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Highly enantioselective homogeneous catalysis of chiral rare earth phosphates in the hetero-Diels–Alder reaction

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Abstract—Two types of novel rare earth (RE) complexes were synthesized and used as a chiral Lewis acid catalyst for the hetero-Diels–Alder reaction of carbonyl compounds with the Danishefsky's diene under homogeneous conditions. The Y[(*R*)-H_8-BNP]$_3$ (**3**-Y)-catalyzed reaction of aromatic aldehydes and the Yb[(*R*)-BNP]$_3$ (**1**-Yb)-catalyzed reaction of phenylglyoxylates afforded the corresponding cycloadducts with excellent optical purities (up to 99% ee) in high yields at room temperature. The successful recycling uses of the scandium catalyst (**3**-Sc) are also described.

The recent development of chiral rare earth metal complexes as Lewis acid catalysts is of significant interest in asymmetric synthesis.[1] While some of them are isolable and storable in air, no successful example of a reusable chiral rare earth complex as a homogeneous Lewis acid catalyst has been reported although a homogeneous catalyst is generally thought to be superior to the corresponding heterogeneous one in terms of efficiency and reproducibility of the reaction. We recently synthesized a series of rare earth metal (RE) complexes having (*R*)-1,1′-binaphthyl-2,2′-diyl phosphate (BNP) as a chiral ligand, RE[(*R*)-BNP]$_3$ (**1**-RE, Fig. 1),[2] and found that the Yb[(*R*)-BNP]$_3$ (**1**-Yb)-catalyzed hetero-Diels–Alder reaction of aldehydes **7** with the Danishefsky's diene **8** proceeded, in the presence of 2,6-lutidine, under homogeneous conditions in dichloromethane at room temperature to afford the corresponding cycloadducts **9** with high ee's (up to 94% ee) and high yields.[3–6] However, the presence of basic additives such as 2,6-lutidine made the reuse of the Lewis acid catalyst difficult. Actually, both the enantioselectivity and the chemical yield were significantly decreased in the reaction using the recovered catalyst. Therefore, we prepared two novel chiral rare earth phosphates, **2**-RE and **3**-RE, expecting that the 2,6-xylyl substituents on the binaphthyl ring of the former or the octahydrobinaphthyl ring[7] of the latter would play an important role not only in increasing the solubility of the catalysts in dichloromethane without 2,6-lutidine, but also in providing a more effective chiral space for the reaction than the catalyst **1**-RE. Also, these catalysts were expected to be easily recoverable after the reaction and could be successfully reused without decreasing the original activity.

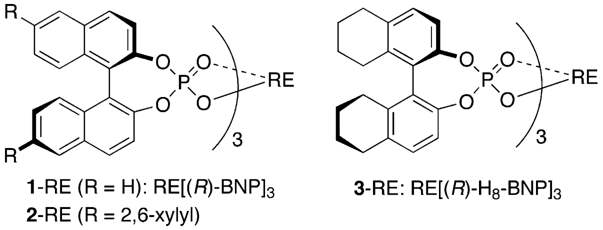

Figure 1. The chiral rare earth phosphates synthesized.

In this paper, we report the **3**-Y catalyzed highly enantioselective hetero-Diels–Alder reaction of aromatic aldehydes with the Danishefsky's diene and also the reaction of phenylglyoxylates catalyzed by **1**-Yb, both of which proceeded under homogeneous conditions at room temperature without any additives.

The chiral ligand precursor of **2**, (*R*)-6,6′-di(2,6-xylyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **6**, was

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Keywords: asymmetric hetero-Diels–Alder reaction; chiral rare earth metal phosphate; Lewis acid catalyst; reusable catalyst.

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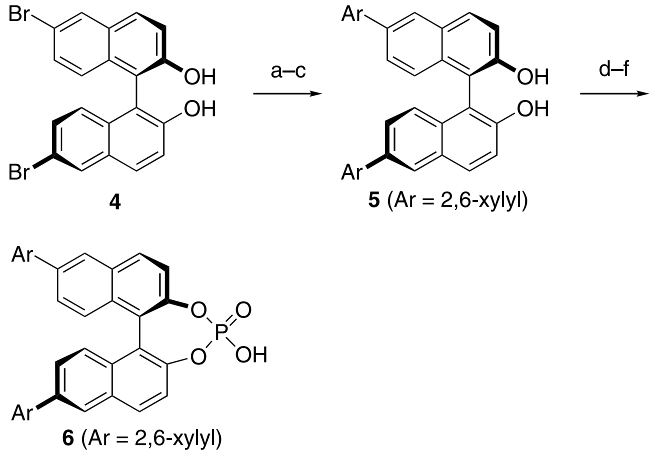
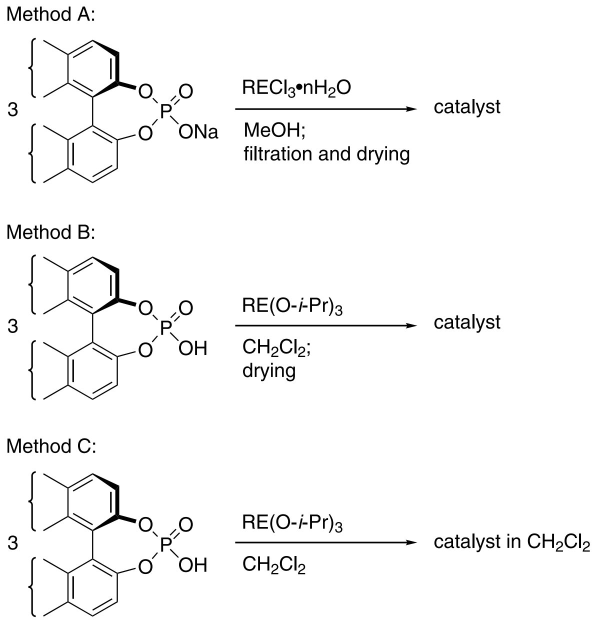


