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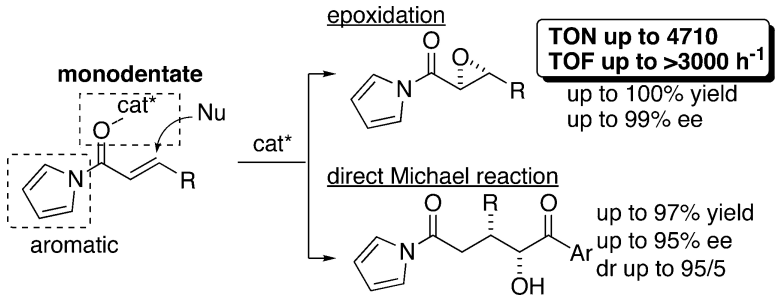

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Catalytic Asymmetric 1,4-Addition Reactions Using α,β-Unsaturated *N*-Acylpyrroles as Highly Reactive Monodentate α,β-Unsaturated Ester Surrogates

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Abstract: Synthesis and application of α,β-unsaturated *N*-acylpyrroles as highly reactive, monodentate ester surrogates in the catalytic asymmetric epoxidation and Michael reactions are described. α,β-Unsaturated *N*-acylpyrroles with various functional groups were synthesized by the Wittig reaction using ylide **2**. A Sm(O-*i*-Pr)$_3$/H$_8$-BINOL complex was the most effective catalyst for the epoxidation to afford pyrrolyl epoxides in up to 100% yield and >99% ee. Catalyst loading was successfully reduced to as little as 0.02 mol % (substrate/catalyst = 5000). The high turnover frequency and high volumetric productivity of the present reaction are also noteworthy. In addition, a sequential Wittig olefination−catalytic asymmetric epoxidation reaction was developed, providing efficient one-pot access to optically active epoxides from various aldehydes in high yield and ee (96→99%). In a direct catalytic asymmetric Michael reaction of hydroxyketone promoted by the Et$_2$Zn/linked-BINOL complex, Michael adducts were obtained in good yield (74−97%), dr (69/31−95/5), and ee (73−95%). This represents the first direct catalytic asymmetric Michael reaction of unmodified ketone to an α,β-unsaturated carboxylic acid derivative. The properties of α,β-unsaturated *N*-acylpyrrole are also discussed. Finally, the utility of the *N*-acylpyrrole unit for further transformations is demonstrated.

Introduction

Enantioselective 1,4-additions of nucleophiles to α,β-unsaturated carbonyl compounds is an important field of study in asymmetric synthesis.[1] Catalytic asymmetric 1,4-additions to α,β-unsaturated esters afford versatile chiral building blocks, because the ester moiety can be easily transformed into various functional groups. Despite great achievements with α,β-unsaturated ketones as substrates,[1] however, there is room for improvement in catalytic asymmetric 1,4-additions to α,β-unsaturated esters, probably due to an intrinsic reactivity of α,β-unsaturated ester that is lower than that of α,β-unsaturated ketone. To address this issue, several functional groups acting as ester surrogates, such as oxazolidinones,[2] pyrrolidinone,[2] acyl phosphonates,[3] acyl pyrrazoles,[4] pyrazolidinone,[5] and imides,[6] have been intensively investigated (Figure 1). With these templates, Lewis acidic chiral catalysts are in many cases thought to coordinate in a bidentate manner and activate substrates,[7] leading to high reactivity and excellent asymmetric induction. In some chiral catalyses, however, bidentate coordination of the substrates is unfavorable and the above-mentioned ester surrogates are not at all suitable. In particular, difficulty arises when chiral catalysts developed for monodentate α,β-unsaturated ketones are applied for bidentate carboxylic acid derivatives.[8] For example, during our ongoing research project on catalytic asymmetric Michael reactions of acyclic substrates[9] and epoxidation of electron deficient olefins,[10] wherein the reaction is

(1) For recent review for catalytic asymmetric 1,4-addition reaction, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 31. (d) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Wiley: New York, 2000; Chapter 8D.

(2) (a) Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*; CRC Press: Boca Raton, 1996. For selected recent examples using oxazolidinone and pyrrolidinone as achiral template in catalytic asymmetric 1,4-addition reactions, see: (b) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (c) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263 and references therein. (d) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240. (e) Kobayashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* **2001**, 983. (f) Miller, S. J.; Guerin, D. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134. (g) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276. See also ref 4c.

(3) (a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H.-W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. For other applications, see also: (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (c) Telan, L. A.; Poon, C.-D.; Evans, S. A., Jr. *J. Org. Chem.* **1996**, *61*, 7455.

(4) For selected examples, see: (a) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615. (b) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (c) Kanemasa, S. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 1073 and references therein.

(5) (a) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181. For other applications, see an excellent review on chiral relay using achiral template: (b) Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, M.; Jasperse, C. P.; Sibi, M. P. *Chem.—Eur. J.* **2003**, *9*, 28. See also: (c) Sibi, M. P.; Ma, Z.-H.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718 and references therein.

(6) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204. (b) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (c) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (d) Goodman, S. N.; Jacobsen, E. N. *Adv. Synth. Catal.* **2002**, *344*, 953. (e) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796.

(7) For imides as substrate, both monodentate and bidentate transition states were proposed, depending on the catalyst and reaction. See ref 6c and e.

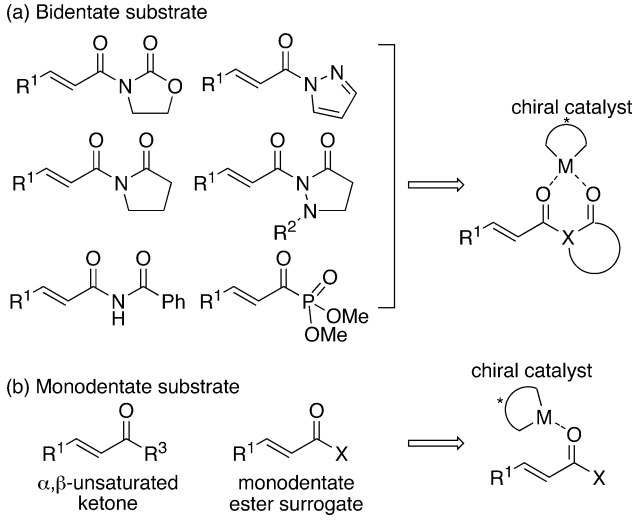


Figure 1. (a) Bidentate α,*β*-unsaturated ester surrogates; (b) Monodentate α,*β*-unsaturated ketone and ester surrogate.

considered to proceed through the 1,4-addition of peroxide such as *tert*-butyl hydroperoxide (TBHP), it was often difficult to apply our catalysts to the above-mentioned carboxylic acid derivatives, which favored bidentate coordination. The mismatched coordination mode of the substrates to the chiral catalysts is assumed to result in significantly decreased enantioselectivity and/or reactivity. Thus, the development of a highly reactive, monodentate ester surrogate is desirable to broaden the substrate generality of asymmetric catalysis, which was originally developed for α,*β*-unsaturated ketones.

Here, we report the utility of α,*β*-unsaturated *N*-acylpyrrole as a monodentate α,*β*-unsaturated ester surrogate, which is a highly reactive and versatile substrate. α,*β*-Unsaturated *N*-acylpyrroles **1** were easily prepared from various aldehydes using a pyrrolylmethylenetriphenylphosphorane (**2**, Figure 2). High reactivity of the α,*β*-unsaturated *N*-acylpyrrole **1** was first demonstrated in catalytic asymmetric epoxidations with a novel Sm(O-*i*-Pr)$_3$/H$_8$-BINOL complex. Catalyst loading was successfully reduced to as little as 0.02 mol % (substrate/catalyst = 5000), while maintaining high enantiomeric excess (up to 99% ee). With reduced catalyst loading, the reaction was performed under concentrated conditions (up to 3 M). A one-pot sequential Wittig−catalytic asymmetric epoxidation process provided efficient one-pot access to optically active pyrrolyl epoxides from various aldehydes in high yield (72−100%) and

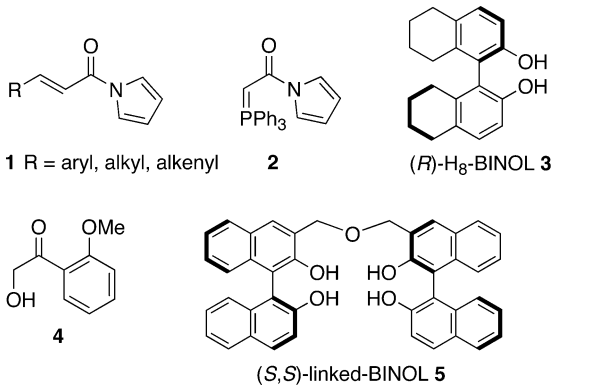


Figure 2. Structure of α,*β*-unsaturated *N*-acylpyrrole **1**, ylide **2**, (*R*)-H$_8$-BINOL **3**, hydroxyketone **4**, and (*S*,*S*)-linked-BINOL **5**.

high ee (96→99.5%).[11] The utility of α,*β*-unsaturated *N*-acylpyrrole **1** was also demonstrated in the first direct catalytic asymmetric Michael reaction of an unmodified ketone to α,*β*-unsaturated carboxylic acid derivatives. The Et$_2$Zn/linked-BINOL **5** catalyst,[12] which was originally optimized for α,*β*-unsaturated ketones,[9a,9b] promoted the Michael reaction of hydroxyketone **4** smoothly to afford products in good yield (73−97%), dr (69/31−95/5), and ee (73−95%). The properties of α,*β*-unsaturated *N*-acylpyrrole transformations of an *N*-acylpyrrole moiety and application to the synthesis of fragments of natural products are also described.

