



## A BINOL–terpyridine-based multi-task catalyst for a sequential oxidation and asymmetric alkylation of alcohols

Xi Chen<sup>a</sup>, Qiang Liu<sup>a</sup>, Hong-Bao Sun<sup>a</sup>, Xiao-Qi Yu<sup>a,\*</sup>, Lin Pu<sup>b,\*</sup>

<sup>a</sup>Department of Chemistry, Key Laboratory of Green Chemistry and Technology (Ministry of Education), Sichuan University, Chengdu 610064, China

<sup>b</sup>Department of Chemistry, University of Virginia, Charlottesville, VA 22904-4319, USA

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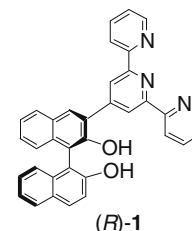
### ABSTRACT

Treatment of a BINOL–terpyridine compound with RuCl<sub>3</sub> generates a Ru(II) complex (*R*)-**6**. This complex is found to be a novel multi-task catalyst capable of conducting a sequential oxidation and asymmetric alkyl addition to convert primary alcohols to chiral secondary alcohols. The terpyridine–Ru(II) site of (*R*)-**6** catalyzes an efficient oxidation of primary alcohols to aldehydes which then undergo an enantioselective alkylation to generate chiral secondary alcohols when the BINOL site of (*R*)-**6** is combined with ZnEt<sub>2</sub> and Ti(O<sup>i</sup>Pr)<sub>4</sub>.

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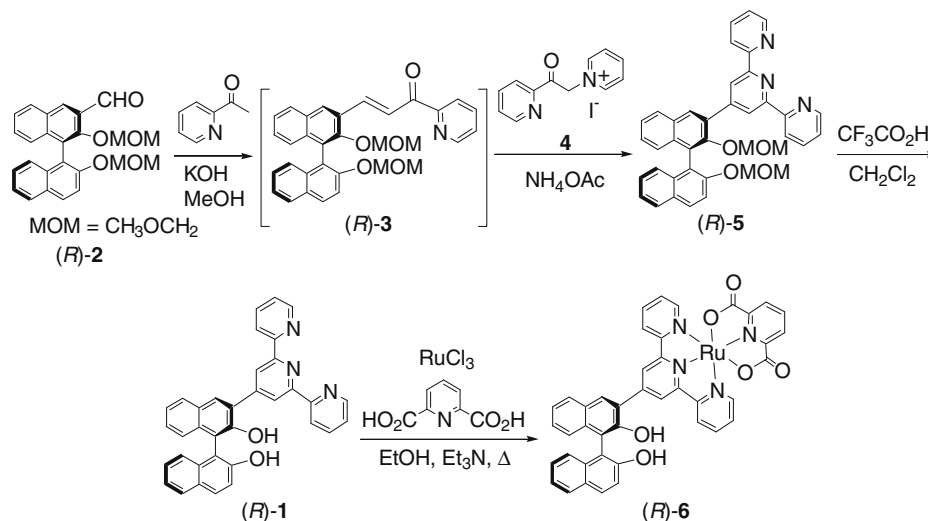
The hydroxyl groups of 1,1'-bi-2-naphthol (BINOL) and its derivatives allow the incorporation of a variety of Lewis acidic metal centers (*hard* metals) to catalyze diverse asymmetric organic reactions.<sup>1</sup> 2,2':6',2''-Terpyridine-based ligands can coordinate to late transition metals (*soft* metals) for many applications.<sup>2</sup> The distinctively different coordination ability of the BINOL and terpyridine ligands presents a great opportunity to develop a novel class of multi-task catalysts by joining BINOL and terpyridine together.<sup>3,4</sup> Previously, the 6-position of BINOL was linked with a terpyridine to build dendritic materials,<sup>5</sup> but no catalyst was developed from the BINOL–terpyridine conjugate. Recently, we have prepared the BINOL–terpyridine compound (*R*)-**1** and found that this compound can catalyze the asymmetric reaction of methyl propiolate with aldehydes.<sup>6</sup> In this process, the BINOL and terpyridine units cooperate with each other to achieve the high enantioselectivity. Herein, we report the use of the BINOL–terpyridine compound to generate a novel multi-task catalyst for a sequential oxidation and alkylation process. We have introduced a Ru(II) center to coordinate to the terpyridine unit of (*R*)-**1** to catalyze an efficient oxidation of primary alcohols to aldehydes. The resulting aldehydes are then catalyzed by the BINOL unit of (*R*)-**1**

