

Enantioselective Radical Conjugate
Addition to α' -Phosphoric Enones[†]

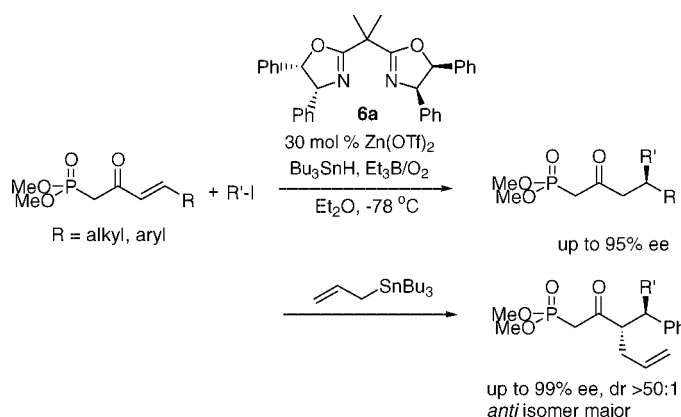
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ABSTRACT



Catalytic enantioselective radical conjugate addition reactions using α' -phosphoric enone templates have been studied. The C_2 -symmetric bisoxazoline–zinc(II) complex proves to be effective for high enantioselectivities and chemical yields. In addition, intermediate α -carbonyl alkyl radicals could be trapped with allyltributylstannane to afford *anti*-isomers as major products with high enantioselectivities.

During the last several decades, enantioselective C–C bond-forming reactions were intensively investigated. Among the various methods to achieve highly efficient enantioselective C–C bond formations, enantioselective radical conjugate addition reactions have been studied with great interest to take advantage of unique features of radical chemistry.¹ Since oxazolidinone templates were extensively studied for the 1,4-addition of nucleophilic radicals to electrophilic double bonds by Sibi,² several additional bidentate templates including imide,³ pyrazole,⁴ pyrazolidinone,⁵ and α' -hydroxyketone

groups⁶ have attracted recent attention. However, α,β -unsaturated ketones have been rarely used for enantioselective radical conjugate addition reactions.^{6,7}

We have been interested in utilizing α' -phosphoric enone templates in asymmetric reactions and reported asymmetric

[†] Dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

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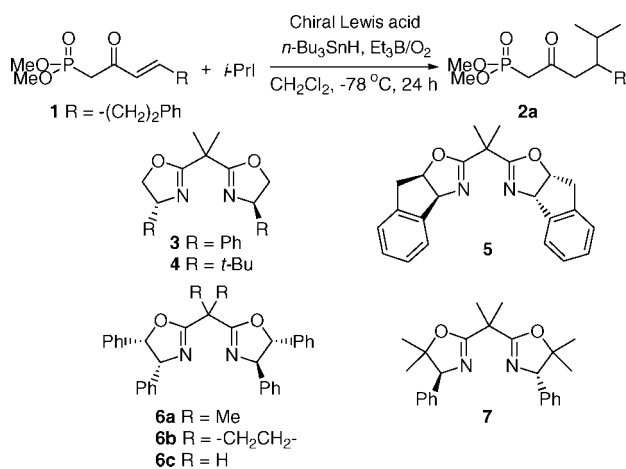
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Friedel–Crafts alkylation,⁸ a Mukaiyama–Michael reaction,⁹ and a 1,3-dipolar cycloaddition reaction,¹⁰ in which the α' -phosphoric enone template showed high chemical reactivities and enantioselectivities with chiral Lewis acids derived from chiral bisoxazoline (Box) derivatives and copper(II) triflate. In addition, compared with previously reported templates, α' -phosphoric enone templates have the unique application scope beyond the territory of carboxylic acid derivatives.

To further extend the synthetic usefulness of α' -phosphoric enone templates, we have studied enantioselective radical conjugate addition reactions using α' -phosphoric enones.

