Dramatically Synergetic Effect of Carboxylic Acid Additive on Tridentate Titanium Catalyzed Enantioselective Hetero-Diels–Alder Reaction: Additive Acceleration and Nonlinear Effect

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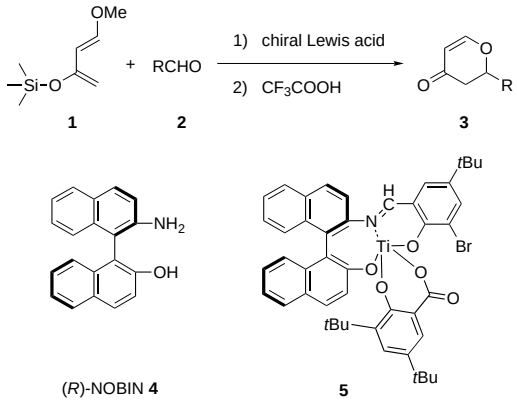
Abstract: This paper describes the successful development of a group of highly efficient chiral tridentate titanium catalysts for hetero-Diels–Alder reaction of Danishefsky's diene and a variety of aldehydes through ligand and additive diversity. Dramatically synergetic effect of carboxylic acid additives and influence of substituent in chiral Schiff base ligands on the enantioselectivities of the reaction are reported. It was found that a chiral drug Naproxen (**A21**) was a highly efficient additive for Ti-catalyzed HDA reaction, affording 2-substituted 2,3-dihydro-4*H*-pyran-4-one in up to 97% *ee* and >99% yields. Quantitative study of the effect of chiral carboxylic acid **A21** revealed that the reaction could be accelerated by one order of magnitude. Another interesting feature of present catalytic system is the existence of significant positive nonlinear effect, which indicates that the heterochiral Schiff base-titanium complexes may have higher stability than their homochiral counterparts. As a result, the homochiral Schiff base–titanium complexes with higher *ee* than that of starting ligand will react with carboxylic acid additive to form the more active species and predominate the catalytic process. The isolation and characterization of stable heterochiral $((\pm)\text{-}\mathbf{L1})_2$Ti complex has also been successful, which strongly supported the explanation for positive nonlinear effect observed in the catalytic system.

Keywords: asymmetric catalysis · Diels–Alder reaction · nonlinear effect · titanates · tridentate ligands

Introduction

Asymmetric catalysis of organic reactions that provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry.[1] Enantioselective hetero-Diels–Alder (HDA) reaction of carbonyl compounds with 1,3-dienes constitutes one of the most important asymmetric C–C bond forming reactions in organic synthesis.[2, 3] The reaction between 1-methoxy-3-(trimethylsilyloxyl)buta-1,3-diene (Danishefsky's diene) (**1**) and aldehydes **2** provides a powerful access to 2-substituted 2,3-dihydro-4*H*-pyran-4-one (**3**), a type of heterocycles with extensive applications for natural or unnatural product synthesis. Various chiral Lewis acids, such as aluminum, boron, transition and lanthanide metal complexes, have been employed for this type of reaction.[4–11]



Recently, 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN, **4**), a non-*C*2 symmetric chiral scaffold, and its derivatives have received extensive interests in asymmetric catalysis.[12] Particularly, chiral Ti^{IV} Lewis acid (**5**) modified by NOBIN-derived tridentate Schiff base ligand and 3,5-di-*tert*-butylsalicylic acid showed excellent asymmetric induction in aldol type reactions.[12a–c] As the extension of our previous work on the HDA reaction,[6d] in the present paper we report our new results on

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Supporting information (experimental details for the evaluation of catalyst library and full data of characterization of the dihydropyrone products) for this article is available on the WWW under http://www.chemeurj.org or from the author.

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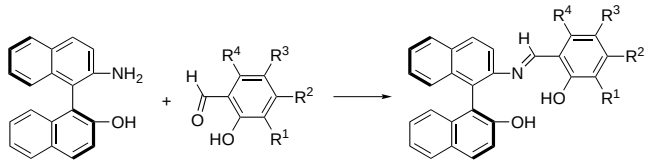
the first development of highly efficient tridentate Ti^{IV} catalysts derived from NOBIN scaffold for enantioselective HDA reaction of Danishefsky's diene with aldehydes through ligand and additive diversity-based approach. The effect of carboxylic acid additive on the efficiency and enantioselectivity of the reaction is also reported. On the basis of observed nonlinear effect and the racemic titanium complex [((±)-**L1**)$_2$Ti] isolated in the present catalytic system, a possible working model for asymmetric induction process is also discussed.

Results and Discussion

Preparation of the NOBIN-derived schiff base ligand library: The NOBIN-derived Schiff base ligands (*S*)-**L1**–(*S*)-**L22** were prepared by simple condensation of (*S*)-2-amino-2′-hydroxy-1,1′-binaphthyl [(*S*)-**4**] with the corresponding salicylaldehydes by parallel solution-phase synthesis in 58–99% yields. Enantiomerically pure NOBIN could be easily obtained by optical resolution of racemic **4** through molecular complexation with *N*-benzylcinchonidium chloride,[13a] where racemic NOBIN was prepared by effcient cross-coupling of 2-naphthol and 2-naphthylamine with $FeCl_3$ in water.[13b] The 22 Schiff base ligands shown in Scheme 1 were all characterized by ^{1}H NMR, MS, IR and elemental analysis.



(*S*)-NOBIN **4** **5** (*S*)-**L1**-(*S*)-**L22**

(*S*)-**L1**: $R^1 = R^2 = R^3 = R^4 = H$
(*S*)-**L2**: $R^1 = R^3 = Cl$, $R^2 = R^4 = H$
(*S*)-**L3**: $R^1 = R^3 = Br$, $R^2 = R^4 = H$
(*S*)-**L4**: $R^1 = R^3 = I$, $R^2 = R^4 = H$
(*S*)-**L5**: $R^3 = F$, $R^1 = R^2 = R^4 = H$
(*S*)-**L6**: $R^3 = Cl$, $R^1 = R^2 = R^4 = H$
(*S*)-**L7**: $R^3 = Br$, $R^1 = R^2 = R^4 = H$
(*S*)-**L8**: $R^3 = I$, $R^1 = R^2 = R^4 = H$
(*S*)-**L9**: $R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$
(*S*)-**L10**: $R^2 = OCH_3$, $R^1 = R^3 = R^4 = H$
(*S*)-**L11**: $R^3 = OCH_3$, $R^1 = R^2 = R^4 = H$
(*S*)-**L12**: $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
(*S*)-**L13**: $R^3 = CH_3$, $R^1 = R^2 = R^4 = H$
(*S*)-**L14**: $R^1 = t$Bu, $R^2 = R^3 = R^4 = H$
(*S*)-**L15**: $R^3 = t$Bu, $R^1 = R^2 = R^4 = H$
(*S*)-**L16**: $R^1 = R^3 = t$Bu, $R^2 = R^4 = H$
(*S*)-**L17**: $R^1 = t$Bu, $R^3 = CH_3$, $R^2 = R^4 = H$
(*S*)-**L18**: $R^1 = Br$, $R^3 = CH_3$, $R^2 = R^4 = H$
(*S*)-**L19**: $R^1 = Br$, $R^3 = OCH_3$, $R^2 = R^4 = H$
(*S*)-**L20**: $R^1 = Br$, $R^3 = t$Bu, $R^2 = R^4 = H$
(*S*)-**L21**: $R^1 = OCH_3$, $R^3 = Br$, $R^2 = R^4 = H$
(*S*)-**L22**: R^3 - R^4 = -$(CH)_4$-, $R^1 = R^2 = H$

