

Heterobimetallic Catalysis in Asymmetric 1,4-Addition of *O*-Alkylhydroxylamine to Enones

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Catalytic asymmetric 1,4-additions are one of the most important fields of study in asymmetric catalysis,¹ and various methods have been reported during the past decade. 1,4-Addition of amines to α,β -unsaturated carbonyl compounds provides a direct and attractive strategy for the construction of optically active β -amino carbonyl units,² which are often found in biologically interesting compounds. Among them, a few highly enantioselective Lewis acid catalyses for 1,4-additions of *O*-alkylhydroxylamines were recently reported,³ providing versatile chiral building blocks. Although high enantioselectivity was achieved, catalyst loading remained a problem. For good yield and ee in the precedents, 10–30 mol % of catalysts were necessary,^{3,4} probably because amines or products deactivated the chiral Lewis acids. Thus, a practical, more amine-tolerant, asymmetric catalysis for this useful reaction is desirable. Herein, we demonstrate the utility of heterobimetallic multifunctional catalysis⁵ in asymmetric 1,4-addition of *O*-alkylhydroxylamine. High ee and yield were achieved using as little as 0.5–3 mol % of a YLi₃tris(binaphthoxide) (Figure 1, YLB **1a**, 1.5–9 mol % based on a chiral ligand).

Initially, we screened various heterobimetallic complexes containing rare earth metals and alkaline metals for the addition of **3a** to **2a**, and YLB **1a** gave the best reactivity and enantioselectivity. As shown in Table 1, the reaction proceeded smoothly with 10 mol % of **1a** at –20 °C to give **4a** in 94% yield and 97% ee (entry 1). In contrast to the previous results using the YLB–H₂O complex,⁶ the addition of H₂O somewhat retarded the reaction. We speculated that even a small amount of H₂O derived from a possible side reaction (oxime formation) would be problematic for reducing the catalyst loading. Thus, various desiccants were screened to attain good reproducibility (entries 2–5), and Drierite (CaSO₄) gave the best results (entry 5). BnONH₂ also gave good results (entry 6). With the optimal conditions (YLB, **3a**: 1.2 equiv, Drierite), catalyst loading was reduced. As summarized in entries 7–11, the reaction proceeded without any problem with as little as 0.5–1 mol % of **1a**, giving **4a** in good yield and ee (entry 9, y. 95% and 96% ee; entry 10, y. 96% and 96% ee). The low catalyst loading is noteworthy. Other advantages of the present method are as follows: (i) Commercially available, cheap *O*-methylhydroxylamine gave high ee.⁷ (ii) Volumetric productivity of the present reaction is high (2.1 M in entry 10, 2.5 M in entry 9). The result suggested that inhibition of the Lewis acidic catalyst **1a** by an amine or product was negligible in the present system even under highly concentrated conditions. Scalability of the reaction was also demonstrated in entry 11. The reaction proceeded without any problems on a 10 g scale (2.1 M).

We then examined the substrate scope of the reaction (Table 2). For convenience, most reactions were performed with 3 mol % of **1a**. For selected substrates including **2k** with an electron-donating substituent on the aromatic ring, reactions were also performed with 1 mol % of **1a**, and similar results were obtained (entries 1, 3, 5, 12, 15 vs 2, 4, 6, 13, 16). β -Aryl substituted enones with various

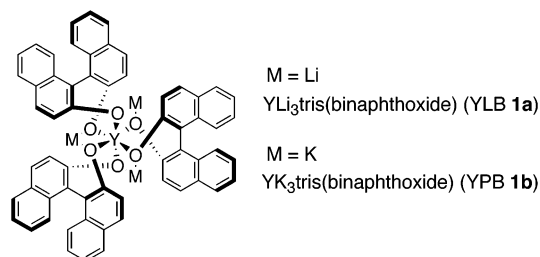


Figure 1. Structure of YM₃tris(binaphthoxide) (YLB, **1a** and YPB, **1b**).