We initially examined the effectiveness of several chiral Lewis acids derived from chiral Box ligands and metal salts. As shown in Table 1, several features are noteworthy. First,

Table 1. Effect of Lewis Acids and Ligands^a



entry	Lewis acid	ligand	yield (%) ^b	ee (%) ^c
1	none	none	57(25) ^d	–
2	MgBr ₂ Et ₂ O	(<i>R</i>)- 3	82	11
3	MgBr ₂ Et ₂ O	(<i>S</i>)- 4	22	0
4	MgBr ₂ Et ₂ O	(<i>S</i>)- 5	73	46
5	Cu(OTf) ₂	(<i>S</i>)- 5	39(50) ^d	20
6	Zn(OTf) ₂	(<i>R</i>)- 3	56(37) ^d	29
7	Zn(OTf) ₂	(<i>S</i>)- 4	41(47) ^d	0
8	Zn(OTf) ₂	(<i>S</i>)- 5	78	70
9	Zn(OTf) ₂	(4 <i>R</i> ,5 <i>S</i>)- 6a	88	82
10	Zn(OTf) ₂	(4 <i>R</i> ,5 <i>S</i>)- 6b	83	73
11	Zn(OTf) ₂	(4 <i>R</i> ,5 <i>S</i>)- 6c	95	72
12	Zn(OTf) ₂	(<i>S</i>)- 7	81	2
13	Zn(NTf) ₂	(4 <i>R</i> ,5 <i>S</i>)- 6a	83	5

^a Typical reaction conditions: 1.0 equiv of substrate, 0.3 equiv of chiral Lewis acid, 10.0 equiv of alkyl iodide, 4.0 equiv of Bu₃SnH, and 3.0 equiv of Et₃B were used. ^b Isolated yield. ^c ee's were determined using chiral HPLC. ^d Recovered starting material.

among several metal salts tested in this study, zinc triflate gave the best result. Second, bisphenyl-substituted Box ligands **6** gave higher enantioselectivities than *t*-butyl,

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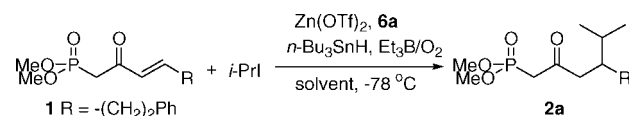
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indanyl, and monophenyl substituted Box ligands (entries 9–11). Among several bridges in **6**, the dimethyl-substituted Box ligand **6a** was the most effective, yielding the highest enantioselectivity (82% ee) (entry 9). Third, chiral ligands **7** and **4** were totally ineffective (entries 7 and 12). It is noteworthy that the radical conjugate addition reaction was very slow with sterically bulky Box **4** (entry 7). Finally, when the counteranion was changed from triflate anion to bistriflimide anion, surprisingly, almost a racemic mixture was obtained (entry 13).

Next, the solvent effect was examined with Zn(OTf)₂ and **6a** (Table 2). When the reaction was carried out in

Table 2. Effect of Solvent^a



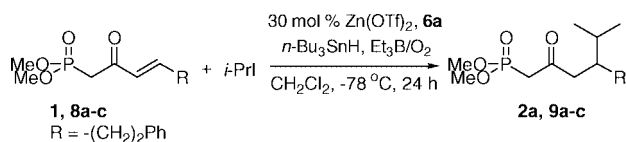
entry	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	CH ₂ Cl ₂	6	88	82
2	CHCl ₃	24	86(13) ^{d,e}	63
3	CH ₃ CN	24	57(35) ^{d,f}	6
4	THF	24	87	70
5	toluene	6	95	86
6	Et ₂ O	12	90	91

^a Typical reaction conditions: 1.0 equiv of substrate, 0.3 equiv of chiral Lewis acid, 10.0 equiv of alkyl iodide, 4.0 equiv of Bu₃SnH, and 3.0 equiv of Et₃B were used. ^b Isolated yield. ^c ee's were determined using chiral HPLC. ^d Recovered starting material. ^e At –60 °C. ^f At –40 °C.

chloroform at –60 °C, the reaction slowed down to some extent, and the enantioselectivity was dropped considerably (entry 2). In acetonitrile, the inferior result was obtained in terms of the chemical yield and the enantioselectivity (entry 3). Among the solvents tested in this study, toluene and diethyl ether were better than dichloromethane. The reaction was faster in toluene (entry 5), but the higher enantioselectivity was realized in diethyl ether (entry 6). Apparently, the reaction slowed down to some extent due to the strong coordination ability of etheral solvents toward zinc triflate (entries 4 and 6).

The effect of structural modifications on the phosphonate was briefly studied and is shown in Table 3. Dimethyl phosphonate **1** gave the best result. When the methyl group was changed to sterically bulkier isopropyl and phenyl groups, the enantioselectivities were dropped to 72% and 13%, respectively. Furthermore, cyclic phosphonate **8c** was totally ineffective. The reaction was very slow, and a racemic mixture was isolated.