Results and Discussion

(A) Synthesis of α,*β*-Unsaturated *N*-Acylpyrrole: Although the potential of *N*-acylpyrroles to function as ester surrogates was reported two decades ago,[13] it was only recently that *N*-acylpyrroles were used in fine organic synthesis, such as asymmetric synthesis.[14] Inspired by recent reports on the unique reactivity of *N*-acylpyrroles by Evans et al.,[15a] we investigated the properties of α,*β*-unsaturated *N*-acylpyrroles in detail.[16] Although Arai reported an efficient synthesis of α,*β*-unsaturated *N*-acyl-2-substituted-pyrroles,[14d] the method was not applicable to an unsubstituted pyrrole, probably due to the high reactivity of pyrrole at the 2-position. The reaction of lithiated pyrrole with α,*β*-unsaturated acyl halide gave unsatisfactory results. In the literature, the most efficient synthesis of α,*β*-unsaturated

(8) For example, catalytic asymmetric addition of organozinc reagents to α,*β*-unsaturated carboxylic acid derivatives remained problematic until Hoveyda's recent excellent report (ref 2g). Hoveyda et al. developed a *novel* chiral ligand to achieve catalytic asymmetric 1,4-addition of R$_2$Zn to bidentate substrates in high selectivity, suggesting that conventional various chiral ligands developed for enones were not suitable for 1,4-addition of R$_2$Zn to bidentate substrates with chiral metal catalysts. Appropriate tuning of chiral ligands was necessary. For representative recent examples of catalytic asymmetric 1,4-addition of organozinc reagents, see ref 1a and 2g and references therein.

(9) For selected recent examples of 1,4-addition reactions of acyclic α,*β*-unsaturated ketone from our group, see: (a) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582. (b) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251. (c) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.*, **1998**, *39*, 7557. (d) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178.

(10) Epoxidation of α,*β*-unsaturated ketone: (a) Bougauchi, M.; Watanabe, T.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329. (b) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725. See, also (c) Daikai, K.; Kamaura, M.; Inanaga, J. *Tetrahedron Lett.* **1998**, *39*, 7321. For other examples, see ref 20.

(11) A portion of this article was communicated previously. Kinoshita, T.; Okada, S.; Park, S.-R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680.

(12) For the synthesis of linked-BINOL **5**, see: (a) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252. (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3. Both enantiomers of linked-BINOL are also commercially available from Wako Pure Chemical Industries, Ltd. Catalog No. for (*S*,*S*)-**5** is No. 152-02431 and (*R*,*R*)-**5**, No. 155-02421.

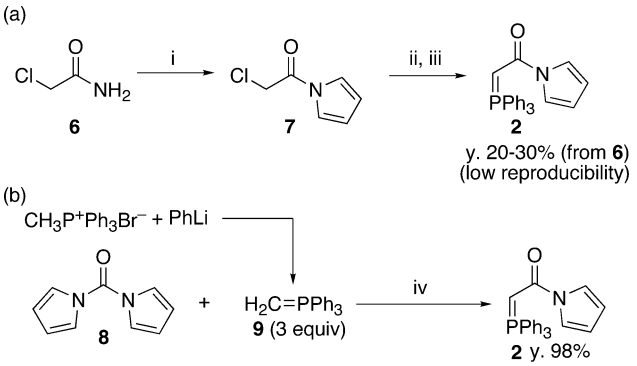
(13) (a) Lee, S.-D.; Brook, M. A.; Chan, T.-H. *Tetrahedron Lett.* **1983**, *24*, 1569. (b) Brandange, S.; Rodriguez, B. *Acta Chem. Scand., Ser. B* **1987**, *41*, 740.

(14) Application to catalytic asymmetric reactions: (a) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595. (b) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (c) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006. Application to diastereoselective reactions: (d) Arai, Y.; Matsuda, T.; Masaki, Y. *Chem. Lett.* **1997**, 145. (e) Arai, Y.; Ueda, K.; Xie, J.; Masaki, Y. *Chem. Pharm. Bull.* **2001**, *49*, 1609. (f) Arai, Y.; Kasai, M.; Ueda, K.; Masaki, Y. *Synthesis* **2003**, 1511 and references therein.

(15) (a) Evans, D. A.; Borg, G.; Scheidt, K. A.*Angew. Chem., Int. Ed.* **2002**, *41*, 3188. For other applications of pyrrole carbinol as useful building blocks, see: (b) Dixon, D. J.; Scott, M. S.; Luckhurst, C. A. *Synlett* **2003**, 2317.

(16) Although Arai et al. reported the utility of α,*β*-unsaturated *N*-acyl-2-substituted-pyrrole as a Michael acceptor, it might not function as a monodentate substrate because of the coordinating functional group at 2-position. See ref 14e and f.

Scheme 1. Preparation of Pyrrolylmethylenetriphenylphosphorane (Ylide **2**)[a]



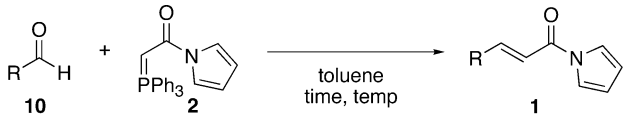
[a] Conditions: (i) 2,5-dimethoxytetrahydrofuran, AcOH, 100 °C; (ii) PPh_3, toluene, 100 °C; (iii) 2 M aq NaOH, CH_2Cl_2/H_2O; (iv) THF/Et_2O, −78 to 25 °C.

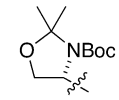
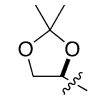
N-acylpyrrole was the condensation of cinnamamide and 2,5-dimethoxytetrahydrofuran in acetic acid at 100 °C [15a] (or with $SOCl_2$ at rt 80 °C),[17] affording **1a** in 60−68% yield. For the synthesis of α,β-unsaturated *N*-acylpyrroles with various functional groups, however, a milder method was necessary. One reason that α,β-unsaturated *N*-acylpyrrole has not been widely used as an acceptor for 1,4-addition reactions might be the lack of efficient preparation methods under mild conditions.

We examined the Wittig reaction using pyrrolylmethylenetriphenylphosphorane (ylide **2**). Initially, ylide **2** was prepared from chloroacetamide in three steps as shown in Scheme 1a. Low reproducibility of the first condensation step and the lachrymatory property of intermediate *N*-chloroacetyl pyrrole prompted us to examine a different route for ylide **2**. Following the reported procedure for the reaction of *N*-acylimidazole and methylenetriphenylphosphorane **9** to afford alkanoylmethylenetriphenylphosphorane,[18] the reaction of carbonyldipyrrole **8**[19] with **9** was examined (Scheme 1b). For the preparation of **9** from methyltriphenylphosphonium bromide, PhLi was used instead of BuLi. With BuLi as the base, ylide containing a pyrrole moiety and one butyl group derived from nucleophilic substitution at the phosphorus atom was obtained as a side product. We obtained **2** as a colorless to pale brown powder in 98% yield when 3 equiv of **9** were used, and **2** could be stored at ambient temperature under air for at least 5 months.

The substrate scope and limitations of the Wittig reaction using ylide **2** and various aldehydes **10** are summarized in Table 1. With aromatic (entries 1−9) and heteroaromatic (entries 10−12) aldehydes, both chemical yield and *E*/*Z* ratio were good. Both the electron donating (entries 3 and 4) and withdrawing (entries 5 and 6) substituents at the *para*-position gave products in high yield and *E*/*Z* ratio (>20/1). With *ortho*-substituents, the *E*/*Z* ratio decreased to 7/1 (entry 8) and 10/1 (entry 9). Various linear and branched aliphatic aldehydes were also applicable (entries 13−25). The *E*/*Z* ratio was dependent on the substrate, ranging from 3/1 to >20/1. Sterically crowded aldehydes (entries 16 and 17) required a high reaction temperature and a long reaction time but still afforded products in moderate yield (entry 16, 63%, *E*/*Z* = >20/1 and entry 17, 63%, *E*/*Z* = >20/1). Benzyl ether (entry 17), *p*-methoxybenzyl ether (entry 18), benzyloxymethyl ether (entry 19), *tert*-butyldimethylsilyl ether (entry 20), methyl ketone (entry 21), olefin (entry 22), *N*-Boc (entry 24), and acetonide (entry 25) were compatible under the reaction conditions. α,β-Unsaturated aldehyde also gave product in good yield (entry 23).

