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Catalytic Asymmetric Synthesis of 2,2-Disubstituted Terminal Epoxides via Dimethyloxosulfonium Methylide Addition to Ketones

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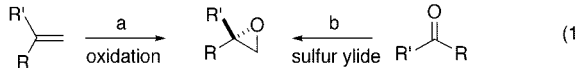
Optically active epoxides are versatile building blocks for the synthesis of biologically active natural and unnatural compounds. Although various useful catalytic asymmetric epoxidation methods have been reported,[1] 2,2-disubstituted terminal epoxides remain particularly challenging target compounds. Catalytic asymmetric epoxidations of geminally disubstituted terminal unfunctionalized alkenes (eq 1, path a) have been studied using enzymes,[2] chiral metal and organo-catalysts,[3] but the enantioselectivity, yield, and/or substrate generality of these reactions are not satisfactory.



(1)

Considering the importance of 2,2-disubstituted epoxides as key building blocks for valuable chiral tertiary alcohols, a new strategy to synthesize chiral 2,2-disubstituted terminal epoxides is highly desirable.[4,5] Herein, we report an alternative approach based on Corey−Chaykovsky epoxidation[6] of ketones (eq 1, path b). A La−Li_3-tris(binaphthoxide) (LLB **1a**, Figure 1) complex with an Ar_3P═O additive (Ar = 2,4,6-trimethoxyphenyl) promoted the addition of dimethyloxosulfonium methylide to ketones, giving 2,2-disubstituted terminal epoxides in >88−99% yield and 91−97% ee.

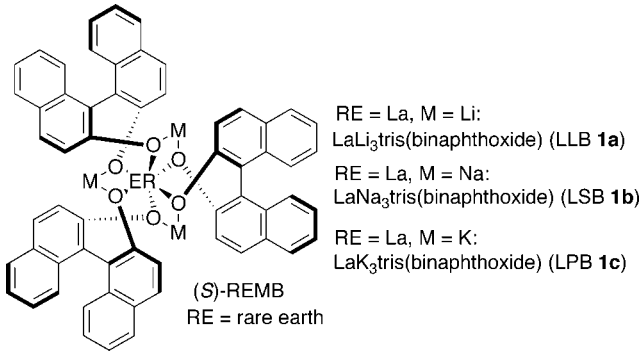
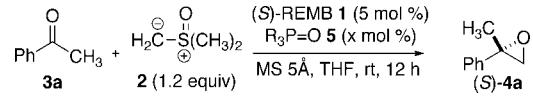


Figure 1. Structures of (*S*)-RE-M_3-tris(binaphthoxide) complex (REMB, RE = rare earth), LLB **1a**, LSB **1b**, and LPB **1c**.

Initial screening of several chiral multimetallic catalysts developed in our group revealed that heterobimetallic rare earth−alkali metal RE-M_3-tris(binaphthoxide) complexes (REMB, Figure 1)[7,8] were the most promising candidates for the addition of a sulfur ylide to ketones. Optimization studies with dimethyloxosulfonium methylide **2** and ketone **3a** using REMB complexes are summarized in Table 1. LLB **1a** promoted the reaction at room temperature in 79% yield, but the enantioselectivity was poor (entry 1, 15% ee). In the presence of MS 5Å, enantioselectivity improved to 72% ee (entry 2). Other metal combinations, such as La−Na (LSB, **1b**) and La−K (LPB, **1c**), resulted in much less satisfactory yield and enantioselectivity (entry 3, 25% yield, 14% ee, entry 4, 17% yield, 52% ee). Many trials to improve the enantioselectivity revealed that the addition of achiral phosphine oxide **5** was effective. In the presence of 5 mol % of Ph_3P═O **5a**, **4a** was obtained in 80% ee (entry 5). Among the various types of phosphine oxides screened (entries 5−13),[9] Ar_3P═O **5i** (Ar = 2,4,6-trimethoxyphenyl) was the best, giving **4a** in 98% isolated yield and 96% ee after 12 h (entry 13). A molar ratio of LLB **1a**:Ar_3P═O **5i** = 1:1 was sufficient to achieve high enantioselectivity (entries 13−15).