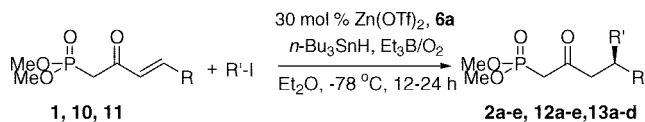
To determine the scope and limitation of the present method, the reaction was carried out with several structurally different α' -phosphoric enones using the chiral Lewis acid (30 mol %) derived from Zn(OTf)₂ and **6a** in diethyl ether at –78 °C, and the experimental results are summarized in Table 4. In general, the reaction proceeded cleanly, yielding the addition products in high yields. The enantioselectivities

Table 3. Modification of α' -Phosphoric Enones^a

entry	R'	product	yield (%) ^b	ee (%) ^c
1	1a MeO	2a	85	91
2	8a <i>i</i> -PrO	9a	76	72
3	8b Ph	9b	93 ^d	13
4	8c	9c	34(22) ^e	0

^a Typical reaction condition: 1.0 equiv of substrate, 0.3 equiv of chiral Lewis acid, 10.0 equiv of alkyl iodide, 4.0 equiv of Bu₃SnH, and 3.0 equiv of Et₃B were used. ^b Isolated yield. ^c ee's were determined using chiral HPLC. ^d CH₂Cl₂ was added to solve starting material. ^e Recovered starting material.

of the products are generally high, ranging from 82% to 95% ee, and the best enantioselectivity was as high as 95% ee

Table 4. Addition of Alkyl Radicals to α' -Phosphoric Enones^a

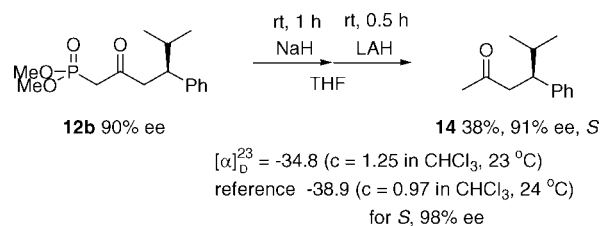
entry	R	R'	product	yield (%) ^b	ee (%) ^c
1	1 CH ₂ CH ₂ Ph	Et	2b	76	89
2	1	<i>i</i> -Pr	2a	85	91
3	1	<i>c</i> -Hexyl	2c	61	84
4	1	<i>t</i> -Bu	2d	77	91
5	1	(CH ₃) ₂ C(CH ₂) ₃ Cl	2e	69	83
6	10 Ph	Et	12a	68	82
7	10	<i>i</i> -Pr	12b	93	90
8	10	<i>c</i> -Hexyl	12c	79	84
9	10	<i>t</i> -Bu	12d	98	95
10	10	(CH ₃) ₂ C(CH ₂) ₃ Cl	12e	90	88
11	11 Me	Et	13a	84	86
12	11	<i>i</i> -Pr	13b^d	90	88
13	11	<i>t</i> -Bu	13c^d	93	92
14	11	(CH ₃) ₂ C(CH ₂) ₃ Cl	13d	96	83

^a Typical reaction conditions: 1.0 equiv of substrate, 0.3 equiv of chiral Lewis acid, 5.0 equiv of alkyl iodide, 3.0 equiv of Bu₃SnH, and 2.0 equiv of Et₃B were used. ^b Isolated yield. ^c ee's were determined using chiral HPLC. ^d The reaction time was 6 h.

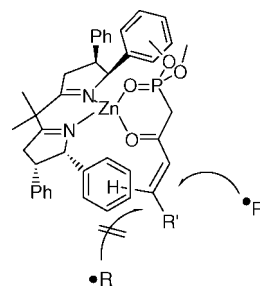
when unsaturated enone **10** was reacted with *t*-butyl iodide (entry 9). The size of the alkyl radical did not have a large impact on the chemical yields and enantioselectivities. Furthermore, the method works equally well with three phosphoric enone substrates. In the case of phosphoric enone **11**, the reaction was somewhat faster than similar substrates

1 and **10**, but the enantioselectivities remained as the same level (entries 10–14).