Scheme 1. Preparation of a library of chiral Schiff base ligands.

Molecular structures of (*R*)-L1, (*R*)-L7 and (*R*)-L12: In order to understand the possible coordination pattern of chiral ligands in their metallic complexes, molecular structures of three kinds of Schiff base ligands (*R*)-**L1**, (*R*)-**L7** and (*R*)-**L12** were determined by X-ray crystallographic analysis. As shown in Figure 1, two binaphthyl rings adopt a nearly perpendicular arrangement and their dihedral angles range from 75.61 to 102.60° with different substituents situated at salicylidene moiety (Table 1). The imino naphthyl ring and salicylidene phenyl ring are almost coplanar in the cases of (*R*)-**L7**, where the dihedral angle is 1.86°. The imino naphthyl ring and

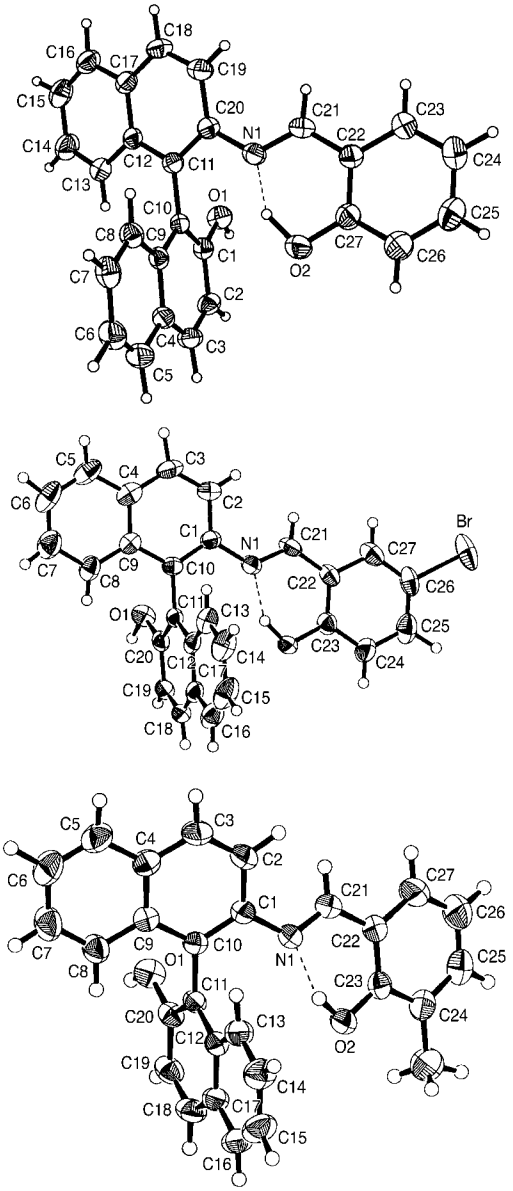


Figure 1. The X-ray structures of (*R*)-**L1** (top), (*R*)-**L7** (middle) and (*R*)-**L12** (bottom).

Table 1. Comparison of dihedral angles in Schiff base ligands (*R*)-**L1**, (*R*)-**L7** and (*R*)-**L12**.

Ligand	Dihedral angle between plane I[a] and II[b] [°]	Dihedral angle between plane I and III[c] [°]
(*R*)-**L1**	75.61	23.51
(*R*)-**L7**	96.61	1.86
(*R*)-**L12**	102.60	22.78

[a] Plane I: imino naphthyl ring. [b] Plane II: hydroxy naphthyl ring. [c] Plane III: salicylidene phenyl ring.

salicylidene phenyl ring in (*R*)-**L1** and (*R*)-**L12** take a slightly twist arrangement with dihedral angles of 23.51 and 22.78°, respectively. The short distances of N1–H(O2) (1.47–1.75 Å) suggested that the imino nitrogen atom forms strong intramolecular hydrogen bond with hydroxy group of salicylidene moiety rather than that of naphthyl unit.

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Asymmetric catalysis of HDA reaction of Danishefsky's diene (1) and benzaldehyde (2a) with (*S*)-L1/Ti complex: We started this work by focusing our effort on the investigation of the influence of titanium complex of Schiff base ligand (*S*)-**L1** on the asymmetric induction for HDA reaction of Danishefsky's diene and benzaldehyde. It was observed that Danishefsky's diene **1** slowly underwent cycloaddition with freshly distilled benzaldehyde (**2a**) at room temperature in the presence of 10 mol% of Schiff base-Ti^{IV} complex prepared by in situ reaction of (*S*)-**L1** and $Ti(OiPr)_4$. However, the product, 2-phenyl-2,3-dihydro-4*H*-pyran-4-one (**3a**), was found to be nearly racemic with 46% yield (Table 2, entry 1).

Table 2. Effect of additives on chiral Schiff base-Ti^{IV} catalyzed asymmetric HDA reaction of Danishefsky's diene with benzaldehyde.[a]

1 + PhCHO **2a** → 1) (*S*)-**L1**-Ti /additives 2) CF_3COOH → (*S*)-**3a**

	4 Å MS	Solvent	Benzoic acid [%]	Yield [%][b]	*ee* [%][c]
1	0	toluene	0	46	1.0
2	+	toluene	0	34	13
3	0	toluene	0[d]	75	68
4	+	toluene	5	80	85
5	+	toluene	10	69	78
6	+	dichloromethane	5	trace	–
7	+	diethyl ether	5	44	40

[a] All of the reactions were carried out with ligand/$Ti(OiPr)_4$/substrate = 0.2:0.1:1 at room temperature. [b] Isolated yields for two steps. [c] The enantiomeric excesses were determined by HPLC on Chiralcel OD column. [d] Aged benzaldehyde was used.