Scheme 1. Synthesis of the novel chiral phosphoric acid **6**. *Reagent and conditions:* (a) BnBr, NaH, THF–DMF, rt, 94%; (b) $ArB(OH)_2$, $Pd(PPh_3)_4$, $Ba(OH)_2$, DME–H_2O, 80°C, 99%; (c) H_2, Pd/C, *i*-Pr_2NEt, AcOEt, rt, 95%; (d) Cl_3PO, NEt_3, CH_2Cl_2, rt; (e) Na_2CO_3, H_2O, 80°C; (f) HCl(aq.), 95°C, 33% from **5** after recrystallization (ethanol).



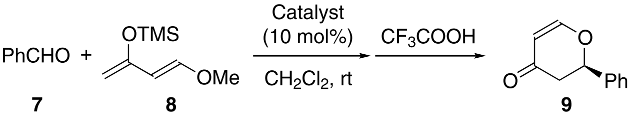
Scheme 2. The preparation methods of the catalysts.

synthesized from the commercially available (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol **4** in six steps (Scheme 1), and that of **3**, (*R*)-H_8-BNP–H, was similarly prepared via the phosphorylation of (*R*)-octahydro-1,1′-bi-2-naphthol.[8] The corresponding rare earth complexes **1**–**3** were prepared using three types of methods according to Scheme 2.[9,10]

As we expected, the asymmetric hetero-Diels–Alder reaction of benzaldehyde **7** with the Danishefsky's diene **8** catalyzed by complex **2** or **3** proceeded under homogeneous conditions in dichloromethane without any additives (Table 1). It is interesting to note that the catalyst **2**-Yb caused the opposite sense of enantioselection compared with the **1**-Yb catalyzed reaction thus affording **9** with an *S* configuration, although the two xylyl groups at the 6,6′-positions of the ligand of **2**-Yb appeared to be rather far from the catalytic center (entries 5 versus 3 or 4). On the other hand, the **3**-RE-catalyzed reactions afforded the cycloadduct **9** with an *R* configuration in excellent ee's (entries 6–16). The catalyst prepared in situ (Method C) showed almost the same activity and enantioselectivity as the once-isolated one (Method B) (entries 13 versus 12). The effect of the metal ions of the complex **3**-RE on the enantioselectivity was not high, but the heavy lanthanides tended to afford higher ee's than the lighter ones (entries 10–11 versus 15–16). The yttrium complex **3**-Y afforded the highest ee of 99% (entry 12).

Based on the fact that the complex **1**-Yb becomes soluble in dichloromethane with the addition of 1 equiv. of a Lewis base like 2,6-lutidine, we anticipated that the reaction of glyoxylates would be effectively catalyzed by **1**-Yb under homogeneous conditions because of the favorable coordination of the substrate to the catalyst as a bidentate ligand. As expected and shown in Table 2, **1**-Yb worked as a highly efficient homogeneous catalyst for the asymmetric reaction of phenylglyoxylates **10** with the diene **8** to give almost enantiopure cycloadducts **11** in excellent yields (entries 1 and 5). Thus, quaternary asymmetric carbon centers

Table 1. Asymmetric hetero-Diels–Alder reaction of **7** with **8** catalyzed by **1**–**3**



Entry	Catalyst	Method	Yield (%)[a]	Ee (%)[b]
1[c]	**1**-Sc	A	93	56
2[d]	**1**-Sc	A	94	81
3[c]	**1**-Yb	A	77	70
4[d]	**1**-Yb	A	94	89
5	**2**-Yb	A	76	*ent*-57
6	**3**-Sc	A	99	93
7[e]	**3**-Sc	A	99	94[f]
8	**3**-Sc	B	64	84
9	**3**-Yb	A	92	91
10	**3**-Yb	B	73	98
11	**3**-Er	B	76	98
12	**3**-Y	B	81	99
13	**3**-Y	C	80	98
14	**3**-Dy	B	58	91
15	**3**-Sm	B	79	93
16	**3**-La	B	68	92

The reaction proceeded under homogeneous conditions unless otherwise noted.