The absolute stereochemistry was determined by converting phosphonate **12b** to the previously known compound **14**. Treatment of **12b** with NaH and LAH in THF at room temperature in 1 h afforded **14** (−34.8 in CHCl₃ at 23 °C) (Scheme 1).¹¹ On the basis of the previously reported value

Scheme 1. Absolute Configuration

of the optical rotation, the stereochemistry was assigned as *S*.¹² A tentative model which accommodates the observed face selectivity is shown in Figure 1. In this model, Zn²⁺

**Figure 1.** Tetrahedral transition state.

that could have a tetrahedral geometry occupied the center of the transition state.¹³ Two coordination sites would be filled with nitrogen atoms of the Box ligand, and the remaining two sites are for the oxygen atoms of the starting phosphoric enone. A phenyl group of the 4-position in the ligand shielded only the *Re* face of the reactive double bond, and another phenyl group at the 5-position blocked the rotation of the nearby 4-phenyl group to maintain an effective face shielding. Furthermore, it is assumed that the control of the conformation of α' -phosphoric enones could result from a π - π stabilization of the transition state.¹⁴

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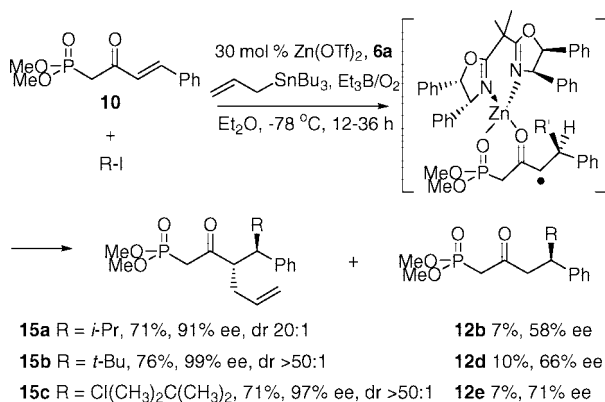
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To achieve sequential conjugative addition and α -alkylation, an electrophilic radical intermediate was trapped using allyltributylstannane (Scheme 2). When phosphoric ester **10** was reacted with isopropyl iodide in the presence of

Scheme 2. Trapping of the α -Carbonyl Alkyl Radical with Allyltin



allyltributylstannane, only one diastereoisomer bearing 91% ee was obtained. The high diastereoselectivity was noted previously.^{2c} Interestingly, the change of isopropyl iodide to bulkier *t*-butyl iodide caused a significant increase in the enantioselectivity (99% ee). In addition, a small amount of the reduced side product (10%) was obtained with a lowered enantioselectivity (66% ee). A similar observation was obtained with another bulky tertiary iodide (product **15c**: 97% ee).

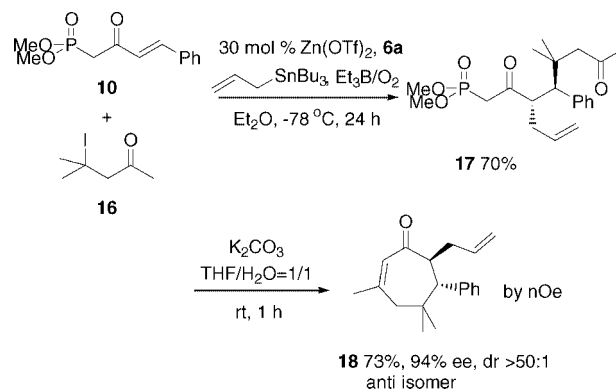
The increase in selectivity could be explained by a kinetic resolution between chiral Lewis acid and β -stereocenter. A matched major enantiomer reacted much faster with allyltributylstannane than a mismatched minor enantiomer. The minor enantiomer mainly reacted with Et₃B to afford the reduced product.¹⁵ As a result, most of the allylation product came from the major enantiomer, and the enantiomeric excess could exceed the ee value of 100% catalyst loading (97% ee for compound **12d**).

The relative stereochemistry was determined by making a cyclic compound using an intramolecular Horner–Emmons

(15) Brown, H. C.; Kabalka, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 714.

reaction (Scheme 3). A phosphoric ester **10** was reacted with tertiary iodide **16** and allyltributylstannane to produce 70%

Scheme 3. Relative Stereochemistry



of addition/allylation product **17** in 24 h. This product was further treated with K₂CO₃ in THF/H₂O at room temperature to provide the cyclic compound **18** in 73% yield (94% ee). By NOE experiment, the relative stereochemistry of the α and β center was defined as an *anti*-isomer that agrees with a previous reported case.^{2c}

In summary, α' -phosphoric enones are highly efficient substrates for the enantioselective conjugate radical addition reactions and work well with various alkyl iodides. When allyltributylstannane was used as the radical trapping agent, allylation products were formed with high diastereo- and enantioselectivities. In addition, optically active cycloheptenone derivatives can be prepared via intramolecular Horner–Emmons reactions of conjugate radical addition products.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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