Table 1. Synthesis of Various α,β-Unsaturated *N*-Acylpyrrole **1**



entry	aldehyde R		product	temp (°C)	time (h)	yield (%)	E/Z
1	Ph-	**10a**	**1a**	100	48	97	>20/1
2	2-naphthyl	**10b**	**1b**	100	48	quant	>20/1
3	4-Me-C_6H_4-	**10c**	**1c**	100	48	98	>20/1
4	4-MeO-C_6H_4-	**10d**	**1d**	110	84	97	>20/1
5	4-Br-C_6H_4-	**10e**	**1e**	100	36	98	>20/1
6	4-Cl-C_6H_4-	**10f**	**1f**	100	24	quant	>20/1
7	3-Cl-C_6H_4-	**10g**	**1g**	100	24	98	>15/1
8	2-Cl-C_6H_4-	**10h**	**1h**	100	24	95	7/1
9	1-naphthyl	**10i**	**1i**	100	48	quant	10/1
10	2-furyl	**10j**	**1j**	100	48	91	>15/1
11	2-thienyl	**10k**	**1k**	100	36	quant	>20/1
12	4-pyridyl	**10l**	**1l**	100	48	quant	>20/1
13	$PhCH_2CH_2$-	**10m**	**1m**	80	24	quant	5/1
14	$Ph(CH_2)_4$-	**10n**	**1n**	80	24	quant	8/1
15	*cyclo*-hexyl	**10o**	**1o**	100	72	quant	12/1
16	$PhCH_2C(CH_3)_2$-	**10p**	**1p**	110	84	63	>20/1
17	$BnOCH_2C(CH_3)_2$-	**10q**	**1q**	110	84	63	>20/1
18	$PMBOCH_2CH_2$-	**10r**	**1r**	80	24	quant	14/1
19	$BOMOCH_2CH_2$-	**10s**	**1s**	80	24	quant	6/1
20	$TBSO(CH_2)_6$	**10t**	**1t**	80	36	88	3/1
21	$CH_3C(O)CH_2CH_2$-	**10u**	**1u**	80	36	97	8/1
22	$CH_2=CH(CH_2)_8$-	**10v**	**1v**	100	25	96	7/1
23	*trans*-$CH_3(CH_2)_2C=C$-	**10w**	**1w**	100	72	99	6/1
24		**10x**	**1x**	85	35	92	9/1
25		**10y**	**1y**	85	24	75	4/1

(B) Application to Catalytic Asymmetric Epoxidation: To evaluate the reactivity of α,β-unsaturated *N*-acylpyrroles, we examined catalytic asymmetric epoxidation using α,β-unsaturated *N*-acylpyrrole **1a** as a substrate. Catalytic asymmetric epoxidation of α,β-unsaturated carbonyl compounds is one of the most important transformations in organic synthesis.[20] Although we[10] and others[10,20] have achieved efficient catalytic asymmetric epoxidation of α,β-unsaturated ketones, there are

(17) Ekkati, A. R.; Bates, D. K. *Synthesis* **2003**, 1959 and references therein. The scope of the reaction was limited to aromatic amides and cinnamamide.
(18) Miyano, M.; Stealey, M. A. *J. Org. Chem.* **1975**, *40*, 2840.
(19) Synthesis and application of carbonyldipyrrole **8** was reported by Evans et al. See ref 15a.
(20) Recent reviews: (a) Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215. (b) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 94. Polyamino acid catalysis: (c) Porter, M. J.; Roberts, S. M.; Skidmore, J. *Bioorg. Med. Chem.* **1999**, *7*, 2145. Chiral ketone as catalyst: (d) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. For selected leading references, see also: (e) Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1725. (f) Elston, C. L.; Jackson, R. F. W.; MacDonald, S. J. F.; Murray, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 410.

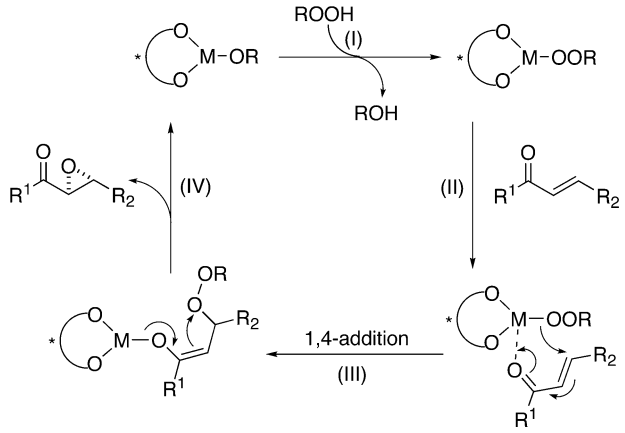


Figure 3. Postulated reaction mechanism of catalytic asymmetric epoxidation promoted by lanthanide-BINOL complex.

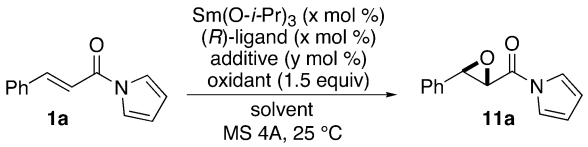
only a few examples of α,β-unsaturated esters as substrates using a salen-Mn complex[21] or chiral ketones[22] as the catalysts. In both cases, except for Shi's recent report,[22a] only β-aryl-substituted α,β-unsaturated esters were used. Although Shi et al. reported excellent results with a few β-alkyl substituted substrates, *trans*-β-alkyl-substituted α,β-unsaturated ester was not applicable, thus leaving room for improvement in substrate generality.

The proposed catalytic cycle of the asymmetric epoxidation reaction is shown in Figure 3. A lanthanide alkoxide moiety would change to lanthanide-peroxide through proton exchange (I). The lanthanide−BINOL complex also functions as a Lewis acid to activate electron deficient olefins through monodentate coordination (II). Enantioselective 1,4-addition of lanthanide-peroxide gave intermediate enolate (III), followed by epoxide formation to regenerate catalyst (IV). In the transition state for the 1,4-addition step, the lanthanide-BINOL complex is postulated to favor the monodentate coordination mode for high enantioselectivity. Although lanthanide-BINOL complexes were highly reactive and enantioselective for the catalytic asymmetric epoxidation of α,β-unsaturated ketones,[10] it was rather difficult to apply lanthanide−BINOL complexes to α,β-unsaturated esters due to its low reactivity. When using bidentate α,β-unsaturated oxazolidinone amide as a substrate, epoxide was obtained in only 73% yield and 87% ee, using as much as 20 mol % catalyst loading after 24 h.[23] Recently, we partially solved this substrate limitation problem by using α,β-unsaturated carboxylic acid imidazolide[23] and α,β-unsaturated morpholinyl amide[24] as substrates. Although moderate to high enantiomeric excess was achieved using substrates with β-aryl- and β-alkyl-substituents (imidazolide, 79−94% ee; amide, 99% ee), many problems remain from a practical viewpoint. (a) Catalyst loading and reaction rate: 5−10 mol % catalyst loading was essential for good conversion; in many cases it was impossible to complete the conversion with less than 5 mol %. Turnover frequency of the catalyst was, in most cases, approximately 1−3 h^{-1}. (b) Oxidant: explosive TBHP was essential for good reactivity. From a practical viewpoint, it is desirable to use less explosive (less reactive) cumene hydroperoxide (CMHP). (c) The preparation of β-alkyl α,β-unsaturated acid imidazolides from aldehydes was lengthy. (d) Some of the β-alkyl α,β-unsaturated acid imidazolides were very unstable. (e) Volumetric productivity of the reported epoxidation was rather low (0.1 M), which is not suitable for practical synthesis on a large scale. Because the concentration of the lanthanide catalyst was maintained at less than 1−10 mM to achieve high enantioselectivity, it was difficult to improve volumetric productivity unless catalyst loading was improved.[25] The low solubility of acid imidazolides is also problematic for improving volumetric productivity.

The catalytic asymmetric epoxidation of **1a** proceeded smoothly, as summarized in Table 2. With 10 mol % of the Sm(O-*i*-Pr)$_3$/(*R*)-BINOL complex[26] and 10 mol % of $Ph_3As(O)$,[10] the reaction was complete within 0.5 h and afforded **11a** in 93% yield and 94% ee (entry 1). The reaction rate was much faster than when using acid imidazolide and morpholinyl amide and as fast as that using α,β-unsaturated ketone.[27] The reaction also proceeded smoothly with 5 mol % catalyst (entry 2: y. 85%, 96% ee).[28] To improve the enantioselectivity, various BINOL derivatives were screened to determine that H_8-BINOL functioned best. The H_8-BINOL complex gave better results than the BINOL complex, probably due to the large bite angle.[29] With a novel Sm(O-*i*-Pr)$_3$/(*R*)-H_8-BINOL complex, **11a** was obtained in 99% ee (entry 3). $Ph_3P(O)$ was also effective for the present substrate[10] (entries 4−6). THF/toluene mixed solvent produced better results than THF alone, and **11a** was obtained in 96−99% ee depending on the amount of $Ph_3P(O)$ (entries 7−9). Both the reaction rate and selectivity were highest with 100 mol % of $Ph_3P(O)$ (entry 9). Under the best conditions (THF/toluene, $Ph_3P(O)$: 100 mol %), less explosive and less reactive cumene hydroperoxide (CMHP) was also applicable and the reaction reached completion within 0.2 h with 5 mol % catalyst (entry 10, y. 91%, >99.5% ee).[30] The result in entry 10 gave additional practical benefits to the present system compared with previous reports.[23,24]

(21) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323.
(22) (a) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792. (b) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (c) Solladié-Cavallo, A.; Bouérat, L. *Org. Lett.* **2000**, *2*, 3531. (d) Seki, M.; Furutani, T.; Imashiro, R.; Kuroda, T.; Yamanaka, T.; Harada, N.; Arakawa, H.; Kusama, M.; Hashiyama T. *Tetrahedron Lett.* **2001**, *42*, 8201. See also: (e) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491.
(23) α,β-Unsaturated carboxylic acid imidazolide: (a) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474. (b) Ohshima, T.; Nemoto, T.; Tosaki, S.-y.; Kakei, H.; Gnanadesikan, V.; Shibasaki, M. *Tetrahedron* **2003**, *59*, 10485.
(24) (a) α,β-Unsaturated amide: Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14544. (b) Tosaki, S.-y.; Nemoto, T.; Ohshima, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495. Application to 1,3-polyol synthesis: (c) Tosaki, S.-y.; Horiuchi, T.; Nemoto, T.; Ohshima, M.; Shibasaki, M. *Chem.—Eur. J.* **2004**, *10*, 1527.
(25) Our mechanistic studies suggested that several species exist in equilibrium in the mixture of the Ln(O-*i*-Pr)$_3$/BINOL complex. Catalyst concentration should be kept low (<5−10 mM) to achieve the best enantioselectivity, because undesired dimeric and oligomeric species would increase under concentrated conditions. See ref 10b for mechanistic studies.
(26) Standard condition for catalytic asymmetric epoxidation is lanthanide metal alkoxide/BINOL derivative = 1/1 with $Ph_3As(O)$ or $Ph_3P(O)$ as an additive. Among lanthanide metals screened (La, Pr, Nd, Sm, Gd, Er, and Yb), Sm had best reactivity and selectivity. La, Pr, Nd, Gd, and Er complexes also afforded **11a** in >90% ee and >80% yield. Yb was not suitable for **1a**. Sm(O-*i*-Pr)$_3$ was purchased from Kojundo Chemical Laboratory Co., Ltd. (Fax: +81-492-84-1351. sales@kojundo.co.jp).
(27) Reaction time for imidazolide: with 10 mol % of La-BINOL catalyst, at room temperature, 3.5 h, 86% yield and 5 mol % of La-BINOL catalyst, at room temperature, 12 h, 73% yield. Reaction time for amide: 5−10 mol % Sm-BINOL catalyst, at room temperature, 3−24 h, >90% yield. See refs 23 and 24.
(28) With imidazolide or amide as substrate, 5−10 mol % catalyst loading was essential for completion of the reaction.
(29) Review for H_8-BINOL: Terry, T.-L. A.-Y.; Chan, S.-S.; Chan, A. S. C. *Adv. Synth. Catal.* **2003**, *345*, 537.
(30) With less reactive CMHP as oxidant, acid imidazolide resulted in low chemical yield (18 h, 47% yield with 10 mol % catalyst). See ref 23.