[a] Isolated yield.

[b] Determined by HPLC using Daicel CHIRALCEL OD except entry 7.

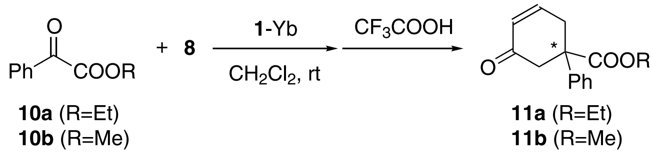
[c] The reaction proceeded under heterogeneous conditions.

[d] 2,6-Lutidine was used as an additive.

[e] 4-Methoxybenzaldehyde was used instead of **7**.

[f] Determined by HPLC using Daicel CHIRALPAK AD.

Table 2. Asymmetric hetero-Diels–Alder reaction of **10** with **8** catalyzed by **1**-Yb



Entry	Keto Ester	Catalyst (mol%)	Yield (%)[a]	Ee (%)[b]
1	**10a**	10	90	>99
2[c]	**10a**	10	80	91
3	**10a**	5	88	>99
4	**10a**	2	89	96
5	**10b**	10	99	98
6	**10b**	5	99	97

[a] Isolated yield.

[b] Determined by HPLC using chiral column (Daicel CHIRALPAK AD).

[c] The reaction was carried out in the presence of 2,6-lutidine.

were easily created.[11] The enantioselectivity rather decreased by the addition of 2,6-lutidine (entry 2), which indicates the simultaneous coordination of the two oxygen atoms of the keto esters to form the rigid transition structure is crucial for the realization of such high enantioselectivities.

Finally, the recycling use of the catalyst **3**-Sc was examined as shown in Figure 2. After the hetero-Diels–Alder reaction of **7** with **8** in dichloromethane, the solvent was evaporated. To the residue was added ether and the resulting precipitate was filtered by passing it through a Celite column and then eluting with THF. After evaporation of the THF, the residual complex was dried under vacuum at room temperature for 3 h. The recovered catalyst was used for the next round of reactions. Although the enantioselectivity gradually decreased, the high catalytic activity of **3**-Sc was retained even in the third round of reactions thus affording **9** with an 87% ee in 95% yield.

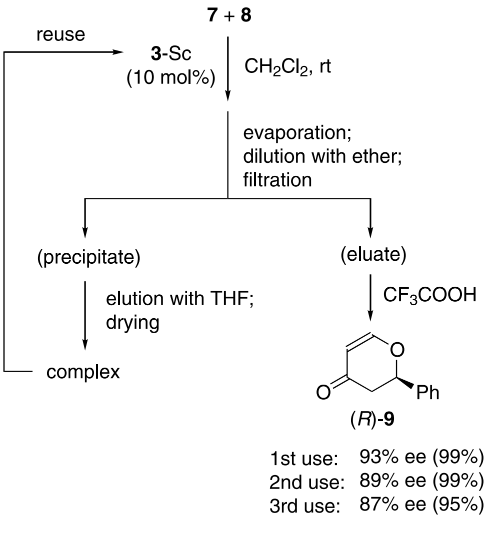


Figure 2. The recovery and the reuse of the catalyst **3**-Sc.

In conclusion, we succeeded in the development of novel chiral rare earth metal complexes that function as excellent homogeneous Lewis acid catalysts for the asymmetric hetero-Diels–Alder reactions. Further investigation into the development of reusable chiral homogeneous Lewis acid catalysts is now in progress.

Acknowledgements

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9. Isolated yields of the complexes: By method A: **1**-Sc, 92%; **1**-Yb, 96%; **2**-Yb, 94%; **3**-Sc, 83%; **3**-Yb, 80%. By method B: quantitative for all the complexes.
10. Selected analytical data of the complex: For **2**-Yb: IR(KBr) 3853, 3649, 3307, 1240, 1103 cm^{-1}. $[\alpha]_{D}^{23} = -147.7$ (*c* 1.00, CHCl$_3$). Anal. calcd for $C_{108}H_{84}O_{12}P_3Yb \cdot 5H_2O$: C, 67.22; H, 4.91. Found: C, 67.08; H, 4.71. For **3**-Sc: IR(KBr) 2931, 2854, 1471, 1448, 1437, 1423, 1252, 1225, 1111, 1057, 962, 889, 877, 833, 812 cm^{-1}. $[\alpha]_{D}^{22} = -246.8$ (*c* 1.02, EtOH). Anal. calcd for $C_{60}H_{60}O_{12}P_3Sc \cdot 4H_2O$: C, 60.91; H, 5.79. Found: C, 61.05; H, 5.45.
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