Table 1. Optimization of the 1,4-Addition of *O*-Alkylhydroxylamine with YLB **1a**

entry	additive	amine: R	catalyst (xmol %)	time (h)	yield (%)	ee (%)
1	none	3a (Me–)	10	24	94	97
2	MS 3A	3a	10	24	85	96
3	MS 4A	3a	10	24	67	96
4	MS 5A	3a	10	24	44	97
5	Drierite	3a	10	24	94	97
6	Drierite	3b (Bn–)	10	26	91	91
7	Drierite	3a	5	42	94	96
8	Drierite	3a	3	42	97	95
9	Drierite	3a	1	48	95	96
10	Drierite	3a	0.5	80	96	96
11 ^a	Drierite	3a	1	48	98	95

^a 48 mmol scale (10 g of **2a** was used).

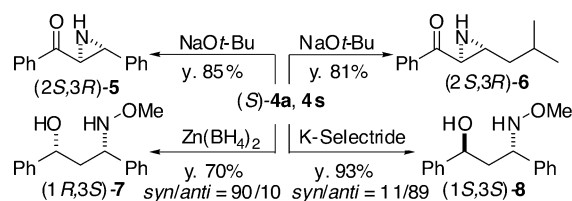
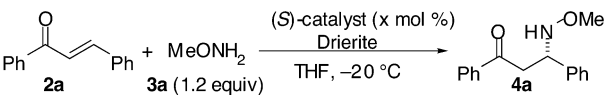
substituents (entries 1–19) afforded 1,4-adducts in 81–96% ee and 85–98% yield. For the less reactive substrate, 2–3 equiv of **3a** was used. β -Heteroaromatic (entries 20–22) and β -aliphatic (entries 23–27) enones, and dienone (entry 28) also gave products in good ee. At present, R¹ of **2** is limited to an aromatic ring. To exemplify the utility of the 1,4-adducts, **4a** and **4s** were converted into acyl aziridines **5**, **6**,^{3c,d} *syn*-1,3-amino alcohol **7**, and *anti*-1,3-amino alcohol **8**, as summarized in Scheme 1.

Several preliminary experiments were performed to gain mechanistic insight into the present catalysis. As summarized in Tables 2 and 3, neither the Li–BINOL nor the Y–BINOL complex afforded products. YPB **1b** (Figure 1) was also not effective. Only YLB **1a** promoted the reaction smoothly in high enantioselectivity. Thus, the cooperative function of Y and Li metals (heterobimetallic catalysis) was important to achieve high catalyst turnover in the reaction. Initial rate kinetics suggested that only one catalyst is involved in the reaction sequence.⁸ On the basis of previous mechanistic studies on heterobimetallic catalysis,^{5b} Y metal might function as the Lewis acid that activates the enone. Considering the pK_a value of the amine proton, however, it is unlikely that Li-binaphthoxide functions as a Brønsted base and activates the amine

Table 2. Catalytic Asymmetric 1,4-Addition of *O*-Methylhydroxylamine (**3a**) Promoted by YLB **1a**


