ee (Entry 1, n = 0.2). When 0.2 eq. of **29** was used, enantioselectivity was not satisfactory (Entry 2, n = 0). However, enantiomeric enhancement was still observed by addition of the product-like racemic additive **32** to give **31Aa** with improved enantioselectivity (Entry 2, n = 0.2). Utilization of a mixed zinc species PhZnMe, prepared *in situ* from Ph_2Zn and Me_2Zn,

achieved the highest enantioselectivity of 92% ee (Entry 3). Asymmetric additions of phenylzinc reagents to several other nitrones **38** were performed to furnish the corresponding *N*-(propargylic)hydroxylamines **31** with high enantioselectivities (Table 8). It was confirmed that the addition of the product-like racemic additive **32** was effective to improve enantioselectivity as shown in the column of n = 0.2 in Table 8. Not only in the case of *C*-(aryl-substituted alkynyl) nitrones **38a**, **38b**, **38e**, but also in the case of *C*-(alkyl-substituted alkynyl) nitrone **38c**, the enantiomeric excess was remarkably enhanced in the presence of additive *rac*-**32**. Furthermore, higher enantioselectivity was accomplished by the use of PhZnMe (Entries 3 and 9).[34]

Table 8. Asymmetric addition of phenylzinc reagents to nitrones **38** in the presence of a product-like racemic additive **32**.



							n = 0.2		n = 0	
Entry	R	**38**	X	m	*t*/h	**31**	Yield of **31**/%	ee/%	Yield of **31**/%	ee/%
1	Ph	**a**	Ph	1.0	0.5	**Aa**	72	88	70	64
2			Ph	0.2	0.5		63	56	34	36
3[a)]			Me	1.0	1		75	92		
4	$^{p}MeC_6H_4$	**b**	Ph	1.0	1	**Ab**	75	87	80	77
5[a)]			Me	1.0	1		66	87		
6	$^{p}BrC_6H_4$	**e**	Ph	1.0	1	**Ae**	64	90	68	53
7[a)]			Me	1.0	1		70	90		
8	^{n}Hex	**c**	Ph	1.0	1	**Ac**	67	82	61	52
9[a)]			Me	1.0	1		67	87		

a) PhZnMe was prepared *in situ* from 0.5 eq. of Ph_2Zn and 0.5 eq. of Me_2Zn.

The origin of "*enantiomeric enhancement with a product-like racemic additive*" is not yet clear. We observed that racemic or enantiomerically low *N*-(propargylic)hydroxylamines **31** tend to readily solidify and/or crystallize in contrast to enantiomerically high **31**. This

observation might indicate that (*R*)- and (*S*)-*N*-(propargylic)hydroxylamines **31** are readily associated each other to form hydrogen-bonded racemic heterodimers. Based on this observation, we can speculate the reaction mechanism for "*enantiomeric enhancement with a product-like racemic additive*" as follows: In the case of methylzinc salt of *N*-(propargylic)hydroxylamines **31**, methylzinc salt of (*R*)- and (*S*)-*N*-(propargylic)hydroxylamines are also readily associated each other to form zinc-bridging heterodimers. When the heterodimer is once produced, it would make a new complex involving DTBT moiety via zinc metals, which acts as an effective real catalyst to control the enantioselectivity.

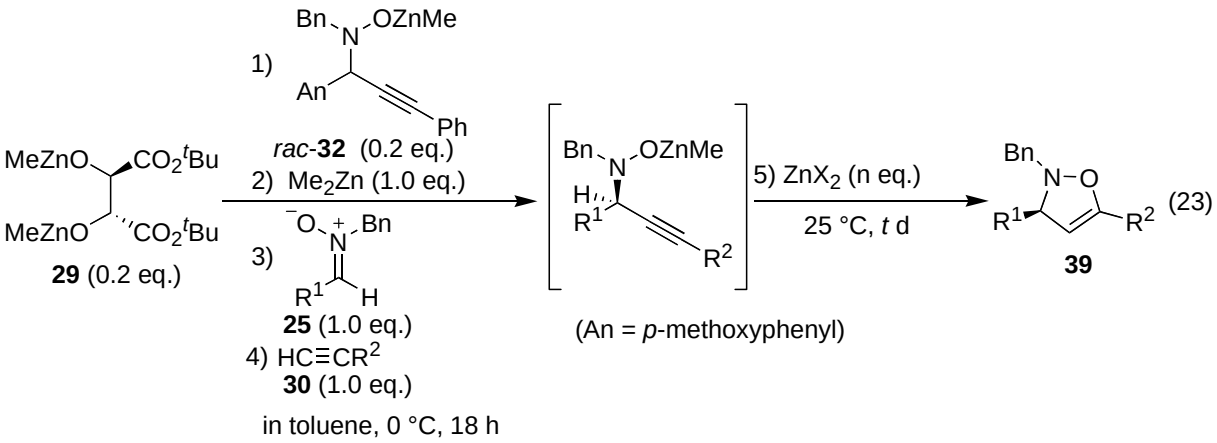
Asymmetric One-Pot Addition/Cyclization Reaction Using Alkynylzincs and Nitrones