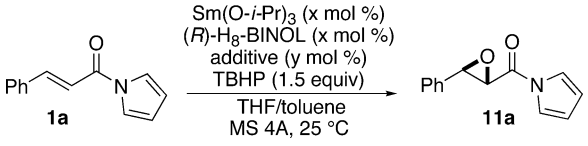
Table 2. Catalytic Asymmetric Epoxidation Reaction of α,β-Unsaturated *N*-Acylpyrrole **1a**



entry	Sm(O-*i*-Pr)$_3$ (x mol %)	ligand (x mol %)	additive (y mol %)	solvent	oxidant[a]	time (h)	yield[b] (%)	ee[c] (%)
1	10	BINOL (10)	$Ph_3As(O)$ (10)	THF	TBHP	0.5	93	94
2	5	BINOL (5)	$Ph_3As(O)$ (5)	THF	TBHP	0.5	85	96
3	5	H_8-BINOL (5)	$Ph_3As(O)$ (5)	THF	TBHP	0.5	94	99
4	5	H_8-BINOL(5)	$Ph_3P(O)$ (15)	THF	TBHP	0.5	84	94
5	5	H_8-BINOL (5)	$Ph_3P(O)$ (50)	THF	TBHP	0.5	88	98
6	5	H_8-BINOL(5)	$Ph_3P(O)$ (100)	THF	TBHP	0.5	85	97
7	5	H_8-BINOL (5)	$Ph_3P(O)$ (15)	THF/toluene	TBHP	0.4	85	96
8	5	H_8-BINOL(5)	$Ph_3P(O)$ (50)	THF/toluene	TBHP	0.5	92	99
9	5	H_8-BINOL (5)	$Ph_3P(O)$ (100)	THF/toluene	TBHP	0.2	97	99
10	5	H_8-BINOL(5)	$Ph_3P(O)$ (100)	THF/toluene	CMHP	0.2	91	>99.5

[a] TBHP in decane or CMHP in toluene was used. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Table 3. Trials to Reduce Catalyst Loading in Catalytic Asymmetric Epoxidation Reaction of α,β-Unsaturated *N*-Acylpyrrole **1**

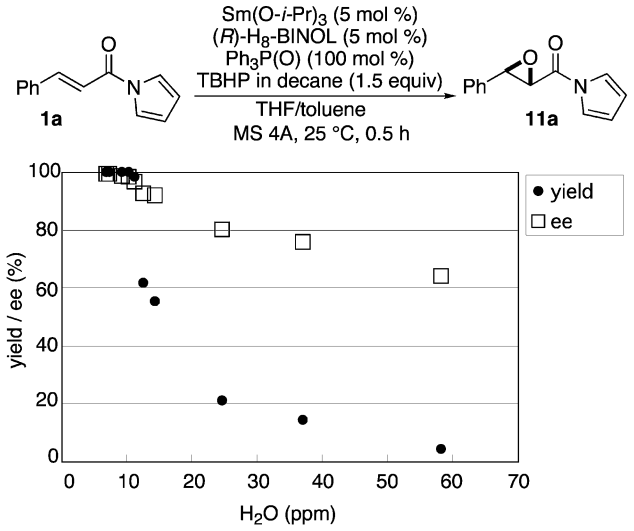


entry	Sm(O-*i*-Pr)$_3$ (x mol %)	H_8-BINOL (x mol %)	additive (y mol %)	MS 4 Å (mg/mmol of **1a**)	concn of [**1a**] (M)	time (h)	yield[a] (%)	ee[b] (%)
1[c]	5	5	$Ph_3P(O)$ (100)	1000	0.1	0.2	97	99
2[c]	1	1	$Ph_3P(O)$ (100)	500	1	0.3	94	99
3[d]	0.5	0.5	$Ph_3P(O)$ (100)	250	1	0.6	100	97
4[d]	0.2	0.2	$Ph_3P(O)$ (100)	100	2	1	99	97
5[d]	0.1	0.1	$Ph_3P(O)$ (100)	100	2	2	90	96
6[d]	0.1	0.1	$Ph_3As(O)$ (0.1)	100	3	0.6	100	99
7[d]	0.05	0.05	$Ph_3As(O)$ (0.05)	100	3	1	100	98
8[d]	0.02	0.02	$Ph_3As(O)$ (0.02)	100	3	1.5	94	99

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] TBHP in decane was used. [d] Anhydrous TBHP in toluene (dried with MS 4A) was used.

We then tried to reduce the catalyst loading. As expected, based on the high reaction rate with 5 mol % catalyst loading in Table 2, catalyst loading was easily reduced. As summarized in Table 3, the epoxidation reaction of **1a** completed using as little as 1, 0.5, 0.2 mol % of Sm(O-*i*-Pr)$_3$/H_8−BINOL complex with 100 mol % of $Ph_3P(O)$, giving product **11a** in high yield (94−100%) and high enantiomeric excess (96−99% ee) after 0.3 h (entry 2), 0.6 h (entry 3), and 1 h (entry 4). The reaction proceeded well with as little as 0.1 mol % catalyst loading (substrate/catalyst = 1,000), affording product in 90.4% yield (TON = 904) and 96% ee (entry 5). With the Sm(O-*i*-Pr)$_3$/H_8−BINOL/$Ph_3As(O)$ = 1/1/1 complex, catalyst loading was further reduced to 0.1, 0.05, and 0.02 mol % (substrate/catalyst = up to 5000) as summarized in entries 6−8. After 1.5 h, 2.01 g of **11a** (94.2% yield) was obtained in 99% ee using 0.589 mg of H_8-BINOL (0.02 mol % catalyst loading) and 0.644 mg of $Ph_3As(O)$ in entry 8. The high catalyst turnover number (TON = 4710 based on the metal and chiral ligand used) and the catalyst turnover frequency (TOF = up to >3000 h^{-1}) in the present system were far better compared with previous reports from our group with carboxylic acid imidazolide (substrate/catalyst = <10, TOF = 2.5 h^{-1} with the La-BINOL catalyst)[23] and morpholinyl amide (substrate/catalyst = 10−20, TOF = <2 h^{-1} with the Sm-BINOL catalyst).[24] For precise comparison of the reactivity using the same Sm-H_8-BINOL catalyst, see section E.[31] Because the commercially available TBHP solution in decane (5−6 M) contains up to 4% water, the use of the wet TBHP solution in decane was not suitable for reduced catalyst loading (entries 3−8). Thus, TBHP in toluene (ca. 6 M) dried with MS 4A (water content ≤ 0.4%) was alternatively used to avoid decomposition of the Sm(O-*i*-Pr)$_3$/H_8-BINOL catalyst by too much H_2O. TBHP in toluene was added slowly to the mixture of the Sm(O-*i*-Pr)$_3$/H_8-BINOL catalyst, either $Ph_3P(O)$ or $Ph_3As(O)$, **1a**, and MS 4A in THF/toluene. To reduce the catalyst loading, it was also important to keep the concentration of the catalyst within 1−5 mM, which is similar to the best conditions with 5 mol % catalyst loading ([Sm(O-*i*-Pr)$_3$/H_8-BINOL] = 5 mM). Thus, the concentration of substrate **1a** increased accordingly when the reaction shown in Table 3 was performed. For example, [**1a**] was 2 M in entry 5 and 3 M in entries 6−8. In previous reports from our group on the catalytic asymmetric epoxidation reaction, the standard substrate concentration for substrates was approximately 0.1 M, because the concentration of the catalyst needed to be kept low ([cat] = <5−10 mM) to achieve best enantioselectivity due to the equilibrium between many catalyst species.[25] Thus, the much

(31) Difference in reaction rate is in part ascribed to the difference in metal and chiral ligand used in previous reports (refs 23 and 24). For the precise comparison of reactivity of α,β-unsaturated *N*-acylpyrrole, *N*-acylimidazole, ketone, and amide under exactly the same conditions, see section E. α,β-Unsaturated *N*-acylimidazole showed the best reaction rate as long as 5 mol % Sm-H_8-BINOL catalyst was used, although the reaction did not proceed well with 1 mol % catalyst loading in the case of *N*-acylimidazole as substrate (section E, Scheme 4).