The addition of activated 4 Å molecular sieves (MS) to the reaction system slightly enhanced the enantioselectivity (entry 2). Interestingly, the reaction of aged benzaldehyde under the same conditions afforded (*S*)-**3a** in 68% *ee* and 75% yield. GC analysis of the aged benzaldehyde showed that 4.8% of benzoic acid was present due to its auto-oxidation under air. The reaction was therefore carried out with freshly distilled benzaldehyde in the presence of 5 mol% of benzoic acid (**A1**) and 4 Å MS. The enantioselectivity of the reaction could be dramatically increased to 85% (entry 4). Upon further increase of the loading of **A1** to 10 mol%, the enantioselectivity and yield of the reaction dropped to some extent (entry 5). The solvent effect was found to be evident in the present catalytic system. Only trace amount of product was obtained when the reaction was carried in dichloromethane (entry 6) and the reaction in diethyl ether showed much lower enantioselectivity (40% *ee*) and overall reactivity (44% yield) than those in toluene (entry 4 vs 7). Therefore, in the following screening of chiral ligands and carboxylic acid additives, the reaction was carried out in toluene with a molar ratio of ligand/$Ti(OiPr)_4$/additive/substrate 0.2:0.1:0.05:1 as the standard conditions.

Substituent effect of Schiff base ligands on the enantioselectivity of the reaction—Screening of highly efficient chiral ligands: A key issue to obtain an efficient catalyst for asymmetric reactions is the tuning of the catalyst to make the perfect match between chiral ligand, metallic ion, additive, substrate. The combinatorial approach has been found to be highly efficient for tuning a variety of modifications in lead optimization and also for determining the most efficient catalysts for asymmetric reactions.[14] With the lead results mentioned above, we turned our efforts to improve the enantioselectivity of the reaction through ligand diversity by altering the substituents attached to salicylidene moiety. Accordingly, a library of 22 different NOBIN-derived Schiff bases (Scheme 1) was rapidly screened in the presence of benzoic acid and 4 Å MS. As shown in Figure 2, Schiff bases

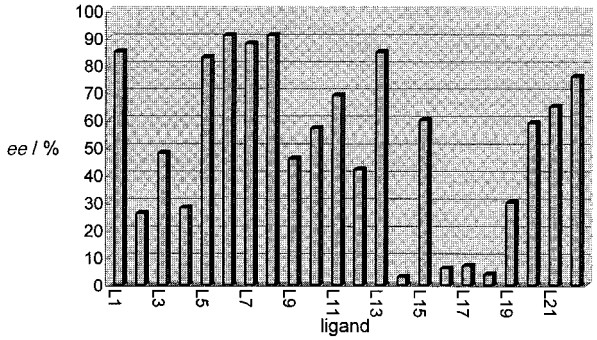

Figure 2. Ligand optimization by variation of substituent(s) in NOBIN-derived Schiff bases.

(*S*)-**L1**, (*S*)-**L5**-(*S*)-**L8** and (*S*)-**L13** in which the *ortho*-position of phenol is without any substituents, were found to be more effective in the Ti-catalyzed HDA reaction, whereby 85.0–90.7% *ee* could be achieved. This result is obviously different from that observed in Schiff base/titanium complex catalyzed aldol-type reactions,[12a–c] in which the steric hindrance at the *ortho*-position of phenol of Schiff base ligand is critical to obtain high levels of enantioselectivity.

The effect of various carboxylic acid additives on the enantioselectivity of the reaction—Screening of highly efficient acid additive: Encouraged by the dramatically synergetic effect of benzoic acid additive on the enantioselectivity of the reaction mentioned above, we then tried to further improve the enantioselectivity of the reaction through carboxylic acid diversity. Accordingly, 36 carboxylic acids (**A1**–**A36**, Scheme 2), including aromatic, aliphatic, salicylic, amino acids, were used to obtain asymmetric induction in the (*S*)-**L1**/Ti-catalyzed HDA reaction. As shown in Figure 3, achiral carboxylic acids could improve the enantioselectivity of the titanium catalysts in many cases. Interestingly, one chiral carboxylic acid, (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid (Naproxen, **A21**), was found to be particularly effective in the reaction with a quantitative yield and 97% *ee* of the product. A catalyst prepared by combining (*R*)-**L1**, $Ti(OiPr)_4$ and **A21** showed much lower enantioselectivity (*R*, 76% *ee*) for the reaction; this indicates a mismatch between the chiralities of ligand and additive. Moreover, the addition of salicylic acids (e.g. **A26**, **A29**) to the (*S*)-**L1**/Ti catalyst system gave the product in low to moderate enantioselectivities. It can be assumed that the carboxylic acid additive was involved in the coordination sphere of titanium catalyst, although the

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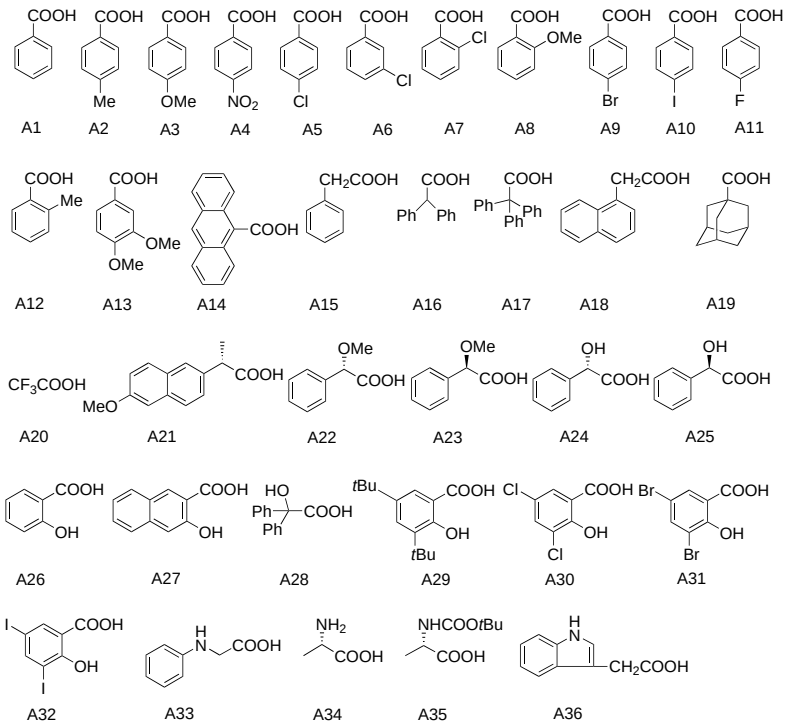


Scheme 2. Carboxylic acid additives employed for the modification of chiral titanium catalyst.

