

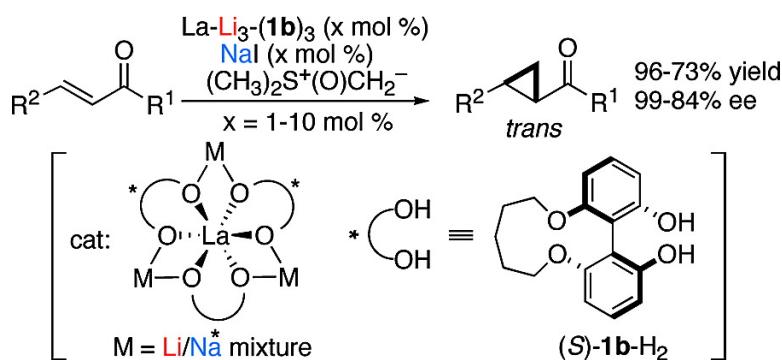
Communication

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Catalytic Asymmetric Cyclopropanation of Enones with Dimethyloxosulfonium Methylide Promoted by a La–Li₃–(Biphenyldiolate)₃ + NaI Complex

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The cyclopropane unit is a common structural motif in biologically active natural and unnatural compounds. Its unique reactivity and structural properties have led chemists to develop a new methodology for cyclopropanation.¹ Among the methods available, cyclopropanation using ylides proceeds chemoselectively with electron deficient olefins.² Therefore, the method is complementary to other variants, such as the Simmons–Smith type reaction and the carbenoid-mediated reaction. Catalytic highly enantioselective Simmons–Smith-type and carbenoid-mediated cyclopropanations have been established;^{1,3} however, catalytic asymmetric cyclopropanation of electron deficient olefins with ylides is rare.^{4,5} Aggarwal^{4a} and Gaunt^{4b} reported pioneering studies on enantioselective cyclopropanations via the catalytic generation of chiral sulfonium and ammonium ylides. On the other hand, MacMillan realized high enantiocontrol by activating the electrophiles, α,β -unsaturated aldehydes, with an organocatalyst.^{5a,6} High enantioselectivity was achieved using stabilized sulfonium ylides with a β -ketone unit. With a Lewis acidic metal complex, a more reactive sulfonium ylide was applicable; however, stoichiometric amounts of a chiral ligand and a Lewis acid were required to obtain high enantioselectivity (>90% ee).⁷ Thus, the development of a *catalytic* cyclopropanation with a reactive ylide is desirable. Herein we report a catalytic asymmetric Corey–Chaykovsky cyclopropanation of enones² with dimethyloxosulfonium methylide promoted by a La–Li₃–(biphenyldiolate)₃ + NaI system (Figure 1, **1a–c**). A NaI additive as well as biphenyldiol **1b** both had a key role in achieving high enantioselectivity (up to 99% ee).

Initial optimization studies with dimethyloxosulfonium methylide **2** and enone **3a** using heterobimetallic La–Li₃–(ligand)₃ complexes⁸ are summarized in Table 1. On the basis of our recent finding that biphenyldiols are sometimes superior to BINOL in rare earth metal catalysts,⁹ we examined both BINOL and biphenyldiols as ligands. When using ylide **2** prepared from trimethyloxosulfonium iodide and NaH (entries 1–2), **4a** was obtained in 38% ee with ligand **1a** (entry 2), while the use of BINOL resulted in 1% ee (entry 1). With ylide **2** prepared from trimethyloxosulfonium chloride and NaH, however, the enantioselectivity decreased to 6% ee (entry 4, ligand **1a**). We assumed that the difference in entries 2 and 4 was due to NaI included in the ylide **2** solution in entry 2. The beneficial effects of NaI on enantioselectivity were confirmed by the reaction of ylide **2** prepared from trimethyloxosulfonium chloride and NaH with 30 mol % of NaI additive, giving **4a** in 37% ee (entry 5). Further optimizations of the NaI amount (entry 6), the solvent (entry 7), biphenyldiols (entries 7–11, **1a–c**), and additive (entries 10–11, MS 4 Å) revealed that 10 mol % of the La–Li₃–(**1b**)₃ complex with NaI (10 mol %) and MS 4 Å additives was the best combination, giving **4a** in 86% yield and 89% ee (entry 11). Slow addition of enone **3a** over 1.5 h was effective to improve enantioselectivity, giving **4a** in 97% yield and 97% ee (entry 12).