H_2O (ppm)	6.8	7.3	9.3	10	11	13	14	25	37	58	134	588
yield (%)	100	100	100	100	98	62	55	21	15	5	1	0
ee (%)	99	99	99	98	97	93	92	80	76	64	57	—

Figure 4. Effects of H_2O on chemical yield and ee.

higher volumetric productivity of the present system together with reduced catalyst loading is noteworthy for large scale synthesis. Because the amount of MS 4A needed depends on the amount of solvent used, the amount of MS 4A was also successfully reduced from 1000 mg/mmol substrate to 100 mg/mmol under the optimized conditions (entries 4−8), which is also a practical advantage of the present system. Further experiments to reduce catalyst loading were unsuccessful, because it was difficult to maintain the appropriate concentration of Sm catalyst due to solubility problems of product **11a**.[32]

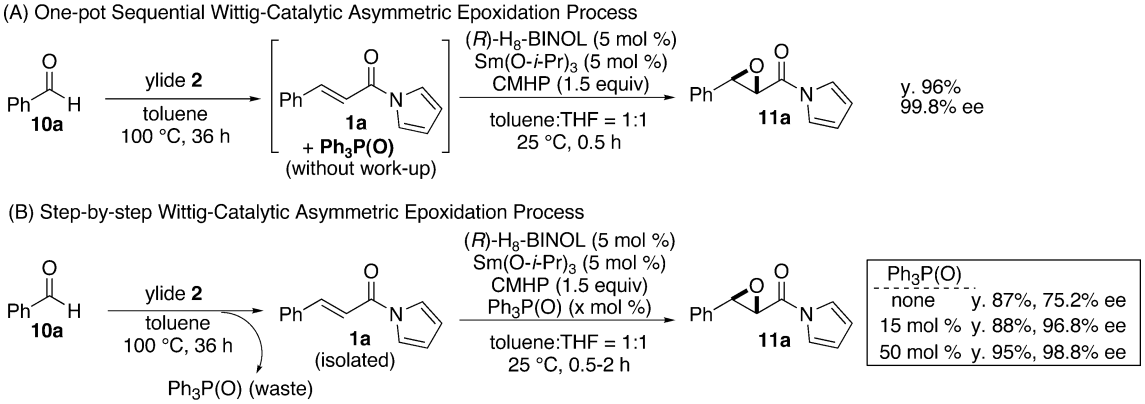
The amount of H_2O present during preparation of the Sm catalyst greatly affected the reaction rate and enantioselectivity in the epoxidation reactions. The amount of H_2O in the reaction mixture depended on the conditions of MS 4A used. The relations between H_2O concentration and reactivity, yield, and ee are summarized in Figure 4. The highest ee and reactivity were achieved when TBHP in decane was added to the Sm(O-*i*-Pr)$_3$/H_8-BINOL complex and MS 4A with an H_2O concentration of less than 10 ppm. As summarized in Figure 4, both reactivity and selectivity of the catalyst decreased significantly with an H_2O concentration of more than 10 ppm. Because a small increase in the H_2O concentration drastically retarded the reaction, it is recommended to dry MS 4A at 160 °C for 1−3 h under 0.7 KPa prior to use to achieve reliable and reproducible results. When using activated MS 4A and 5 mol % catalyst, commercially available TBHP in decane, which might contain up to 4% H_2O, was used directly as received without any problems. The results indicate that the H_2O content during catalyst formation from Sm(O-*i*-Pr)$_3$ and H_8-BINOL is important and is not very problematic in the presence of peroxide as long as 5 mol % catalyst was used.

(C) Sequential Wittig Olefination−Catalytic Asymmetric Epoxidation: Although the functional group compatibility of the Wittig reaction is good because of its mild reactivity, the Wittig reaction is generally considered less efficient due to the production of waste $Ph_3P(O)$. We hypothesized that reusing waste $Ph_3P(O)$ in the epoxidation reaction as a useful modulator for the Sm-H_8-BINOL complex would partially compensate for the disadvantage of the Wittig reaction. Thus, a sequential Wittig−catalytic asymmetric epoxidation reaction was designed in which the waste $Ph_3P(O)$ from the first Wittig reaction was reused as an additive in the second epoxidation reaction. A sequential Wittig−catalytic asymmetric epoxidation of **10a** afforded **11a** in 96% yield (2 steps) and 99.8% ee (er 999/1; Scheme 2A). As expected, the selectivity and reactivity were much lower when the reaction was performed step-by-step without adding $Ph_3P(O)$ in the second step (none 75.2% ee, er 7.06/1; Scheme 2B). By adding external $Ph_3P(O)$ (15 mol % and 50 mol %) in the second step after isolation of intermediate **1a** and $Ph_3P(O)$ (1 equiv) as waste, **11a** was obtained in 96.8% ee (er 61.5/1) and 98.8% ee (er 166/1), respectively (Scheme 2B). These results suggested that (a) $Ph_3P(O)$ functioned as an effective additive to improve yield and ee but (b) only a portion of 1 equiv of waste $Ph_3P(O)$ was necessary to achieve high ee in the second reaction. Comparison of the purification process (Scheme 2A, once vs Scheme 2B, twice), however, indicated that the total efficiency of the process from aldehyde to epoxide **11a** was highest in the sequential process (A). Total efficiency of the present system is also better than the previous results with acid imidazolide[23] and morpholinyl amide,[24] which were synthesized and purified prior to use.

As summarized in Table 4, the present sequential reaction has broad substrate generality, affording epoxides in excellent enantiomeric excess (96→99.5% ee) and good yield (entries 1−14: y. 72−96% from aldehydes). In the sequential reactions, 1.3 equiv of ylide **2** were employed to complete the Wittig reaction. The remaining ylide **2** had no adverse effects on the subsequent epoxidation step. Aromatic aldehydes with various substituents (entries 1−7), aliphatic linear and branched aldehydes with functional groups (entries 8−13), and α,β-unsaturated aldehyde (entry 14) were applicable to the present catalysis. Because the epoxidation reaction proceeded through 1,4-addition of peroxide, the reaction proceeded chemoselectively in the presence of an unactivated carbon−carbon double bond (entry 13). The reaction proceeded chemoselectively with aldehyde **10u** possessing a methyl ketone unit (entry 12). In entry 14, the epoxidation reaction selectively occurred at the 2,3-position. 4,5-Epoxide was not detected. In many examples, less explosive CMHP was used as an oxidant instead of the explosive TBHP, providing additional practical benefits to the present methodology. The epoxidation reaction of **1q** derived from α,α-disubstituted aldehyde **10q** as the substrate was not successful, probably due to steric hindrance. The *E*/*Z* ratio in the first Wittig olefination step partially affected the total chemical yield in the sequential reactions (two steps) with aliphatic aldehydes (entries 8−14) and aromatic aldehydes with an *ortho*-substituent (entries 6−7). The epoxidation of *Z*-α,β-unsaturated *N*-acylpyrrole proceeded rather slowly. For example, isolated *Z*-α,β-unsaturated *N*-acylpyrrole **12** gave *cis*-epoxide **13** as the major product in 32% yield and 86% ee after 1 h using 10 mol % Sm catalyst, 5 mol % $Ph_3As(O)$ as an additive, and TBHP as an oxidant (Scheme 3). The chemical yield was not improved, even after a longer reaction time. When **12** was used as the substrate, no *trans*-epoxide was observed. Under the sequential reaction

(32) With 0.01 mol % Sm(O-*i*-Pr)$_3$ ([Sm-cat] = 0.3 mM), epoxide was obtained in less than 10% yield.

Scheme 2. Wittig−Catalytic Asymmetric Epoxidation Reaction with (A) One-Pot Sequential Process and (B) Step-by-Step Process with External $Ph_3P(O)$



conditions, that is with 100 mol % of $Ph_3P(O)$, most of the *Z*-isomer remained after the second epoxidation reaction as observed by TLC analysis. Only trace amounts of the *cis*-epoxide were obtained under the sequential reaction conditions.

With chiral aldehyde **10z**, the sequential reaction proceeded in an almost completely catalyst-controlled manner (Table 5). The epoxide was obtained in a ratio of **14**/**15** = >99/1 with the (*R*)-catalyst (matched pair, entry 1) and **14**/**15** = 1/36 with the (*S*)-catalyst (mismatched pair, entry 3). In the case of the mismatched pair, TBHP was required to attain good reactivity (entry 2 vs entry 3). With achiral oxidating reagents, there was much lower selectivity (dr = 54/46).[33]

(D) Application of α,β-Unsaturated *N*-Acylpyrrole to a Direct Catalytic Asymmetric Michael Reaction: To further demonstrate the utility of α,β-unsaturated *N*-acylpyrrole as a monodentate ester surrogate, we examined the direct catalytic asymmetric Michael reaction of hydroxyketone **4** promoted by the Et_2Zn/linked-BINOL complex. Because the Et_2Zn/linked-BINOL complex was effective for the Michael reaction of α,β-unsaturated ketone,[9a,b,34] the system was chosen as a model reaction. Direct catalytic asymmetric Michael addition of unmodified ketone or aldehyde was recently studied intensively.[35] Although a few efficient catalyses were reported recently using α,β-unsaturated ketone and nitro-olefin, several critical problems remain to be addressed. One is the extension of a highly enantioselective direct catalytic asymmetric Michael addition of unmodified ketone or aldehyde to α,β-unsaturated carboxylic acid derivatives.