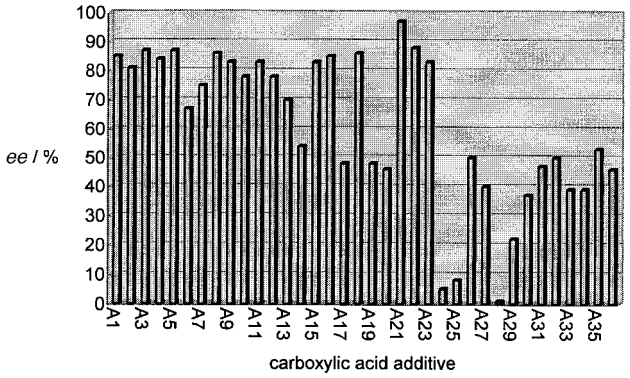
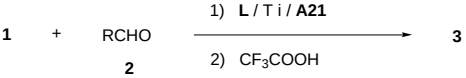


Figure 3. Effect of various carboxylic acid additives on the enantioselectivity of the reaction.

effect of salicylic acids in the present catalytic system was significantly different from that observed in aldol-type reaction.[12a–c] In our previous work on H_4-BINOL- and H_8-BINOL-Ti complexes catalyzed HDA reaction, solvent-free conditions were found to be critical to carry out the reaction at a lower catalyst loading.[6d] Therefore, 1 mol% of (*S*)-**L1**/Ti combined with 0.5 mol% of **A21** was used in the reaction in the absence of solvent. Unfortunately the *ee* value (54%) of the product dropped significantly even though the yield of product was as high as 96%, which again demonstrates the importance of the solvent effect on the reaction.

Screening of highly efficient chiral catalysts for the reaction: Two-stage screenings of chiral ligands and carboxylic acid additives led us to understand the importance of less steric hindrance in Schiff base ligands and chiral carboxylic acid additives. To combine the advantages of these two aspects, the catalysts prepared by combination of the superior Schiff base ligands (*S*)-**L1**, (*S*)-**L5**-(*S*)-**L8** or (*S*)-**L13** with Ti(O*i*Pr)$_4$ and the best additive **A21** in the presence of 4 Å MS were finally evaluated for the reaction at room temperature. We were pleased to find that the catalysts derived from (*S*)-**L1** and (*S*)-**L5**-(*S*)-**L8** showed excellent activity and enantioselectivity for the reaction of Danishefsky's diene and benzaldehyde, affording the product in quantitative yields and 93.5–97% *ee*. With these catalysts at hand, the adaptability between catalysts and substrates were then screened in parallel manner, because there is not one catalyst that is universal for all substrates. As shown in Table 3, the optimized catalysts were applicable for the

Table 3. Parallel screening of matched substrate/catalyst pairs for Schiff base-Ti^{IV} catalyzed HDA reaction of Danishefsky's diene with aldehydes.[a]



	R	Yield/%[b] (*ee*/%)[c]				
		L1/Ti/A21	**L5/Ti/A21**	**L6/Ti/A21**	**L7/Ti/A21**	**L8/Ti/A21**
1	phenyl (a)	>99 (97.0)	>99 (93.5)	>99 (95.8)	>99 (95.9)	>99 (96.3)
2	4-chlorophenyl (b)	>99 (96.7)	>99 (85.2)	94 (93.6)	>99 (93.5)	>99 (93.3)
3	4-bromophenyl (c)	98 (95.2)	81 (77.6)	>99 (93.4)	>99 (95.5)	97 (94.9)
4	4-nitrophenyl (d)	91 (83.3)	85 (82.8)	91 (87.8)	93 (89.7)	91 (86.1)
5	3-bromophenyl (e)	83 (85.7)	95 (92.3)	90 (91.6)	51 (69.3)	77 (91.7)
6	3-methylphenyl (f)	81 (95.5)	94 (94.5)	91 (95.7)	87 (96.0)	78 (90.8)
7	3-methoxyphenyl (g)	96 (92.1)	94 (93.2)	>99 (91.4)	97 (91.6)	96 (91.4)
8	2-methoxyphenyl (h)	>99 (81.5)	>99 (80.7)	>99 (81.9)	>99 (55.3)	85 (57.1)
9	2-furyl (i)	90 (74.9)	98 (71.3)	59 (63.7)	51 (45)	>99 (87.6)
10	*trans*-cinnamyl (j)	96 (83.4)	>99 (91.8)	94 (86.3)	93 (91.3)	>99 (93.4)
11	phenylethyl (k)	83 (75)	81 (76.2)	81(61.6)	57 (42.7)	50 (61.2)

[a] All of the reactions were carried out with Ligand/Ti(O*i*Pr)$_4$/**A21**/substrate = 0.2:0.1:0.05:1 in toluene in the presence of 4 Å MS at room temperature. [b] Isolated yields for two steps. [c] The enantiomeric excesses were determined by HPLC on Chiralcel OD or AD column.

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promotion of HDA reaction of **1** with a variety of aldehydes **2a–k**, including aromatic, olefinic and aliphatic derivatives, to give corresponding 2-substituted 2,3-dihydro-4*H*-pyran-4-ones **3a–k** in high yields and enantioselectivities.

Development of exceptionally efficient catalysts for HDA reaction: Although the selectivities of 97% have been achieved in the HDA reaction of aldehydes with Danishefsky's diene using tridentated titanium complexes combined with a chiral carboxylic acid, a major drawback of the catalytic system has been its high catalyst loading (10 mol%). The development of extraordinarily active and enantioselective catalysts for HDA reaction is particularly important in terms of practical reasons. It was found that titanium complexes of 5,6,7,8-trtrahydro-1,1′-bi-2-naphthol (H_4-BINOL) and 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (H_8-BINOL) were exceptionally efficient for the same reaction, especially under solvent-free conditions, to afford dihydropyrone derivatives **3** with up to quantitative yield and 99.8% *ee*.[6d] As shown in Table 4, these two catalyst systems are applicable for various aldehydes, including aromatic, olefinic, and aliphatic derivatives. Particularly, in the cycloaddition of furfural to Danishefsky's diene, 0.005 mol% of H_4-BINOL/Ti/H_8-BINOL could promote the reaction smoothly to give the corresponding cycloadduct in 63% yield with 96.3% *ee*. To the best out our knowledge, this is the lowest catalyst loading in Lewis acid catalyzed asymmetric reactions.[15] Therefore, the present catalytic system provides an attractive protocol to various optically active dihydropyrones in terms of following features: i) all chemicals are 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; v) exceptionally low catalyst loading (0.1–0.005 mol%) is sufficient to achieve high yields and optical purities of the products.