The optimized reaction conditions were applicable to various enones, giving exclusively trans adducts in all entries (Table 2).

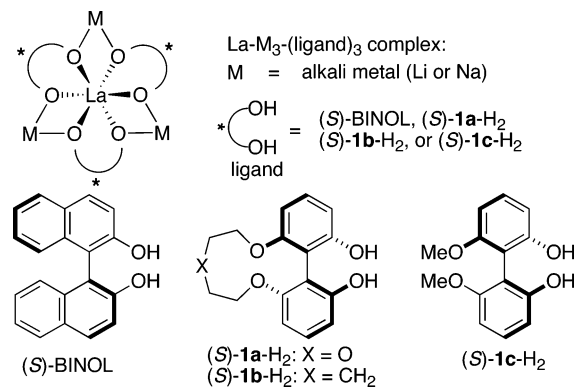


Figure 1. Structures of (S)-La–M₃–(ligand)₃ complex, (S)-BINOL, and (S)-biphenyldiols **1a**-H₂, **1b**-H₂, and **1c**-H₂.

Table 1. Optimization of Reaction Conditions

entry	ligand	additive (mol %)	solvent	slow addition	time (h)	yield (%)	ee (%)
1 ^a	BINOL	none	THF	–	72	71	1
2 ^a	1a	none	THF	–	72	72	38
3 ^b	BINOL	none	THF	–	72	71	1
4 ^b	1a	none	THF	–	20	51	6
5 ^b	1a	NaI (30)	THF	–	30	37	37
6 ^b	1a	NaI (10)	THF	–	24	36	53
7 ^b	1a	NaI (10)	THF/tol ^c	–	24	45	55
8 ^b	1b	NaI (10)	THF/tol ^c	–	18	43	51
9 ^b	1c	NaI (10)	THF/tol ^c	–	24	42	13
10 ^b	1a	NaI (10) + MS 4 Å	THF/tol ^c	–	18	69	82
11 ^b	1b	NaI (10) + MS 4 Å	THF/tol ^c	–	18	86	89
12 ^b	1b	NaI (10) + MS 4 Å	THF/tol ^c	+ ^d	20	97	97

^a Ylide **2** was prepared from trimethyloxosulfonium iodide and NaH.

^b Ylide **2** was prepared from trimethyloxosulfonium chloride and NaH.

^c THF/toluene = 4/5. ^d **3a** in THF/toluene was added slowly over 1.5 h.

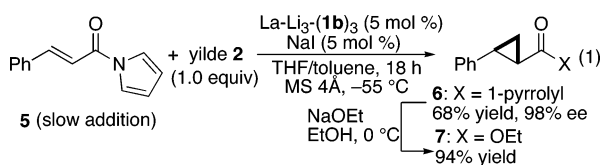
Chalcone derivatives with either electron-withdrawing or electron-donating substituents (entries 2–5) as well as heteroaryl-substituted enones (entries 6–8) were applicable with 5 mol % catalyst loading, giving products in high enantioselectivity (93–99% ee). Reaction of **3i** with two carbon–carbon double bonds proceeded chemoselectively at the electron deficient carbon–carbon double bond (entry 9). With dienone **3j**, 1,4-addition proceeded selectively, and the *trans*- α,β -cyclopropyl adduct **4j** was obtained in 89% yield and 91% ee (entry 10). Alkyl ketones **3k** and **3l** were also applicable (entries 11–12). Catalyst loading was successfully reduced to 2.5 and 1 mol %, while maintaining good enantioselectivity (entries 13–15). Equation 1 illustrates preliminary investigation to further extend the substrate scope to a carboxylic acid derivative. Cyclopropanation of α,β -unsaturated *N*-acylpyrrole **5** proceeded smoothly using 5 mol % of catalyst and 1.0 equiv of ylide **2**, giving product