During the course of the investigation of the enantiomeric enhancement, it was observed that a part of the addition product cyclized giving the corresponding 4-isoxazoline **39Aa** at the later stage of the reaction. Compounds bearing a 4-isoxazoline ring are versatile synthetic intermediates and the key components of optically active nitrogen-containing substances, which have potentially high value in chemical and medicinal fields.[35] One of the most attractive approaches to the synthesis of 4-isoxazolines is 1,3-diplolar cycloaddition of nitrones to acetylenes, however, the method often suffered with poor regioselectivity. Alternative route to 4-isoxazolines is condensation of unsaturated ketones with hydroxylamines. Ring-closure reaction of *N*-(propargylic)hydroxylamines catalyzed by zinc or palladium salt also gave 4-isoxazolines.[36] Furthermore, direct ring-closure reaction of zinc salt of *N*-(propargylic)hydroxylamines, generated *in situ* by addition of alkynylzinc reagents to nitrones, was reported.[37] However, it was mentioned that an ester or amide group was necessary in the nitrone for the promotion of the cyclization, and the cyclization took place for a simple nitrone only when an alkyne contained an acetyl group.

First, an asymmetric addition reaction of alkynylzinc to *N*-benzyl nitrone **25A** followed by cyclization was examined (Table 9); *i.e.*, to a mixture of 0.2 eq. of bis(methylzinc) salt of (*R*,*R*)-DTBT **29** and 0.2 eq. of methylzinc salt of racemic *p*-methoxyphenyl substituted hydroxylamine **32** in toluene, 1.0 eq. of dimethylzinc, nitrone **25A** and phenyl acetylene (**30a**) were successively added at 0 °C. After stirring for 18 h at 0 °C, the reaction mixture was warmed up to room temperature (25 °C) and kept for 24 h to give the cyclized product, (*S*)-2-benzyl-3,5-diphenyl-2,3-dihydroisoxazole (**39Aa**), in 51% yield with 90% ee (Entry 1). In order to improve the cyclization step, 1.0 eq. of zinc iodide dissolved in THF was added as a promoter after the initial addition reaction. Though the corresponding **39Aa** was obtained with enantioselectivity of 91% ee, the chemical yield lowered to 32% (Entry 2).