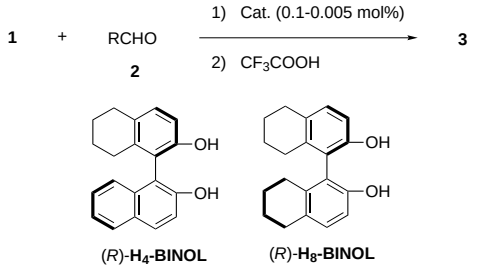
Quantitative effect of A21 on the reaction rate and nonlinear effect in the catalytic system: Although the detailed mechanism for titanium catalyzed HDA reaction of aldehydes with Danishefsky's diene remains unknown, the influence of carboxylic acid additives on the reaction by the catalysis of tridentated titanium complexes provided a convenient probe for understanding the activation effect in the catalysis. Therefore, the quantitative effect of **A21** on the reaction rate was investigated by rapid-quench of the reaction and HPLC analysis of yields with biphenyl as an internal standard. The reactions were carried out at 25 °C for 30 min in the absence of **A21** or in the presence of 5 mol% of **A21** and then quenched with trifluoroacetic acid (see Table 5). It was found that 4 Å

Table 5. Quantitative effect of Naproxen on the yield of the reaction between **1** and **2a**.

Catalyst system	(*S*)-**L1**/Ti	(*S*)-**L1**/Ti+4 Å MS	(*S*)-**L1**/Ti/**A21**+4 Å MS
Yield [%]	2.6	2.0	24.0[a]

[a] With 96% *ee* in *S* configuration.

Table 4. Solvent-free asymmetric HDA reaction of aldehydes with Danishefsky's diene.[a]



(*R*)-H_4-BINOL (*R*)-H_8-BINOL

Aldehyde	(*R*)-H_4-BINOL/Ti/(*R*)-H_4-BINOL				(*R*)-H_4-BINOL/Ti/(*R*)-H_8-BINOL			
	Loading [%]	*t* [h]	Yield [%][b]	*ee* [%][c]	Loading [%]	*t* [h]	Yield [%][b]	*ee* [%][c]
benzaldehyde (a)	0.05	24	>99	99.3	0.05	24	82	99.4
4-chlorobenzaldehyde (b)	0.05	48	>99	91.2	0.05	48	>99	99.1
4-bromobenzaldehyde (c)	0.05	48	>99	98.0	0.05	48	>99	98.4
4-nitrobenzaldehyde (d)	0.05	48	>99	97.3	0.05	24	>99	99.4
3-bromobenzaldehyde (e)	0.1	48	>99	97.4	0.05	48	98.3	97.6
3-tolylaldehyde (f)	0.1	48	95	98.5	0.05	48	92	99.5
3-anisylaldehyde (g)	0.05	48	81	96.6	0.05	48	82.6	99.8
2-anisylaldehyde (h)	0.05	48	95	75.1	0.05	48	>99	95.1
furfural (i)	0.05	48	>99	99.2	0.05	48	>99	99.7
furfural (i)	0.01	96	37	94.7	0.01	96	>99	97.7
furfural (i)					0.005	144	63	96.2
trans-cinnamaldehyde (j)	0.1	96	82	98.4	0.05	96	56.6	96.6
3-phenylpropionaldehyde (k)	0.05	96	>99	97.9	0.05	96	>99	98.3
4-anisylaldehyde (l)	0.05	48	>99	90.8	0.05	48	>99	98.0
1-naphthylaldehyde (m)	0.05	48	55	85.6	0.05	48	65	98.5
4-cyanobenzaldehyde (n)	0.1	48	>99	92.9	0.05	48	98.4	97.9

[a] All of the reactions were carried out at room temperature (20 °C). [b] Isolated yields. [c] Enantiomeric excesses of products were determined by HPLC on Chiralcel OD or Chiralpak AD column.

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MS scarcely influenced the catalyst reactivity (2.0–2.6% yield) and the chiral acid additive **A21** significantly enhanced the reaction rate by one order of magnitude (2.0–2.6% vs 24% yield). It was again confirmed that the carboxylic acid additive has been involved in the catalytic process and accelerated the formation of product in high enantioselectivity.[16]

After considering the dramatically synergetic effect of chiral acid on the enantioselectivity and reactivity of hetero-Diels–Alder reaction, titanium complex of racemic **L1** (10 mol%) was employed for asymmetric catalysis in the presence of 5 mol% of **A21**. It is interesting to find that 55% *ee* (*S*) of product **3a** can be obtained in 70% yield. This result clearly demonstrates that **A21** is able to activate selectively the (*S*)-enantiomer of racemic **L1**/Ti complex and therefore able to catalyze the reaction enantioselectively.[16]

The search for nonlinear effects (NLE) in a given system has become a useful probe for analyzing the nature of the catalytic species or the nonreacting species involved in an asymmetric synthesis.[17] In order to further understand the role of acid additive in the catalytic process, partially resolved (*S*)-**L1** with different *ee* values was employed for asymmetric induction in the presence of **A21**. As shown in Figure 4, 93%

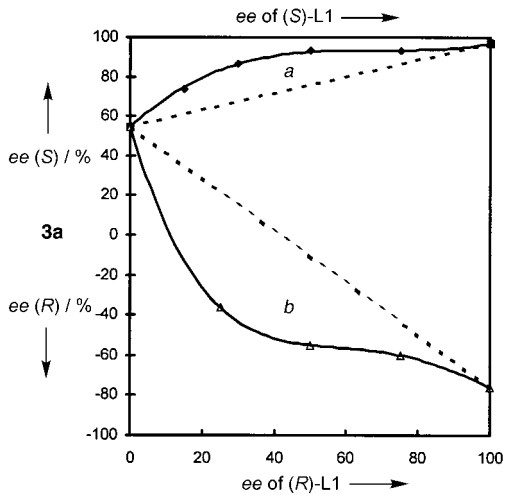

Figure 4. Enantioselectivity for the reaction of **1** with **2a** catalyzed by the titanium complexes of partially resolved (*S*)-**L1** (a) and (*R*)-**L1** (b) in the presence of **A21**. The broken lines indicate the expected values when the reactivity difference between (*S*)-**L1**/Ti/**A21** and (*R*)-**L1**/Ti/**A21** was not considered.

ee of product (*S*) can be obtained by using 50% *ee* of (*S*)-**L1**, which is much higher than that expected (curve a). Moreover, when partially resolved (*R*)-**L1** was utilized in the reaction, the configuration of product was switched to *R* (curve b). The *ee* of product was found to be higher than that expected as well, even though its asymmetric induction level is not as high as that achieved by the catalysis of (*S*)-**L1**/Ti/**A21**. It is obvious that a significant positive nonlinear effect is present in this catalytic system. Even in the presence of achiral carboxylic acid **A1**, the positive nonlinear effect was evident (Figure 5). An enantiomeric excess of 82% for the product (*S*) could be obtained by using the (*S*)-**L1** with only 45% *ee*, which is close to the asymmetric induction level using enantiopure (*S*)-**L1**.