Table 1. Optimization of Reaction Conditions



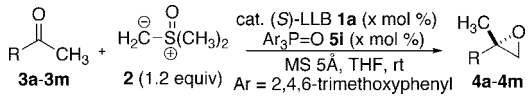
entry	REMB **1**	R: **5** (*x* mol %)		time (h)	yield[a] (%)	ee (%)
1[b]	LLB **1a**	none		48	79	15
2	LLB **1a**	none		12	80	72
3	LSB **1b**	none		12	25	14
4	LPB **1c**	none		12	17	52
5	LLB **1a**	Ph− (5)	**5a**	12	77	80
6	LLB **1a**	4-Cl-C_6H_4− (5)	**5b**	12	99	74
7	LLB **1a**	C_6F_5− (5)	**5c**	12	61	48
8	LLB **1a**	*n*Bu (5)	**5d**	12	87	75
9	LLB **1a**	cyclohexyl (5)	**5e**	12	99	76
10	LLB **1a**	2,4,6-Me_3-C_6H_2− (5)	**5f**	12	97	75
11	LLB **1a**	4-MeO-C_6H_4− (5)	**5g**	12	82	77
12	LLB **1a**	2,6-$(MeO)_2$-C_6H_3− (5)	**5h**	12	84	93
13	LLB **1a**	2,4,6-$(MeO)_3$-C_6H_2− (5)	**5i**	12	98[c]	96
14	LLB **1a**	2,4,6-$(MeO)_3$-C_6H_2− (10)	**5i**	12	94	95
15	LLB **1a**	2,4,6-$(MeO)_3$-C_6H_2− (15)	**5i**	12	92	92

[a] Yield determined by ^{1}H NMR analysis of crude mixture. [b] Reaction was run in the absence of MS 5Å. (*R*)-**4a** was obtained in major. [c] Isolated yield after purification by column chromatography.

The optimized reaction conditions using an LLB **1a**:Ar_3P═O **5i** = 1:1 mixture were applicable to various ketones (Table 2). Aryl methyl ketones **3a**−**3h** gave epoxides in >93−99% yield and 92−97% ee (entries 1−8). Ketones **3c**−**3e** with an electron-withdrawing substituent at either the *para*-, *meta*-, or *ortho*-positions gave epoxides in high yield and enantioselectivity (entries 3−5). The broad generality of aryl methyl ketones is synthetically useful because the methods for producing chiral 2-aryl-2-methyl terminal epoxides in high enantioselectivity are limited to biocatalytic kinetic resolution approaches.[4b,c] It is noteworthy that pyridyl methyl ketone **3i** and alkyl methyl ketones **3j**−**3m** were also applicable and afforded epoxides in >88−99% yield and 91−96% ee (entries 9−13). Catalyst loading was successfully reduced to 2.5 and 1 mol %, and good enantioselectivity was maintained (entries 14 and 15). To demonstrate the synthetic utility of epoxides, transformations of products into chiral tertiary alcohols were investigated (Scheme 1). Ring opening of epoxide with an amine nucleophile proceeded in isopropanol at 90 °C, giving β-amino *tert*-alcohol **6b** in 90% yield. Reaction with alkynyl lithium reagent also proceeded regioselectively and afforded **7b** in >99% yield.