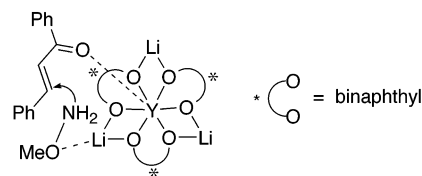
entry	enone		product	YLB (mol %)	time (h)	yield (%)	ee (%)	
	R ¹	R ²						
1	Ph	Ph	2a	4a	3	42	97	95
2	Ph	Ph	2a	4a	1	48	95	96
3	4-Cl-C ₆ H ₄	Ph	2b	4b	3	42	96	96
4	4-Cl-C ₆ H ₄	Ph	2b	4b	1	46	92	96
5	4-F-C ₆ H ₄	Ph	2c	4c	3	54	97	96
6 ^a	4-F-C ₆ H ₄	Ph	2c	4c	1	65	91	96
7	4-Me-C ₆ H ₄	Ph	2d	4d	3	48	96	94
8 ^a	4-MeO-C ₆ H ₄	Ph	2e	4e	3	74	91	96
9	3-Me-C ₆ H ₄	Ph	2f	4f	3	48	96	92
10 ^a	2-furyl	Ph	2g	4g	3	48	95	94
11 ^a	2-thienyl	Ph	2h	4h	3	78	96	93
12	Ph	4-Cl-C ₆ H ₄	2i	4i	3	48	92	92
13	Ph	4-Cl-C ₆ H ₄	2i	4i	1	78	97	93
14	Ph	4-Me-C ₆ H ₄	2j	4j	3	48	96	96
15 ^a	Ph	4-MeO-C ₆ H ₄	2k	4k	3	82	85	95
16 ^a	Ph	4-MeO-C ₆ H ₄	2k	4k	1	74	85	95
17	Ph	3-NO ₂ -C ₆ H ₄	2l	4l	3	42	98	81
18	Ph	3-Cl-C ₆ H ₄	2m	4m	3	48	95	92
19 ^a	Ph	2-Cl-C ₆ H ₄	2n	4n	3	122	92	82
20 ^a	Ph	2-furyl	2o	4o	3	84	80	92
21	Ph	2-thienyl	2p	4p	3	48	96	95
22 ^a	Ph	4-pyridyl	2q	4q	3	60	91	85
23 ^a	Ph	<i>n</i> -C ₅ H ₁₁	2r	4r	3	84	96	84
24 ^a	Ph	<i>i</i> -PrCH ₂	2s	4s	3	48	95	93
25	Ph	<i>i</i> -Pr	2t	4t	3	78	97	86
26	Ph	<i>cyclo</i> -hexyl	2u	4u	3	48	98	82
27 ^a	Ph	<i>t</i> -Bu	2v	4v	3	96	57	82
28 ^b	Ph	<i>trans</i> -PhCH=H	2w	4w	3	84	91	95

^a 2 equiv of **3a** was used. ^b 3 equiv of **3a** was used.

Scheme 1. Transformations of **4****Table 3.** Catalytic Asymmetric 1,4-Addition of *O*-Methylhydroxylamine (**3a**) Using Various Metal Complexes


entry	catalyst (xmol %)	time (h)	yield (%)	ee (%)	config
1	none	42	trace		
2	BuLi/BINOL (9/9)	42	11	12	<i>R</i>
3	Y(HMDS) ₃ /BINOL (3/9)	42	29	16	<i>R</i>
4	YPB 1b (3)	42	19	12	<i>R</i>
5	YLB 1a (3)	42	97	95	<i>S</i>

moiety. Thus, the role of heterobimetallic catalysis appears to be different from that in our previous reports.⁵ On the basis of the different results obtained with Li (YLB) and K (YPB), the oxygen atom of **3** might coordinate to Li. **3** would then be positioned close to enone **4**, and the addition reaction would be accelerated (Figure

**Figure 2.** Postulated model for 1,4-addition of **3a** catalyzed by YLB **1a**.

2). The interaction between the oxygen atom of **3** and K in YPB **1b** should be weaker than that with Li. Further mechanistic investigations are necessary to clarify the role of Li in YLB.

In summary, we demonstrated the utility of heterobimetallic catalysis in an enantioselective 1,4-addition of commercially available *O*-methylhydroxylamine to enones. High catalyst turnover (0.5–3 mol % of YLB **1a**, 1.5–9 mol % based on a chiral ligand), good yield (80–98%), and ee (81–96%) were achieved under concentrated conditions (1.1–2.5 M), although the substrate scope was somewhat limited. These results implied that neither amine nor product inhibited the heterobimetallic catalysis, unlike standard Lewis acid catalysis. Further investigation to broaden substrate generality as well as mechanistic studies to clarify the origin of high catalyst turnover are in progress.

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Supporting Information Available: Experimental procedures, characterization data for new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Inanaga achieved excellent ee (94–99% ee, ref 3d) using *O*-diphenylmethylhydroxylamine, which is not commercially available.
- See the Supporting Information for the detailed results.

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