The Michael reaction proceeded smoothly at 0 °C (Table 6). Because the reactivity of the α,β-unsaturated *N*-acylpyrrole was slightly lower than that of the α,β-unsaturated ketone, all the reactions were performed at 0 °C. Michael adducts were obtained in good dr (81/19−95/5), yield (74−97%), and ee (88−95%) from β-aromatic and heteroaromatic substituted α,β-unsaturated *N*-acylpyrrole. The slightly lower enantioselectivity than that with α,β-unsaturated ketone can be ascribed to the reaction temperature. In the case of β-alkyl substituents (entry 10), the selectivity tendency was similar to that obtained with enone, that is, only modest dr and ee were achieved. To the best of our knowledge, this is the first direct catalytic asymmetric Michael reaction of unmodified ketone to α,β-unsaturated carboxylic acid derivatives. On the basis of our mechanistic studies on Et_2Zn/linked-BINOL **5** catalysis, enantioselectivity in the present reaction would mainly be determined by Re-face shielding of zinc enolate generated from hydroxyketone **4** and Et_2Zn/linked-BINOL **5** complex.[9a,34b] On the other hand, the diastereomeric ratio is supposed to be dependent on the facial selectivity of electrophiles by the zinc catalyst. The good diastereomeric ratio (69/31−95/5, Table 6) observed in the present Michael reaction suggested that facial selectivity of α,β-unsaturated *N*-acylpyrrole with Et_2Zn/linked-BINOL complex is similar to that of α,β-unsaturated phenyl ketone.[36] These results also supported our assumption that α,β-unsaturated *N*-acylpyrrole enabled application of the catalyst, which was optimized for α,β-unsaturated ketone, to α,β-unsaturated carboxylic acid derivatives. On the other hand, α,β-unsaturated carboxylic acid imidazolide was not applicable in the Michael reaction. Only trace, if any, product was observed under the same reaction conditions as Table 6.

(E) Electronic Properties of α,β-Unsaturated *N*-Acylpyrrole: The high reactivity of α,β-unsaturated *N*-acylpyrrole can be attributed to the delocalization of the nitrogen lone pair in the aromatic system, reducing donation into the carbonyl group. The reactivity of α,β-unsaturated *N*-acylpyrrole is thus expected to be much higher than that of simple amide and ester. To support the hypothesis, the LUMO energy level was calculated[37] and the reaction rates in the epoxidation of various electron deficient olefins were compared. As summarized in Figure 5, the LUMO energy level of α,β-unsaturated *N*-acylpyrrole (−2.06 eV) was lower than those of morpholinyl amide (−1.56 eV) and ester (−1.72 eV) and was rather close to that of phenyl ketone (−2.09 eV), oxazolidinone (−2.05 eV), and methyl

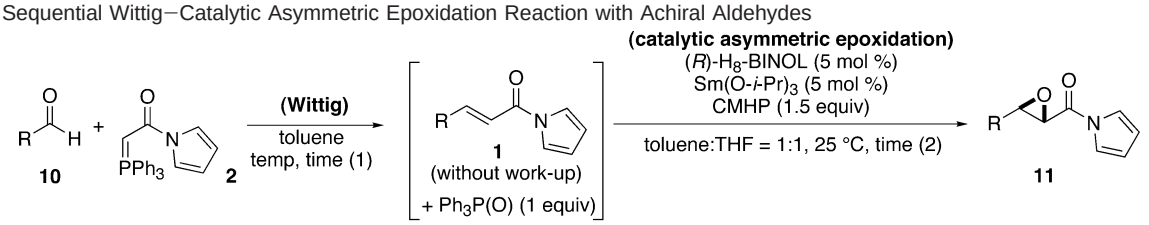
(33) Et_2Zn, *o*-MeO-phenol, *t*-BuOOH afforded epoxide in 76% yield after 18 h at 25 °C, albeit in low selectivity (dr = 54/46). Other conditions, such as H_2O_2-urea with base, *m*CPBA, and *aq*NaClO with phase-transfer catalyst, either resulted in decompositions of enone or afforded product in low yield (<20%).

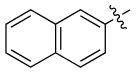
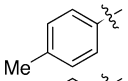
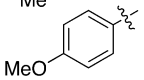
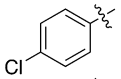
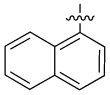
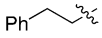
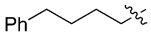
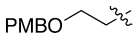
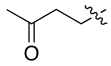
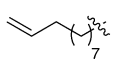
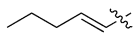
(34) For other applications of Et_2Zn/linked-BINOL catalyst, see Mannich-type reaction: (a) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. Aldol reaction: (b) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169. (c) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539. (d) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.

(35) (a) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441. (c) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (d) Enders, D.; Seki, A. *Synlett* **2002**, 26. (e) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (f) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737. (g) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (h) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151.

(36) Observed diastereomeric ratio for β-aryl substituted phenyl ketone (chalcone type) was 76/24−85/15, and for β-$BOMCH_2CH_2$ substituted phenyl ketone was 77/23. See ref 9a.

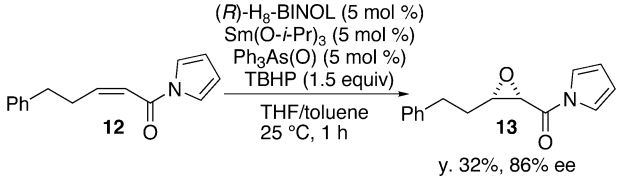
Table 4. Sequential Wittig−Catalytic Asymmetric Epoxidation Reaction with Achiral Aldehydes



entry	aldehyde (R)		(Wittig) temp (°C)	(Wittig) time (1) (h)	(epoxidation) time (2) (h)	(epoxidation) yield (%)[a]	ee (%)[b]	product
1		**10a**	100	48	0.5	96	>99.5	**11a**
2		**10b**	100	48	2	100	99	**11b**
3		**10c**	100	48	2.5	92	99	**11c**
4[c]		**10d**	110	84	0.5	87	98	**11d**
5		**10f**	100	24	0.5	100	99	**11f**
6[c]		**10h**	100	24	0.5	83	97	**11h**
7		**10i**	100	48	0.5	85	99	**11i**
8		**10m**	80	24	0.5	84	97	**11m**
9		**10n**	85	39	0.8	83	96	**11n**
10		**10o**	100	72	2	75	98	**11o**
11		**10r**	80	24	0.5	91	97	**11r**
12		**10u**	80	36	0.5	93	96	**11u**
13		**10v**	100	25	0.5	82	96	**11v**
14[c,d]		**10w**	100	72	2	72	96	**11w**

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] TBHP in decane was used as oxidant. [d] 10 mol % of catalyst was used.

Scheme 3. Catalytic Asymmetric Epoxidation of *Z*-α,*β*-Unsaturated *N*-Acylpyrrole

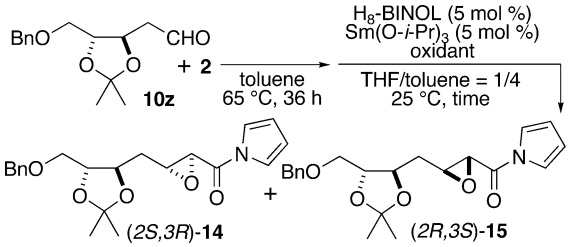


ketone (−1.88 eV). The LUMO energy level was lowest with 4-phenylimidazolide (−2.37 eV). The LUMO energy tendency seemed closely related to the observed reactivity tendency except 4-phenylimidazolide. Because we previously utilized the La-BINOL catalyst for 4-phenylimidazolide,[23] reevaluation of its reactivity was necessary under the same conditions using the same catalyst.

To precisely compare the reaction rates in the epoxidation of α,*β*-unsaturated phenyl ketone **18**, α,*β*-unsaturated methyl ketone **19**, α,*β*-unsaturated *N*-acylpyrrole **1a**, α,*β*-unsaturated

(37) LUMO energy was calculated using the B3LYP method with 6-31G* as basis sets. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, C. D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Van Voorhis, T.; Oumi, M.; Hirata, S.; Hsu, C.-P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M.; Pople, J. A. *J. Computational Chem.* **2000**, *21*, 1532. Spartan'02 Wavefunction, Inc.; Irvine, CA.

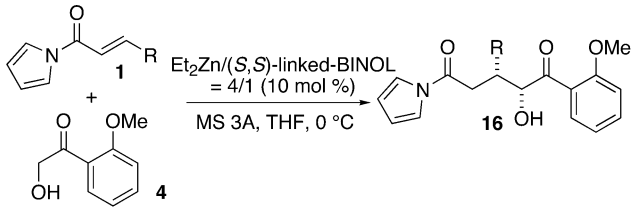
Table 5. Sequential Wittig−Catalytic Asymmetric Epoxidation Reaction with Chiral Aldehyde

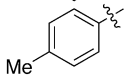
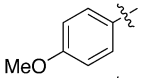
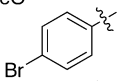
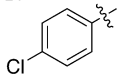
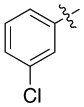
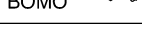


entry	ligand	time (h)	oxidant	yield[a] (%)	dr[b] (14/15)
1	(*R*)-H_8-BINOL	0.7	CMHP	80	>99/1
2	(*S*)-H_8-BINOL	0.9	CMHP	60	1/56
3	(*S*)-H_8-BINOL	0.7	TBHP	78	1/36

[a] Isolated yield. [b] Determined by HPLC analysis.

Table 6. Direct Catalytic Asymmetric Michael Reaction of Hydroxyketone **4** Promoted by Et_2Zn/Linked-BINOL **5** Complex



entry	R	product	time (h)	dr (*syn*/*anti*)	yield[a] (%)	ee[b] (%)
1		**1a** **16a**	17	91/9	85	91
2		**1c** **16c**	12	93/7	82	93
3[c]		**1d** **16d**	24	95/5	77	95
4		**1e** **16e**	13	91/9	94	93
5		**1f** **16f**	12	89/11	84	90
6		**1g** **16g**	13	86/14	93	88
7		**1j** **16j**	17	90/10	80	90
8		**1k** **16k**	17	95/5	74	90
9		**1l** **16l**	13	81/19	97	90
10[c]		**1s** **16s**	12	69/31	89	73

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] 15 mol % of (*S*,*S*)-linked-BINOL and 3 equiv of ketone were used.

carboxylic acid imidazolide **17**, and α,β-unsaturated amide **20**, reaction profiles with these substrates were observed under identical conditions. Because the reaction of α,β-unsaturated *N*-acylpyrrole **1a** and enones **18** and **19** was expected to proceed too fast under standard conditions at room temperature, the

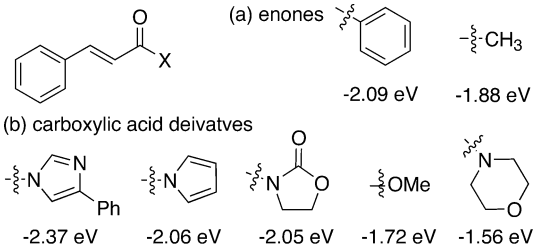


Figure 5. LUMO energy level of (a) α,β-unsaturated ketones and (b) α,β-unsaturated carboxylic acid derivatives.