in combination with ZnEt<sub>2</sub> and Ti(O<sup>i</sup>Pr)<sub>4</sub> to generate chiral secondary alcohols with good enantioselectivity.



The synthesis of the BINOL–terpyridine ligand (*R*)-**1** as shown in Scheme 1 was recently reported.<sup>6</sup> Reaction of the 3-formyl MOM-protected BINOL (*R*)-**2** with 2-acetylpyridine in the presence of KOH gave (*R*)-**3** which was then treated with **4** in the presence of ammonium acetate to give the terpyridine compound (*R*)-**5**. Removal of the MOM-protecting groups of (*R*)-**5** under acidic conditions gave the BINOL–terpyridine compound (*R*)-**1**. We then incorporated a Ru(II) center into (*R*)-**1** to form complex (*R*)-**6** by reaction with RuCl<sub>3</sub> and pyridine-2,6-dicarboxylic acid in the presence of Et<sub>3</sub>N.<sup>7a</sup> The UV spectrum of (*R*)-**6** shows absorptions similar to those of the previously reported Ru(II)(terpyridine)(2,6-pyridine dicarboxylate).<sup>7a</sup> This compound was also characterized by high resolution mass spectrometry and elemental analysis.<sup>8</sup>

\* Corresponding authors. Tel.: +1 434 924 6953; fax: +1 434 924 3710.  
E-mail addresses: [xqyu@tfol.com](mailto:xqyu@tfol.com) (X.-Q. Yu), [lp6n@virginia.edu](mailto:lp6n@virginia.edu) (L. Pu).



**Scheme 1.** Synthesis of the BINOL-terpyridine-Ru(II) complex (*R*)-6.

A Ru(II)(terpyridine)(2,6-pyridinedicarboxylate) in combination with  $\text{H}_2\text{O}_2$  was found to be an environmentally benign method for the oxidation of alcohols to aldehydes by Beller and co-workers.<sup>7b</sup> BINOL and its derivatives in combination with  $\text{Ti}(\text{O}^i\text{Pr})_4$  were also found to catalyze the asymmetric diethylzinc addition to aldehydes with good enantioselectivity.<sup>9</sup> Therefore, we have tested the use of (*R*)-6 as a novel multi-task catalyst for the sequential oxidation of primary alcohols followed by asymmetric alkylzinc addition to generate chiral alcohols.

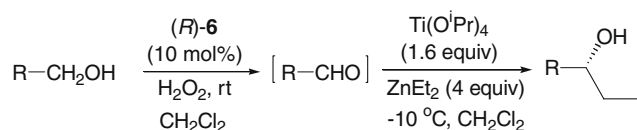
As shown in Scheme 2, the Ru(II) site of (*R*)-6 first catalyzed the  $\text{H}_2\text{O}_2$  oxidation of a primary alcohol to an aldehyde which was then converted to a chiral secondary alcohol product with the addition of  $\text{Ti}(\text{O}^i\text{Pr})_4$  and  $\text{ZnEt}_2$ . In this catalytic system, the use of  $\text{H}_2\text{O}_2$  (aq) in the first step makes it necessary to quench and dry before the alkyl addition in the second step. Table 1 shows the conditions we explored for the oxidation of benzyl alcohol and the subsequent

asymmetric alkyl addition. It was found that when both steps were conducted at room temperature, increasing the amount of  $\text{Ti}(\text{O}^i\text{Pr})_4$  from 50 to 160 mol % led to increased yield and ee (entries 1–5).