10.1021/ja803864p CCC: $40.75

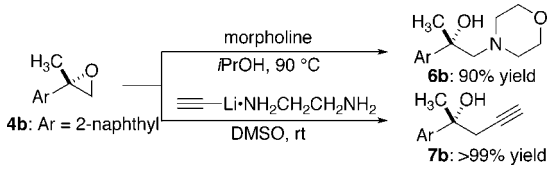
Table 2. Catalytic Asymmetric Synthesis of 2,2-Disubstituted Terminal Epoxides from Various Methyl Ketones[a]



entry	ketone **3**: R		epoxide	cat. **1a/5l** (*x* mol %)	time (h)	yield (%)[b]	ee (%)
1	Ph	**3a**	**4a**	5	12	98	96
2	2-naphthyl	**3b**	**4b**	5	12	97	96
3	4-Cl-C_6H_4	**3c**	**4c**	5	12	>99	94
4	3-Cl-C_6H_4	**3d**	**4d**	5	12	>99	94
5	2-Cl-C_6H_4	**3e**	**4e**	5	12	96	95
6	4-F-C_6H_4	**3f**	**4f**	5	12	94	97
7	4-EtO_2C-C_6H_4	**3g**	**4g**	5	12	94	94
8[c]	4-Me-C_6H_4	**3h**	**4h**	5	12	97	92
9	3-pyridyl	**3i**	**4i**	5	12	97	92
10	$PhCH_2CH_2$	**3j**	**4j**	5	12	99	93
11	*n*-octyl	**3k**	**4k**	5	12	>99	93
12[c]	cyclohexyl	**3l**	**4l**	5	12	88[d]	96
13	EtO_2C-$(CH_2)_3$–	**3m**	**4m**	5	12	>99	91
14	2-naphthyl	**3b**	**4b**	2.5	18	96	94
15	2-naphthyl	**3b**	**4b**	1	60	96	92

[a] Reaction was performed in THF (0.1 M ketone **3**) at room temperature (20−23 °C) with MS 5Å; 1.2 equiv of ylide **2** prepared from trimethyloxosulfonium chloride and NaH were used. [b] Isolated yield after purification by column chromatography. [c] Enantiomeric excess was determined after epoxide ring opening; see Supporting Information for detail. [d] NMR yield was >95%, but the isolated yield decreased because epoxide **4l** was volatile.

Scheme 1. Transformations of 2,2-Disubstituted Terminal Epoxide



In the present system, the best yield and enantioselectivity were obtained with $Ar_3P{=}O$ **5i** additive. The results shown in Table 1, entries 5−13, suggested that the electron-donating and coordinating MeO substituents at the 2,6-positions were key to improving enantioselectivity. ^{31}P NMR analysis of $Ar_3P{=}O$ **5i** alone (3.50 ppm) and $Ar_3P{=}O$ **5i** with LLB (16.3 ppm) indicated that $Ar_3P{=}O$ **5i** coordinates to LLB **1a**. We speculated that the LLB:$Ar_3P{=}O$ **5i** = 1:1 complex would be the active species in the present system. Electron-rich and bulky achiral additive **5i** would suitably modify the chiral environment of LLB,[9,10] resulting in better yield and enantioselectivity in the present reaction. Further mechanistic studies to elucidate the precise role of $Ar_3P{=}O$ **5i** on enantioselectivity are ongoing.

In summary, we developed a catalytic asymmetric Corey−Chaykovsky epoxidation of ketones with dimethyloxosulfonium methylide **2** using an LLB **1a** + $Ar_3P{=}O$ complex. The reaction proceeded smoothly at room temperature, and 2,2-disubstituted terminal epoxides were obtained in high enantioselectivity (91−97% ee) and yield (>88−99%) from a broad range of methyl ketones with 1−5 mol % catalyst loading. The use of achiral additive $Ar_3P{=}O$ **5i** was important to achieve high enantioselectivity. Studies to further broaden the substrate generality to other ketones, such as ethyl ketones, are ongoing.[11]

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Supporting Information Available: Experimental procedures, spectral data of new compounds, determination of absolute configurations, and ^{31}P NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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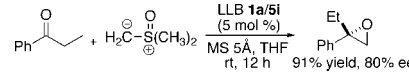
(11) Preliminary investigation with propiophenone gave epoxide in 91% yield and 80% ee (with 5 mol % catalyst, at rt, 12 h). Aldehydes are not suitable substrates under identical conditions. Further optimization studies are ongoing.



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