

Discovery of Exceptionally Efficient Catalysts for Solvent-Free Enantioselective Hetero-Diels–Alder Reaction

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Asymmetric catalysis of organic reactions to provide enantio-merically enriched products is of central importance to modern syn-thetic and pharmaceutical chemistry¹ as many currently accessible methods remain impractical in terms of the efficiency, environ-mental consideration, and other respects.² Therefore the need for truly efficient and practical asymmetric synthesis has been one of the greatest challenges for synthetic chemists. Here we describe the development of highly efficient enantioselective catalysts for hetero-Diels–Alder reaction by high-throughput screening of a combinatorial library of chiral titanium complexes. The reaction of Danishefsky's diene with a variety of aldehydes, a powerful approach for achieving dihydropyrone heterocycles with extensive synthetic application in natural or unnatural products,^{3,4} can be car-ried out with 0.1–0.005 mol % of **L5**/Ti/**L5** or **L5**/Ti/**L6** at room temperature under solvent- and MS-free conditions to afford dihy-dropyrone derivatives with up to quantitative yield and 99.8% ee.

To achieve efficient catalyst for asymmetric reaction, tuning the catalyst to make the perfect match among chiral ligand, metallic ion, additive, substrate and so on is a key point. High-throughput screening is essential for tuning a variety of modifications in lead optimizations and has been found to be an effective technique for finding the most efficient catalysts for asymmetric reactions as well.⁵ Therefore, the generation of a combinatorial library of chiral metal-lic complexes and the expression of the set of constituents of the library in the target model reaction should be a potentially powerful approach to finding the highly efficient enantioselective catalysts.

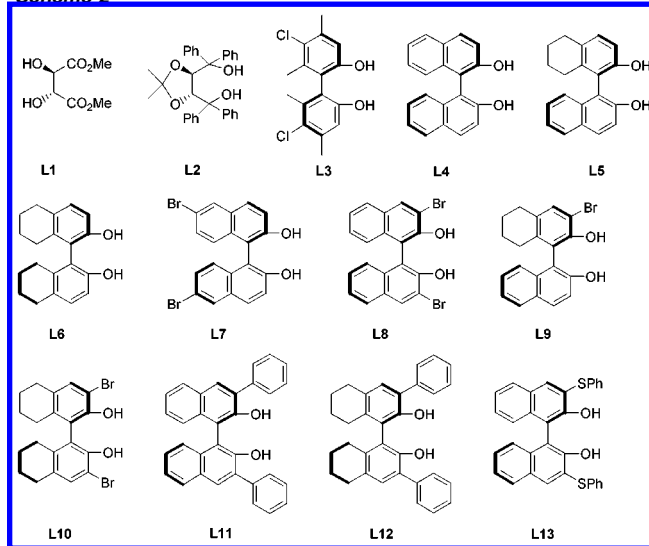
A combinatorial library of chiral metallic complexes was generated by combining a diol ligand (**Lm**) with Ti(OⁱPr)₄ and an alternative diol ligand (**Ln**) in parallel style as shown in Scheme 1. Every member of the **Lm**/Ti/**Ln** library is actually a mixture of titanium complexes because of ligand diversity and the aggregation feature of titanium complexes.^{6,7} These molecular assemblies form spontaneously,⁸ and the composition of the mixtures depends on thermodynamic factors. Therefore, the in situ selection of a highly reactive (and selective) metallic complex from a variety of thermodynamically dictated assemblies by substrate will lead to the highly enantioselective asymmetric catalysis.⁹

The diol ligands (Scheme 2) employed for catalyst preparation include commercially available or easily prepared tartaric acid deriva-tives (**L1**, **L2**), BINOL (**L4**), 6,6'-Br₂-BINOL (**L7**), and others (**L3**, **L9**). Considering the backbone effect and steric hindrance around coordinating oxygen atoms, H₄-BINOL (**L5**), H₈-BINOL (**L6**), 3,3'-Br₂-BINOL (**L8**), 3,3'-Br₂-H₈-BINOL (**L10**), 3,3'-Ph₂-BINOL (**L11**), 3,3'-Ph₂-H₈-BINOL (**L12**), and 3,3'-(SPh)₂-H₈-BINOL (**L13**) were also examined. Therefore, a catalyst library containing 104 members could be generated from a library of 13 chiral ligands, which were then evaluated for the reaction of Danishefsky's diene with benz-aldehyde by using the high-throughput chiral HPLC technique.

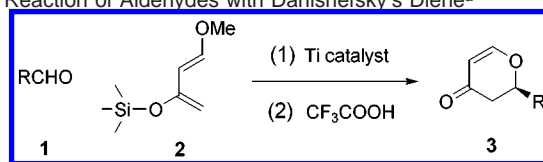
Scheme 1

L0	L1	L2	...	Ln	...	L13
L0	L0ML0	L0ML1	L0ML2			L0ML13
L1		L1ML1	L1ML2	...		L1ML13
L2			L2ML2	...		L2ML13
⋮						
Lm				LmMLn		⋮
⋮						
L13						L13ML13