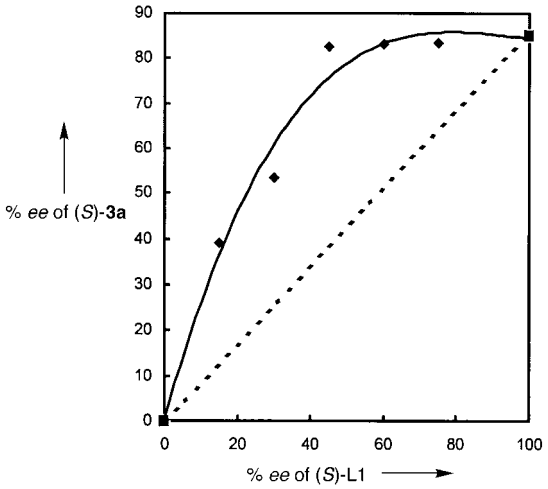

Figure 5. Enantioselectivity for the reaction of **1** with **2a** catalyzed by the titanium complexes of partially resolved (*S*)-**L1** in the presence of benzoic acid (**A1**). The broken lines indicate the expected values when the reactivity difference between (*S*)-**L1**/Ti/**A1** and (*R*)-**L1**/Ti/**A1** was not considered.

On the basis of these facts, it can be assumed that when a partially resolved ligand was used, the higher content of stable and less reactive heterochiral Schiff base/titanium complex may be involved in the catalytic system. In fact, it was possible to successfully isolate the titanium complex of (±)-**L1**. Elemental analysis, ^{1}H NMR, IR and MS spectra of the complex show that ((±)-**L1**)$_2$Ti complex ((±)-**6**) has been formed, which is highly stable under air although its crystal structure is not clear. As a result, the remaining homochiral Schiff base–titanium complex ((*S*)-**7**) with a higher *ee* than that of starting ligand will react with carboxylic acid additive to form the active species and operate the catalytic process.[17a, b]

Mechanistic considerations: Two possible mechanisms for the enantioselective addition of Danishefsky's diene to aldehydes have been reported: Mukaiyama aldol condensation versus a concerted [4+2] cycloaddition.[18] In our reaction systems, ^{1}H NMR spectral determination of crude reaction product before CF_3COOH treatment revealed that [4+2] cycloadduct was formed *exclusively*, which supports a concerted cycloaddition mechanism. Although the reaction mechanism for the catalysis of H_4-BINOL/Ti/H_4-BINOL and H_4-BINOL/Ti/H_8-BINOL remains unclear,[6d] the possible asymmetric induction pathway for the tridentate titanium catalyst system can be illustrated by using the working model depicted in Figure 6 on the basis of molecular structures and coordination constraints of the Schiff base ligands, the sense of asymmetric induction observed in the products, as well as the positive nonlinear effect in the catalytic system. It can be assumed that the catalytically active species should be a monomeric titanium complex. Imino nitrogen atom and two phenoxy oxygen atoms of (*S*)-**L1** coordinate in *cis* form on Ti^{IV} atom, respectively.[19] Naphtholate oxygen atom situated at the axial position and the carboxylate occupy the opposite axial site. As a result, the aldehyde will bind in the remaining equatorial coordination site of Ti^{IV} atom and the R group of aldehyde

0947-6539/02/0821-5038 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 21

adopts down arrangement (Figure 6a) to prevent the repulsion between R group and naphthyl ring caused by the spatial arrangement depicted in Figure 6b. The bound aldehyde can accept the Danishefsky's diene from the *Si* face (Figure 6a) to give the product in (*S*)-configuration.

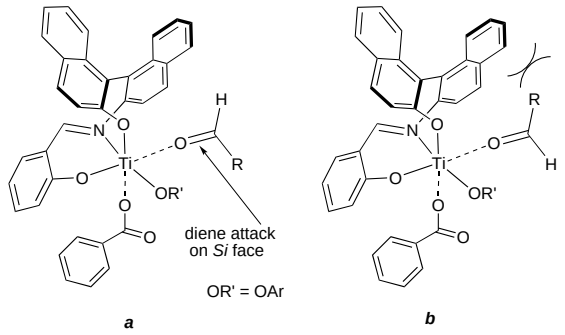

Figure 6. Working model of titanium catalysts with bound benzaldehyde.

Conclusion

In conclusion, a group of highly efficient chiral tridentate titanium catalysts for HDA reaction of Danishefsky's diene and a variety of aldehydes have been discovered through ligand and additive diversity. Dramatically synergetic effect of carboxylic acid additives and the influence of substituent in chiral Schiff base ligands on the enantioselectivities of the reaction were also reported. It was found that a chiral drug Naproxen (**A21**) was a highly efficient additive for Ti-catalyzed HDA reaction, affording 2-substituted 2,3-dihydro-4*H*-pyran-4-one in up to 97% *ee* and >99% yields. The approach taken in this work is a privileged example which demonstrate how one can generate a large number of modular catalysts and screen the various catalyst components. Quantitative study of the effect of chiral carboxylic acid **A21** revealed that the catalysis could be accelerated by one order of magnitude. The positive nonlinear effect found in the present catalytic system demonstrated that the heterochiral Schiff base–titanium complexes probably have higher stability than their homochiral counterparts. As a result, the homochiral Schiff base–titanium complexes with higher *ee* than that of starting ligand will react with carboxylic acid additive to form the more active species which predominates the catalytic process. We hope that our finding in this research will stimulate further work on the understanding of the asymmetric induction mechanism with tridentate titanium catalysts and the designing of new catalytic asymmetric reaction systems with tridentate titanium complexes through ligand and additive diversity.

Experimental Section

General methods: ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM300 at 25 °C. Chemical shifts are reported in ppm with TMS as an internal standard ($\delta = 0$ ppm) for ^{1}H NMR. Optical rotations were measured with a PE-341 automatic polarimeter. Liquid chromatographic analyses were conducted on a JASCO 1580 system. EI mass spectra were obtained on a HP5989A spectrometer. HRMS was determined on a Kratos Concept instrument. Elemental analysis was performed with an elemental VARIO EL apparatus. All the experiments which were sensitive to moisture or air were carried out under argon atmosphere using standard Schlenk techniques. Commercial reagents were used as received without further purification unless otherwise noted. Toluene was freshly distilled from sodium/benzophenone and methanol from magnesium.