Table 2. Catalytic Asymmetric Cyclopropanation of Various Enones^a

entry	enone		cat/NaI (x mol %)	time (h)	yield ^b (%)	ee (%)
	R ¹	R ²				
1	Ph	Ph	3a	5	18	96
2	4-Cl-C ₆ H ₄	Ph	3b	5	18	93
3	4-MeO-C ₆ H ₄	Ph	3c	5	18	95
4	Ph	4-Cl-C ₆ H ₄	3d	5	18	92
5	Ph	4-MeO-C ₆ H ₄	3e	5	18	93
6	Ph	2-furyl	3f	5	18	96
7	Ph	2-thienyl	3g	5	18	94
8	Ph	4-pyridyl	3h	5	18	91
9	4-allyl-O-C ₆ H ₄	Ph	3i	5	18	92
10	Ph	-CH=CHPh	3j	5	18	89
11 ^c	CH ₃	Ph	3k	5	18	74
12	iPr	Ph	3l	10	18	73
13 ^d	Ph	Ph	3a	2.5	18	90
14 ^d	Ph	2-furyl	3f	1	18	82
15 ^d	Ph	2-thienyl	3g	1	18	94

^a Reaction was performed in THF/toluene = 4/5 (0.1 M on enones **3**) at -55 °C with MS 4 Å. Enone **3** in THF/toluene was added slowly over 2 h, and 1.2 equiv of ylide **2** prepared from trimethyloxosulfonium chloride and NaH were used unless otherwise noted. ^b Isolated yield. ^c **4k** was volatile; 1.4 equiv of ylide **2** were used in entry 11. ^d Enone **3** was added slowly over 3 h (entry 13) and 4 h (entries 14–15).

6 in 68% yield and 98% ee. *N*-Acylpyrrole moiety in **6** was readily converted into ethyl ester by treatment with NaOEt in 94% yield.¹⁰



In the present system, the best yield and enantioselectivity was obtained with the NaI additive. ESI-MS analysis supported the idea that a partial alkali metal exchange occurred in the presence of NaI to afford a La–Li₂–Na–(1b)₃ complex in situ.^{11,12} A control experiment with 10 mol % of La–Na₃–(1b)₃ complex alone under the optimized conditions (slow addition, MS 4 Å) gave **4a** from **3a** in only 5% ee and 44% yield, while 10 mol % of La–Na₃–(1b)₃ + LiI complex gave **4a** in 88% ee and 94% yield. The results also support the importance of Li/Na mixture system.^{11,13} On the basis of previous structural analysis of heterobimetallic rare earth–alkali metal–BINOL complexes and the effects of alkali metals on enantioselectivity in other reactions,^{14,15} we speculate that the partial alkali metal exchange in the present system would slightly modify the asymmetric environment, thereby resulting in better yield and enantioselectivity in the present reaction. Further mechanistic studies to elucidate the precise role of NaI on enantioselectivity are ongoing.

In summary, we achieved a catalytic asymmetric cyclopropanation of enones and an *N*-acylpyrrole with dimethyloxosulfonium methylide **2** using a La–Li₃–(biphenyldiolate 1b)₃ + NaI complex. The present system is complementary to previously reported organocatalytic methods in terms of ylide utilized,^{4,5} and products were obtained in good yield (97–73%) and high ee (99–84%) with 1–10 mol % catalyst loading. The use of biphenyldiol 1b-H₂ and the NaI additive was important to achieve high enantioselectivity. Further mechanistic studies¹⁶ as well as applications of the mixed-alkali metal system in other asymmetric reactions are in progress.

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Supporting Information Available: Experimental procedures, spectra data of new compounds, determination of absolute configurations, additive effects, and ESI-MS data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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