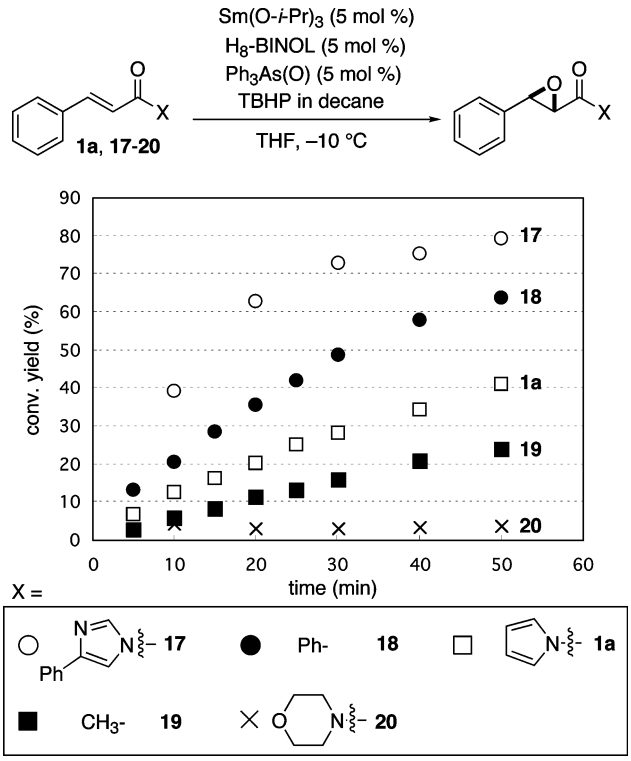
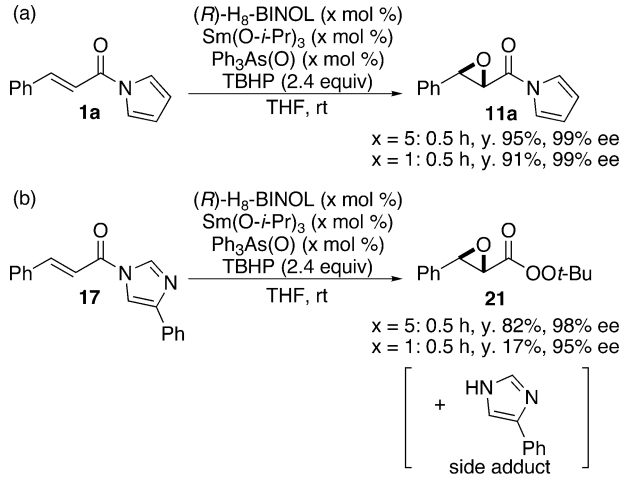


Figure 6. Epoxidationreaction profile of α,β-unsaturated ketones and α,β-unsaturated carboxylic acid derivatives with 5 mol % of Sm (O-*i*-Pr)$_3$, H_8-BINOL, and $Ph_3As(O)$.

reaction profile was observed at −10 °C in THF ([substrate] = 0.05 M) using 5 mol % Sm(O-*i*-Pr)$_3$, 5 mol % of H_8-BINOL, and 5 mol % of $Ph_3As(O)$. The reaction rate tendency was α,β-unsaturated carboxylic acid imidazolide **17**> α,β-unsaturated phenyl ketone **18**> α,β-unsaturated *N*-acylpyrrole **1a** > α,β-unsaturated methyl ketone **19** >> α,β-unsaturated amide **20** (Figure 6). The reaction profiles indicated that the reactivity of α,β-unsaturated *N*-acylpyrrole is slightly better than α,β-unsaturated methyl ketone **19** and slightly worse than phenyl ketone **18**, which was also proportional to the calculated LUMO energy level. As expected from the LUMO energy level, the initial reaction rate of **17** was fastest among those examined under identical conditions, as long as *5 mol % catalyst loading* was used (vide infra). The observed high reaction rate of **17** was quite different from our previous results using the La-BINOL catalyst for **17**. The difference is ascribed to the combination of the lanthanide metal and chiral ligand. With BINOL as a chiral ligand, the La complex gave better results than the Sm complex using α,β-unsaturated carboxylic acid imidazolide.[23b] With the H_8-BINOL ligand, the Sm complex had the highest reactivity and selectivity.

Scheme 4. Catalytic Asymmetric Epoxidation Reaction of (a) α,β-Unsaturated *N*-Acylpyrrole **1a** and (b) *N*-Acylimidazole **17** with 5 and 1 Mol % Sm Catalyst



The results in Figure 6 suggested that α,β-unsaturated *N*-acylpyrrole is as reactive as α,β-unsaturated ketone. On the other hand, the observed highest reactivity with *N*-acylimidazole **17** was rather unexpected on the basis of our previous experiments with various lanthanide metal-BINOL catalysts.[23b] Thus, we focused on the comparison of *N*-acylpyrrole **1a** and *N*-acylimidazole **17** to evaluate which is more suitable as a monodentate α,β-unsaturated ester surrogate. Although α,β-unsaturated carboxylic acid imidazolide was most reactive with 5 mol % catalyst loading (Figure 6), the opposite tendency was observed with 1 mol % catalyst loading (Scheme 4). In contrast to the case with α,β-unsaturated *N*-acylpyrrole, it was impossible to reduce catalyst loading from 5 mol % using **17** as the substrate. When the epoxidation of **17** was examined with 1 mol % of Sm(O-*i*-Pr)$_3$ and 1 mol % of H$_8$-BINOL, epoxide was obtained in only 17% yield (Scheme 4b). On the other hand, the reaction proceeded without any problems with 1 mol % of catalyst loading when using α,β-unsaturated *N*-acylpyrrole **1a** (Scheme 4a, 91% yield, 99% ee). The opposite tendencies can be ascribed to the difference in strength of the C−N amide bond of the *N*-acylimidazole and *N*-acylpyrrole unit. As shown in Scheme 4, the reaction of **17** affords epoxy peroxy ester **21** and liberated 4-phenylimidazole. On the other hand, the *N*-acylpyrrole moiety remains unchanged under the reaction conditions, probably because the leaving ability of pyrrole is relatively poorer. The liberated free imidazole had adverse effects on the reactivity of the Sm catalyst by coordinating to the Sm metal. Thus, the reaction rate dropped suddenly with 1 mol % catalyst loading using *N*-acylimidazole. In fact, in the presence of additional 100 mol % of 4-phenylimidazole, epoxide was obtained in only 22% yield after 30 min at −10 °C using 5 mol % of Sm(O-*i*-Pr)$_3$, H$_8$-BINOL, and Ph$_3$As(O) (same conditions as Figure 6).[38]

These results indicated that both the relatively low LUMO energy level, close to that of α,β-unsaturated ketone, and robust property of *N*-acylpyrrole moiety contributed to the high reactivity and high catalyst turnover number of α,β-unsaturated

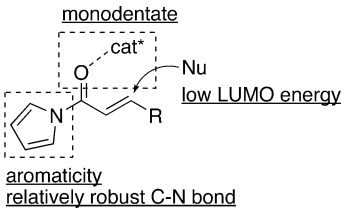
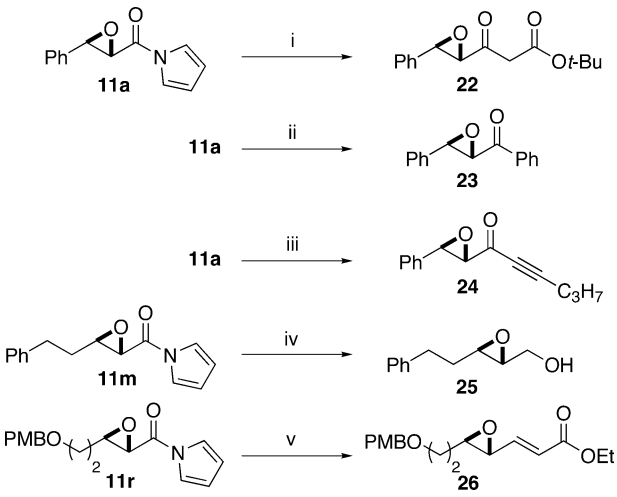


Figure 7. α,β-Unsaturated *N*-acylpyrrole as a monodentate α,β-unsaturated ester surrogate.

Scheme 5. Transformations of Pyrrolyl Epoxides[a]



[a] Conditions: (i) *tert*-butyl acetate, BuLi, THF, −78 °C, 10 min; then DBU, CH_2Cl_2, 25 °C, 20 min, y. 74% (two steps); (ii) PhLi, THF, −78 °C, 10 min; then DBU, CH_2Cl_2, 25 °C, 20 min, y. 88% (two steps); (iii) BuLi, 1-pentyne,THF, −78 °C, 10 min; then DBU, CH_2Cl_2, 0 °C, 10 min, y. 84%(2 steps); (iv) $LiBH_4$, THF, 0 to 25 °C, 1 h; then $NaBH_4$, 25 °C, 4 h, y. 72% (two steps); (v) $LiBH_4$, THF, 25 °C, 5 min; then $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, 25 °C, 4 h, y. 69% (two steps).