Materials: 5-Bromosalicyclaldehyde, 5-chlorosalicyclaldehyde, 2-hydroxy-5-methoxybenzaldehyde, 2-hydroxy-4-methoxybenzaldehyde, 2-hydroxy-3-methoxybenzaldehyde, 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde, 5-bromo-2-hydroxy-3-methoxybenzaldehyde, 2-hydroxy-1-naphthaldehyde and 3-phenylpropionaldehyde were purchased from Aldrich. 3,5-Diiodosalicylaldehyde, 3,5-dichlorosalicylaldehyde, 4-bromobenzaldehyde, 3-bromobenzaldehyde, 3-anisaldehyde and Ti(O*i*Pr)$_4$ were purchased from Acros. 4-Chlorobenzaldehyde, 4-nitrobenzaldehyde and (*S*)-(+)-2-(6-methyl-2-naphthyl)-propionic acid were purchased from TCI. 3-Methylbenzaldehyde, 2-anisaldehyde, 4-anisaldehyde, furfural, cinnamaldehyde, benzaldehyde, salicylaldehyde and all carboxylic acids were purchased from commercial suppliers. 5-Fluorosalicylaldehyde, 5-methylsalicylaldehyde, 3-methylsalicylaldehyde, 5-*tert*-butyl-2-hydroxybenzaldehyde, 3-*tert*-butyl-2-hydroxybenzaldehyde and 3-*tert*-butyl-2-hydroxy-5-methylbenzaldehyde were prepared according to the literature procedures.[20] 3,5-Dibromosalicylaldehyde, 3-bromo-2-hydroxy-5-methoxybenzaldehyde, 3-bromo-2-hydroxy-5-methylbenzaldehyde, 3-bromo-5-*tert*-butyl-2-hydroxybenzaldehyde and 5-iodosalicylaldehyde were prepared following the literature methods.[21] 1-Methoxy-3-(trimethyl-silyloxyl)buta-1,3-diene was prepared according to literature procedure.[22] Racemic NOBIN and enantiopure NOBIN were prepared following the reported procedure.[13]

General procedure for the preparation of Schiff base library: (*S*)-2-Amino-2′-hydroxy-1,1′-binaphthyl (285 mg, 0.1 mmol) and salicylaldehyde (1.2 equiv, 0.12 mmol) were stirred in absolute methanol (20 mL) and the mixture was heated to reflux for 24 h. The solvent was removed in vacuo and the product was isolated by recrystallization or by flash chromatography on silica gel (327 mg, 84%). (*S*)-**L1**;[12a] m.p. 223–224 °C; $[\alpha]_D^{20} = -43^\circ$ ($c = 0.5$, THF); IR (KBr): $\tilde{\nu} = 3412, 3054, 1607, 1570, 1462, 1431, 1382, 1346, 1279, 1152, 1074, 981, 864, 755$ cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.74$ (s, 1H), 8.14 (d, $J = 8.8$ Hz, 1H), 7.99–7.89 (m, 3H), 7.70 (d, 8.8 Hz, 1H), 7.60–7.50 (m, 1H), 7.20–7.45 (m, 8H), 7.03 (d, $J = 8.40$ Hz, 1H), 6.86–6.74 (m, 2H), 5.02 (br s, 1H); EIMS: *m*/*z* (%): 389 (63.36) $[M]^+$, 372 (100.00), 360 (21.21), 268 (70.62), 239 (20.32).

(*R*)-L1: Following the same procedure for the preparation of (*S*)-**1** by using (*R*)-**1** instead of (*S*)-**1**. $[\alpha]_D^{20} = +43.0^\circ$ ($c = 0.5$, THF).

(*S*)-L2: Yield: 86%; m.p. 120–122 °C; $[\alpha]_D^{20} = +76.0^\circ$ ($c = 0.5$, THF); IR (KBr): $\tilde{\nu} = 3450, 3050, 1630, 1610, 1550, 1490, 1440, 1410, 1355, 1310, 1290, 1250, 1180, 1080, 980, 820, 805, 750$ cm^{-1}; ^{1}H NMR (DMSO/TMS): $\delta = 9.13$ (s, 1H), 8.19 (d, $J = 8.8$ Hz, 1H), 8.06 (d, $J = 8.0$ Hz, 1H), 7.95 (d, $J = 9.6$ Hz, 1H), 7.89–7.88 (m, 3H), 7.64 (d, $J = 2.8$ Hz, 1H), 7.58 (d, $J = 2.4$ Hz, 1H), 7.53–7.50 (m, 1H), 7.38–7.32 (m, 2H), 7.24 (t, $J = 1.9$ Hz, 1H), 7.17–7.10 (m, 2H), 6.77 (d, $J = 8.40$ Hz, 1H), 3.17 (s, 3H); elemental analysis calcd (%) for $C_{27}H_{17}Cl_2NO_2 \times CH_3OH$: C 68.58, H 4.32, N 2.86; found: C 68.91, H 4.19, N 2.87.

(*S*)-L3: Yield: 80%; m.p. 270–271 °C; $[\alpha]_D^{20} = -27.2^\circ$ ($c = 0.505$, THF); IR (KBr): $\tilde{\nu} = 3426, 1620, 1557, 1506, 1473, 1431, 1378, 1345, 1278, 1147, 1074, 982, 818, 752$ cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.62$ (s, 1H), 8.13 (d, $J = 8.79$ Hz, 1H), 8.00–7.86 (m, 3H), 7.65 (d, $J = 8.80$ Hz, 1H), 7.60–7.51 (m, 2H), 7.34–7.19 (m, 6H), 6.99 (d, $J = 8.49$ Hz, 1H), 6.64 (d, $J = 8.82$ Hz, 1H), 4.89 (s, 1H); EIMS: *m*/*z* (%): 547 (2.76) $[M]^+$, 467 (40.92), 450 (100.00), 268 (88.71), 239 (32.75); HRMS (EI): calcd for $C_{27}H_{17}Br_2NO_2$: 544.9626; found: 544.9586 $[M]^+$.