**Table 2**  
Results for the sequential oxidation and asymmetric alkylation catalyzed by (*R*)-6<sup>a</sup>

Entry	Primary Alcohol	Product	Yield <sup>b</sup> (%)	ee (%)
1			90	87( <i>R</i> )
2			87	88( <i>R</i> )
3			92	86( <i>R</i> )
4			86	82( <i>R</i> )
5			86	83( <i>R</i> )
6			93	83( <i>R</i> )
7			89	84( <i>R</i> )
8			90	75( <i>R</i> )
9			94	74( <i>R</i> )

<sup>a</sup>  $\text{Et}_2\text{Zn}/\text{alcohol}/\text{Ti}(\text{O}^i\text{Pr})_4/(\text{R})\text{-6} = 4:1:1.6:0.1$ . The reaction was conducted in  $\text{CH}_2\text{Cl}_2$  with the first step at rt and the second step at  $-10\text{ }^\circ\text{C}$ .  
<sup>b</sup> Isolated yields.



**Scheme 2.** Sequential oxidation and asymmetric alkylation catalyzed by (*R*)-6.

**Table 1**  
Conditions for the sequential oxidation and asymmetric alkylation of benzyl alcohol catalyzed by (*R*)-6<sup>a</sup>

Entry	( <i>R</i> )-6 (mol %)	Solvent	$\text{Ti}(\text{O}^i\text{Pr})_4$ (mol %)	Isolated yield (%)	ee (%)
1	10	$\text{CH}_2\text{Cl}_2$	50	37	30( <i>R</i> )
2	10	$\text{CH}_2\text{Cl}_2$	100	58	53( <i>R</i> )
3	10	$\text{CH}_2\text{Cl}_2$	120	70	67( <i>R</i> )
4	10	$\text{CH}_2\text{Cl}_2$	140	81	71( <i>R</i> )
5	10	$\text{CH}_2\text{Cl}_2$	160	91	78( <i>R</i> )
<b>6<sup>b</sup></b>	<b>10</b>	<b><math>\text{CH}_2\text{Cl}_2</math></b>	<b>160</b>	<b>90</b>	<b>87(<i>R</i>)</b>
7 <sup>b,c</sup>	10	$\text{CH}_2\text{Cl}_2$	160	82	83( <i>R</i> )
8 <sup>b</sup>	5	$\text{CH}_2\text{Cl}_2$	160	79	77( <i>R</i> )
9 <sup>b</sup>	20	$\text{CH}_2\text{Cl}_2$	160	92	88( <i>R</i> )
10 <sup>b,d</sup>	10	$\text{CH}_2\text{Cl}_2$	160	90	87( <i>R</i> )

<sup>a</sup> Unless indicated otherwise, following conditions were used:  $\text{ZnEt}_2/\text{benzyl alcohol} = 4:1$ . Both steps at rt.

<sup>b</sup> The first step at rt and the second step at  $-10\text{ }^\circ\text{C}$ .

<sup>c</sup>  $\text{ZnEt}_2/\text{benzyl alcohol} = 3:1$ .

<sup>d</sup>  $\text{ZnEt}_2/\text{benzyl alcohol} = 5:1$ .

Lowering the reaction temperature in the second step to  $-10\text{ }^{\circ}\text{C}$  increased the ee to 87% (entry 6). Decreasing the amount of  $\text{ZnEt}_2$  or the catalyst reduced both the yield and the ee (entries 7 and 8). Increasing the amount of the catalyst to 20 mol % only slightly increased the yield and ee (entry 9). Increasing the amount of  $\text{ZnEt}_2$  did not change the yield and ee (entry 10).