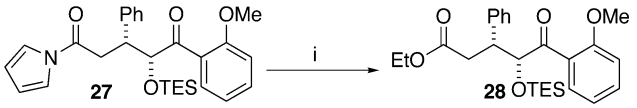
N-acylpyrrole as a monodentate α,β-unsaturated ester surrogate. The characteristic aspects of α,β-unsaturated *N*-acylpyrrole as a monodentate ester surrogate are summarized in Figure 7. The difference in the solubility of *N*-acylimidazole and *N*-acylpyrrole in organic solvent should be also mentioned. Because the direct catalytic asymmetric Michael reaction with Et_2Zn/linked-BINOL **5** had first-order dependency on the concentration of Michael acceptor,[9a] it was difficult to utilize the α,β-unsaturated carboxylic acid imidazolide **17** due to its poor solubility in THF. Michael reaction of **17** and ketone **4** gave trace, if any, product. Although highly concentrated conditions would be required to reduce the catalyst loading in many catalytic asymmetric reactions, it would be impossible to improve the volumetric productivity when using **17** for other 1,4-addition reactions.

(F) Transformation of *N*-Acylpyrrole Unit: As discussed in section E, the robust C−N bond of *N*-acylpyrrole under the conditions for catalytic asymmetric reactions was crucial for achieving good catalyst turnover number in the epoxidation reaction. On the other hand, for synthetic utility, an achiral template should be efficiently cleaved under mild conditions. Too robust a template is not suitable as an ester surrogate for further functional group manipulations. To demonstrate the utility of the *N*-acylpyrrole unit as the ester surrogate,[39] several transformations were performed (Scheme 5). Using the procedure reported by Evans,[15a] reactions with carbon nucleophiles

(38) In addition to the adverse effects of the liberated 4-phenylimidazole, product inhibition by epoxy peroxy ester is also postulated to explain the low reactivity with 1 mol % catalyst (Scheme 4b). Epoxy peroxy ester **21** would function as a bidentate ligand toward the Sm catalyst. Adverse effects of the bidentate coordination were also observed when using an α,β-unsaturated Weinreb amide as a substrate. See ref 24c.

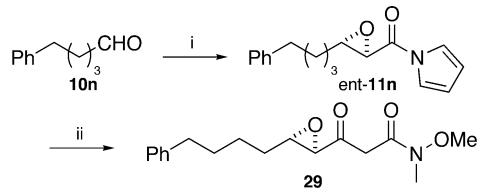
(39) For the conversion of *N*-acylpyrrole unit, see refs 13 and 15 and references therein.

Scheme 6. Transformation of Michael Adduct[a]



[a] Conditions: (i) EtSLi, EtOH, 25 °C, 2 h, y. 96%.

Scheme 7. Preparation of Synthetic Intermediate for Antifungal Natural Product[a]



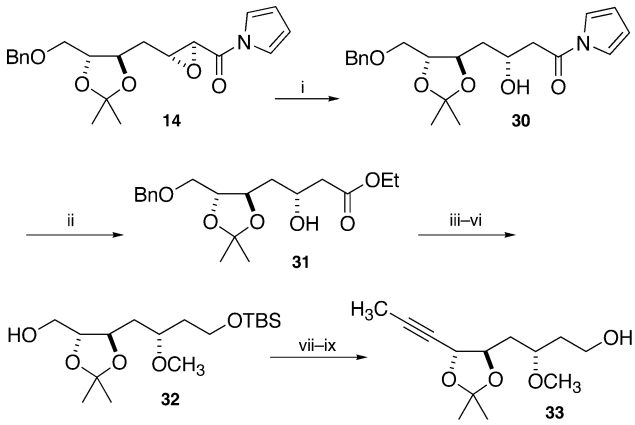
[a] Conditions: (i) ylide **2**, toluene, 85 °C, 39 h; then $Sm(O\text{-}i\text{-}Pr)_3$ (5 mol %), (*S*)-H_8-BINOL (5 mol %), MS 4A, THF/toluene, CMHP, 25 °C, 0.8 h, y. 83% (from **10n**), 96% ee; (ii) $CH_3C(O)N(OCH_3)CH_3$, LHMDS, THF, −78 °C, 20 min; then DBU, CH_2Cl_2, 25 °C, 40 min, y. 63% (two steps).

were examined. Pyrrolyl epoxide **11a** was converted to β-ketoester **22** in 74% yield by the addition of lithium enolate prepared from *tert*-butyl acetate, followed by treatment with DBU. α,β-Epoxy ketone **23** was obtained in 88% yield using PhLi and DBU. The addition of lithiated alkyne gave **24** in 84% yield after treatment with DBU. In two steps, **11m** was reduced to epoxyalcohol **25**; successive treatment with $LiBH_4$ and $NaBH_4$ gave **25** in 72% yield. The pyrrol carbinol intermediate obtained from the reduction of **11r** with $LiBH_4$ was also converted into **26** through the Horner−Wadsworth−Emmons reaction using Masamune−Roush conditions.[15b,40] The addition of EtSLi efficiently promoted alcoholysis of *N*-acylpyrrole in the Michael adduct (Scheme 6). With EtSLi in ethanol, ethanolysis of **27** proceeded within 2 h at 25 °C to give ethyl ester **28** in 96% yield.

We then applied the present method for the synthesis of known intermediates in the total synthesis of natural products. As shown in Scheme 7, a sequential Wittig reaction−catalytic asymmetric epoxidation reaction of **10n** with (*S*)-H_8-BINOL as the ligand afforded ent-**11n** in 83% yield and 96% ee in one-pot. Then, **11n** was easily converted to **29**, the synthetic intermediate for antifungal natural products reported by our group,[24b] with Weinreb acetamide and LiHMDS followed by addition of DBU.

Smith et al. reported **33** in Scheme 8 as a fragment in their total synthesis of phorboxazole A.[41] Sequential Wittig reaction−catalytic asymmetric epoxidation of **10z** afforded **14** in >99/1 dr as determined by HPLC analysis (see, Table 5). Then, **30** was obtained through reductive epoxide opening of **14** using diselenide and $NaBH_4$.[42] EtSLi in ethanol was effective for ethanolysis of **30**. Ethanolysis of **30** proceeded smoothly at room temperature, and ethyl ester **31** was obtained in 92% yield after 40 min. More harsh reaction conditions are required when using metal ethoxide directly in the absence of ethanethiol.[13] Simple functional group manipulation of **31** gave **32** in four steps.

Scheme 8. Synthesis of Intermediate **33** in Smith's Total Synthesis of Phorboxazole A[a]



[a] Conditions: (i) PhSeSePh, $NaBH_4$, EtOH/AcOH, 25 °C, 15 min, y. 94%; (ii) EtSLi, EtOH, 25 °C, 40 min, y. 92%; (iii) CH_3I, Ag_2O, MS 3A, toluene, 45 °C, 36 h, y. 93%; (iv) $LiAlH_4$, Et_2O, 25 °C for 30 min, then reflux for 40 min, y. 85%; (v) TBSCl, imidazole, CH_2Cl_2, 25 °C, 50 min, y. 86%; (vi) H_2 (5 atm), $Pd(OH)_2$, AcOEt/EtOH, $NaHCO_3$, 25 °C, 18 h, y. 96%; (vii) PCC, AcONa, MS 3A, CH_2Cl_2, 25 °C, 20 min; then $(CH_3O)_2P(O)C(N_2)COCH_3$, K_2CO_3, CH_3OH, 25 °C, 80 min, y. 57% (2 steps); (viii) BuLi, THF, −78 °C; then CH_3I, −78 °C to 25 °C, y. 91%; (ix) $Bu_4N^+F^-$, THF, 25 °C, 2.5 h, y. 88%.

Oxidation, alkynylation of aldehyde,[43] methylation of terminal alkyne, and removal of the TBS group gave Smith's intermediate **33**.

Summary

In summary, we demonstrated the utility of α,β-unsaturated *N*-acylpyrrole as a monodentate ester surrogate in the catalytic asymmetric epoxidation reaction and direct catalytic asymmetric Michael reaction. The results suggested that the substrate scope of asymmetric catalysts originally developed for α,β-unsaturated ketone could be broadened to α,β-unsaturated carboxylic acid derivatives with only small, if any, modifications in the reaction conditions using α,β-unsaturated *N*-acylpyrrole. Both a relatively low LUMO energy level and robust pyrrole amide bond were essential to achieve high reactivity. In the epoxidation reactions, the following advantages are noteworthy: (i) Catalyst loading (0.02−5 mol %) and the reaction rate (0.2−2.5 h, TOF up to >3000 h^{-1}) were improved compared with the previously reported reaction with acid imidazolide and morpholinyl amide (5−10 mol %, 1−24 h). The high volumetric productivity (up to 3 M) with reduced catalyst loading (0.02 mol %) is also noteworthy. (ii) The less explosive, thus, more practical CMHP was applicable for α,β-unsaturated *N*-acylpyrrole. (iii) The sequential Wittig-olefination−catalytic asymmetric epoxidation process provided an efficient one-pot access to optically active epoxides from aldehydes. The total efficiency of the asymmetric epoxidation reaction was improved, especially from the viewpoint of purification, including synthesis of the substrate for the epoxidation step. Good yield (y. 72−100% from aldehyde) and excellent ee (96→99.5%) were achieved with broad substrate generality. In the Michael reaction, we succeeded in the first direct catalytic asymmetric Michael reaction of unmodified ketone to α,β-unsaturated carboxylic acid derivatives in

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good yield (74−97%), dr (69/31−95/5), and ee (73−95%). The application of the *N*-acylpyrrole unit to other catalytic asymmetric reactions is ongoing in our group.

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Supporting Information Available: Experimental procedures, characterization of the products, detail data for reaction kinetic profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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