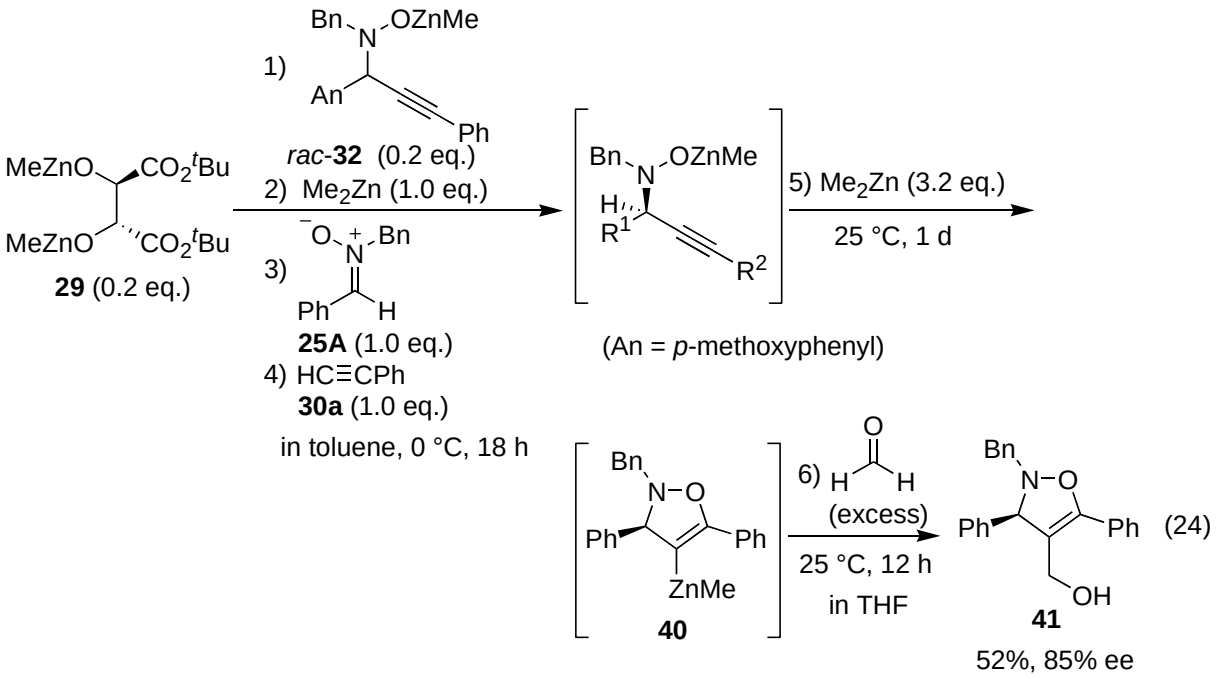
Dimethylzinc was next examined as a promoter instead of zinc iodide. To our delight, the cyclization reaction proceeded smoothly by using 3.2 eq. of dimethylzinc to give **39Aa** in improved 73% chemical yield with 91% ee (Entry 3). Asymmetric addition of several alkynylzinc reagents to other nitrones **25** followed by cyclization was performed under the optimum conditions to furnish the corresponding (*S*)-2-benzyl-4-isoxazolines **39** with high enantioselectivity. The reaction of *o*-bromophenyl substituted nitrone **25B** with phenyl acetylene (**30a**) proceeded smoothly to give the expected product **39Ba** at room temperature with 93% ee (Entry 4). *p*-Bromophenyl substituted nitrone **25C** also gave good enantioselectivity with 86% ee (Entry 5). Other aromatic acetylenes **30e** and **30f** reacted with **25A** to give the corresponding 4-isoxazolines **39Ae** and **39Af** with up to 93% ee (Entries 6 and 7). Aliphatic acetylenes **30c** and **30h** afforded good results in chemical yields as well as in enantioselectivities (Entries 9 and 10).[38] 2,4-Difluorophenyl substituted 4-isoxazoline **39Ag** was known as mitotic kinesin inhibitor and could be synthesized by the present one-pot method in optically active form (Entry 8).[39]

Table 9. Asymmetric addition of alkynylzinc reagents to nitrones **25** followed by cyclization.



Entry	R^1	**25**	R^2	**30**	ZnX_2	n	*t*/d	**39**	Yield of **39**/%	ee/%
1	Ph	**A**	Ph	**a**	--		1	**Aa**	51	90
2					ZnI_2	1.0	1		32	91
3					$ZnMe_2$	3.2	1		73	91
4	$^{o}BrC_6H_4$	**B**	Ph	**a**	$ZnMe_2$	3.2	1	**Ba**	72	93
5	$^{p}BrC_6H_4$	**C**	Ph	**a**	$ZnMe_2$	3.2	1	**Ca**	51	86
6	Ph	**A**	$^{p}BrC_6H_4$	**e**	$ZnMe_2$	3.2	3	**Ae**	62	85
7	Ph	**A**	$^{p}(^{n}Pen)C_6H_4$	**f**	$ZnMe_2$	3.2	3	**Af**	42	93
8	Ph	**A**	$^{2,4}F_2C_6H_3$	**g**	$ZnMe_2$	3.2	3	**Ag**	73	82
9	Ph	**A**	^{n}Hex	**c**	$ZnMe_2$	3.2	3	**Ac**	63	85
10	Ph	**A**	^{n}Bu	**h**	$ZnMe_2$	3.2	3	**Ah**	70	80

Finally, a cyclized zinc intermediate **40** produced by asymmetric one-pot addition/cyclization reaction was trapped with formaldehyde at room temperature to furnish (*S*)-2-benzyl-3,5-diphenyl-2,3-dihydroisoxazol-4-yl)methanol (**41**) in decent chemical yield with 85% ee in the presence of a product-like racemic additive **32** (Eq. 24).



Conclusions

We designed a novel chiral system possessing two or three-metal centers utilizing tartaric acid ester as a chiral auxiliary, and could develop asymmetric [3+2] and [4+2] cycloaddition and asymmetric nucleophilic addition reactions. The ready availability of (*R*,*R*)- and (*S*,*S*)-tartaric acid esters made it possible to prepare both enantiomers of the required substances by simple procedures. The present concept would be widely applicable to develop other asymmetric reactions, since numerous combinations of various metals are possible.

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