We have applied the conditions in entry 6 of Table 1 to the reactions of a variety of benzylic alcohols. As the results summarized in Table 2 show, (R)-**6** exhibits significant efficiency for the sequential reactions. Good yield and enantioselectivity have been achieved for substrates with various substituents on the benzene ring. The absolute configurations of the products are determined by comparing them with those previously reported.

The general procedure for the sequential oxidation and asymmetric alkylation catalyzed by (R)-**6** is described here. (a) To a solution of (R)-**6** (25.6 mg, 0.032 mmol) and benzyl alcohol (32  $\mu\text{L}$ , 0.32 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL),  $\text{H}_2\text{O}_2$  (30 wt %, 0.5 mL) was added. The reaction vessel was sealed and stirred vigorously at room temperature. After benzyl alcohol was consumed completely as indicated by TLC,  $\text{Na}_2\text{SO}_3$  was added. The organic phase was separated and the water phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 3$  mL). The combined organic phase was evaporated to dryness. (b) Under nitrogen, to the above residue,  $\text{CH}_2\text{Cl}_2$  (3 mL, dried),  $\text{ZnEt}_2$  (4 equiv, 1 M solution in hexane), and  $\text{Ti}(\text{O}^i\text{Pr})_4$  (1.6 equiv) were added at  $-10\text{ }^{\circ}\text{C}$  and the mixture was stirred for 96 h. The reaction was then quenched by a dropwise addition of a saturated  $\text{NH}_4\text{Cl}$  solution (3 mL). The organic phase was separated and the water phase was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 3$  mL). The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$  and filtered. Evaporation of the solvent followed by column chromatography on silica gel eluted with petroleum ether/ethyl acetate (8:1) afforded the chiral alcohol product. The ee was determined by HPLC analysis (OD-H column).

In summary, a novel multi-task catalyst (R)-**6** has been prepared by incorporation of a Ru(II) center into a BINOL–terpyridine ligand. The Ru(II) complex (R)-**6** was found to catalyze the sequential oxidation and asymmetric alkyl addition to convert primary alcohols to chiral secondary alcohols. Thus, a single chiral compound is empowered to conduct multiple reactions. This work presents a new and potentially general strategy for the development of multi-task catalysts by joining distinctively different coordination sites together.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.142.

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- Preparation and characterization of (R)-**6**. A solution of (R)-**1** (25.9 mg, 0.050 mmol) and  $\text{RuCl}_3$  (10.4 mg, 0.050 mmol) in ethanol (3 mL) was heated at  $85\text{ }^{\circ}\text{C}$  in air. The color of the mixture turned from light yellow to dark green in 1 h. Pyridine-2,6-dicarboxylic acid (8.4 mg, 0.050 mmol) and  $\text{Et}_3\text{N}$  (23  $\mu\text{L}$ , 0.15 mmol) were then added and the reaction mixture was heated for another 3 h at  $85\text{ }^{\circ}\text{C}$ , during which the color changed to deep purple. After removal of the solvent, the residue was purified by column chromatography on silica gel (200–300 m) eluted with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (30:1). A purple solid was obtained in 65% yield (25.6 mg). Analytical sample was obtained by recrystallization with  $\text{CH}_2\text{Cl}_2/n$ -hexane. UV–vis ( $\text{CH}_2\text{Cl}_2$ ,  $\lambda_{\text{max}}/\text{nm}$ ) (log  $\epsilon$ ): 228 (7.48), 286 (7.06), 323 (7.01), 397 (6.69), 544 (6.59). HR-MS(ES<sup>-</sup>) calcd for ( $\text{C}_{42}\text{H}_{26}\text{N}_4\text{O}_6\text{Ru}-\text{H}$ ) 783.0818, found 783.0916. Elementary Anal. Calcd:  $\text{C}_{42}\text{H}_{26}\text{N}_4\text{O}_6\text{Ru}$ : C, 64.36; H, 3.34; N, 7.15. Found: C, 64.23; H, 3.45; N, 7.09.
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