Scheme 2



With the aim of screening the practical catalysts in mind, the catalyst loading was first set up at the 1 mol % level and the reaction was run in 0.1 mmol scale of substrate in diethyl ether at room temperature. The reaction was quenched with trifluoroacetic acid after 24 h. In the primary screening,¹⁰ **L4**, **L5**, **L6**, and **L7** modified catalysts were found to be outstanding in terms of both enantiose-lectivities (76.7–95.7% ee) and yields (63–100%). The steric hin-drance at the 3,3'-positions were proved to be disadvantageous for the reaction. With these leading results in hand, the catalyst loading of **Lm**/Ti/**Ln** (*m*, *n* = 4–7) was further decreased to the 0.1 mol % level. The reaction only gave a trace amount of product under the same experimental conditions. We then examined the solvent effect on the reaction in both catalyst preparation and the reaction process. It was found that the catalyst prepared in toluene is superior to that obtained in diethyl ether. *The most important point is that the reaction under solvent-free conditions gave quantitative yield and much higher enantioselectivity (up to 99%*

Table 1. Solvent-Free Asymmetric HDA Reaction of Aldehydes with Danishefsky's Diene^a

aldehyde	L5/Ti/L5				L5/Ti/L6			
	loading (%)	time (h)	yield (%) ^b	e.e. (%) ^c	loading (%)	time (h)	yield (%) ^b	e.e. (%) ^c
benzaldehyde	0.05	24	>99	99.3	0.05	24	82	99.4
<i>p</i> -anisylaldehyde	0.05	48	>99	90.8	0.05	48	>99	98.0
<i>m</i> -anisylaldehyde	0.05	48	81	96.6	0.05	48	82.6	99.8
<i>o</i> -anisylaldehyde	0.05	48	95	75.1	0.05	48	>99	95.1
3-phenylpropionaldehyde	0.05	96	>99	97.9	0.05	96	>99	98.3
<i>trans</i> -cinnamaldehyde	0.1	96	82	98.4	0.05	96	56.6	96.6
furfural	0.05	48	>99	99.2	0.05	48	>99	99.7
furfural	0.01	96	37	94.7	0.01	96	>99	97.7
furfural					0.005	144	63	96.2
<i>m</i> -tolyl aldehyde	0.1	48	95	98.5	0.05	48	92	99.5
α -naphthyl aldehyde	0.05	48	55	85.6	0.05	48	65	98.5
<i>p</i> -cyanobenzaldehyde	0.1	48	>99	92.9	0.05	48	98.4	97.9
<i>m</i> -bromobenzaldehyde	0.1	48	>99	97.4	0.05	48	98.3	97.6
<i>p</i> -bromobenzaldehyde	0.05	48	>99	98.0	0.05	48	>99	98.4
<i>p</i> -chlorobenzaldehyde	0.05	48	>99	91.2	0.05	48	>99	99.1
<i>p</i> -nitrobenzaldehyde	0.05	48	>99	97.3	0.05	24	>99	99.4

^a Reactions carried out at room temp (20 °C). ^b Isolated yields. ^c Enantiomeric excesses determined by HPLC on Chiralcel OD or Chiralpak AD column.

ee) of the product. For practical synthesis, solvent-free condition is the ideal process in terms of volumetric productivities and environmental safety.¹¹ However, asymmetric catalytic processes are usually highly sensitive to solvent and concentration of substrates. Our finding promoted us to further optimize the leading catalysts under solvent-free conditions by decreasing the catalyst loading to 0.05 mol %. Under the experimental conditions, **L5/Ti/L5** and **L5/Ti/L6** were found to be the best catalysts. The reactions proceeded efficiently at room temperature to give the product in 99% and 82% yields, respectively, with up to 99% ee.

The reactions promoted by the optimized catalysts (**L5/Ti/L5** and **L5/Ti/L6**) were then carried out in gram scale at the catalyst loading of 0.1–0.005 mol %. It was found that both **L5/Ti/L5** and **L5/Ti/L6** were highly efficient for the reactions of a variety of aldehydes, including aromatic, olefinic, and aliphatic derivatives (Table 1). Particularly, in the cycloaddition of furfural to Danishefsky's diene, 0.005 mol % of **L5/Ti/L6** could promote the reaction smoothly to give the corresponding cycloadduct in 63% yield with 96.3% ee. To the best of our knowledge, this is the lowest catalyst loading in Lewis acid-catalyzed asymmetric reactions.¹²

In conclusion, combinatorial coordination chemistry strategy combined with high-throughput screening techniques has been successfully applied to engineering practical enantioselective catalysts for asymmetric hetero-Diels–Alder reaction. The present catalytic system provides an attractive protocol to various optically active dihydropyrones in terms of the following features: (i) the chemicals are all inexpensive and easily available; (ii) the protocol has a broad scope of substrates; (iii) the reaction shows enhanced enantioselectivity when the amount of catalyst is reduced; (iv) the reaction is environmentally benign and energy-saving because of solvent-free and room-temperature reaction conditions; and (v) exceptionally low catalyst loading (0.1–0.005 mol %) is sufficient to achieve high yield and optical purity of the products. We hope our findings in this research will stimulate further work on practical asymmetric catalysis to achieve more efficient chemical reactions for modern synthetic chemistry. Further insight into the mechanism and application of the combinatorial catalyst libraries to other solvent-free asymmetric reactions is currently under investigation.

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Supporting Information Available: Experimental details and the results of high-throughput evaluation of the catalyst library (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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