(*S*)-L4: Yield: 96%; m.p. 235–237 °C; $[\alpha]_D^{20} = +27.5^\circ$ ($c = 0.525$, THF); IR (KBr): $\tilde{\nu} = 3446, 3054, 2958, 1617, 1603, 1584, 1473, 1431, 1345, 1273, 1154, 1073, 980, 815, 752$ cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.38$ (s, 1H), 8.11 (d, $J = 8.80$ Hz, 1H), 7.99–7.84 (m, 5H), 7.59–7.06 (m, 8H), 6.95 (d, $J = 8.30$ Hz, 1H), 5.02 (s, 1H); EIMS: *m*/*z* (%): 640 (31.97) $[M]^+$, 624 (100.00), 446 (8.91), 374 (19.42), 285 (7.78), 268 (27.26), 239 (8.84); elemental analysis calcd (%) for $C_{27}H_{17}I_2NO_2$: C 50.57, H 2.67, N 2.18; found: C 50.33, H 2.75, N 2.15.

(*S*)-L5: Yield: 90%; m.p. 206–207 °C; $[\alpha]_D^{20} = -42.2^\circ$ ($c = 0.61$, THF); IR (KBr): $\tilde{\nu} = 3359, 3054, 1624, 1575, 1489, 1346, 1274, 1251, 1207, 1143, 808, 747$ cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 11.77$ (s,1H), 8.62 (s, 1H), 8.12 (d,

$J = 8.82$ Hz, 1H), 7.99 – 7.94 (m, 2H), 7.88 (d, $J = 8.09$ Hz, 1H), 7.65 (d, $J =$ 8.83 Hz, 1H), 7.52 – 7.20 (m, 6H), 7.01 – 6.92 (m, 3H), 6.71 – 6.70 (m, 1H), 4.92 (s, 1H); EIMS: m/z (%): 407 (31.08) $[M]^+$, 390 (100.00), 378 (20.08), 268 (54.54), 239 (15.51), 119 (1.97); elemental analysis calcd (%) for $C_{27}H_{18}FNO_2$: C 79.59, H 4.45, N 3.44; found: C 79.39, H 4.32, N 3.41.

(*S*)-L6: Yield: 80%; m.p. 261 – 262 °C; $[\alpha]_D^{20} = -40.2°$ ($c = 0.50$, THF); IR (KBr): $\tilde{\nu} = 3398$, 3054, 1919, 1828, 1620, 1507, 1475, 1431, 1279, 1198, 982, 925, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.62$ (s, 1H), 8.12 (d, $J =$ 8.83 Hz, 1H), 7.98 (d, $J = 8.30$ Hz, 1H), 7.95 (d, $J = 9.12$ Hz, 1H), 7.87 (d, $J = 8.09$ Hz, 1H), 7.64 (d, $J = 8.95$ Hz, 1H), 7.54 – 7.50 (m, 1H), 7.37 – 7.12 (m, 8H), 6.99 (d, $J = 8.31$ Hz, 1H), 6.68 (d, $J = 8.78$ Hz, 1H), 4.92 (s, 1H); EIMS: m/z (%): 423 (44.36) $[M]^+$, 406 (100.00), 268 (70.28), 239 (20.16), 43 (24.10); elemental analysis calcd (%) for $C_{27}H_{18}ClNO_2$: C 76.50, H 4.28, N 3.30; found: C 76.63, H 4.36, N 3.24.

(*S*)-L7: Yield: 85%; m.p. 267 – 268 °C; $[\alpha]_D^{20} = -37.2°$ ($c = 0.545$, THF); IR (KBr): $\tilde{\nu} = 3442$, 1620, 1507, 1473, 1431, 1345, 1279, 1198, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.62$ (s, 1H), 8.13 (d, $J = 8.85$ Hz, 1H), 7.99 (d, $J = 8.52$ Hz, 1H), 7.96 (d, $J = 9.11$ Hz, 1H), 7.88 (d, $J = 7.96$ Hz, 1H), 7.65 (d, $J = 8.81$ Hz, 1H), 7.56 – 7.48 (m, 1H), 7.38 – 7.00 (m, 8H), 6.95 (d, $J =$ 8.30 Hz, 1H), 6.63 (d, $J = 8.85$ Hz, 1H), 4.88 (s, 1H); EIMS: m/z (%): 453 (5.11) $[M]^+$, 375 (11.99), 286 (100.00), 268 (16.05), 257 (20.88), 239 (16.80), 120 (11.47); elemental analysis calcd (%) for $C_{27}H_{18}BrNO_2$: C 69.24, H 3.87, N 2.99; found: C 69.11, H 4.02, N 2.94.

***(R)*-L7**: Following the same procedure for the preparation of (*S*)-**7** by using (*R*)-**1** instead of (*S*)-**1**. $[\alpha]_D^{20} = +37.0°$ ($c = 0.500$, THF).

(*S*)-L8: Yield: 92%; m.p. 254 – 255 °C; $[\alpha]_D^{20} = -39.5°$ ($c = 0.495$, THF); IR (KBr): $\tilde{\nu} = 3360$, 3053, 1622, 1606, 1587, 1505, 1473, 1344, 1281, 1195, 1149, 810, 809, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 12.50$ (s,1H), 9.01 (s, 1H), 8.77 (s, 1H), 8.06 (d, $J = 8.83$ Hz, 1H), 7.96 (d, $J = 8.18$ Hz, 1H), 7.86 – 7.81 (m, 2H), 7.75 – 7.66 (m, 2H), 7.48 – 7.13 (m, 7H), 6.92 (d, $J = 8.34$ Hz, 1H), 6.47 (d, $J = 8.72$ Hz, 1H); EIMS: m/z (%): 515 (32.15) $[M]^+$, 498 (100.00), 486 (13.39), 371 (3.55), 268 (48.31), 239 (12.15), 170 (1.88), 119 (1.65); elemental analysis calcd (%) for $C_{27}H_{18}INO_2$: C 62.93, H 3.52, N 2.72; found: C 62.68, H 3.48, N 2.58.

(*S*)-L9: Yield: 96%; m.p. 180 – 181 °C; $[\alpha]_D^{20} = +15.5°$ ($c = 0.49$, THF); IR (KBr): $\tilde{\nu} = 3446$, 1620, 1506, 1457, 1431, 1397, 1255, 975, 820, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.61$ (s, 1H), 8.06 (d, $J = 8.83$ Hz, 1H), 7.94 (d, $J = 8.09$ Hz, 1H), 7.88 (d, $J = 8.91$ Hz, 1H), 7.82 (d, $J = 7.89$ Hz, 1H), 7.57 (d, $J = 8.85$ Hz, 1H), 7.35 – 7.47 (m, 1H), 7.14 – 7.35 (m, 6H), 6.97 (d, $J =$ 8.32 Hz, 1H), 6.85 – 6.72 (m, 3H), 5.35 (brs, 1H), 3.72 (s, 3H); EIMS: m/z (%): 419 (88.34) $[M]^+$, 402 (100.00), 390 (14.48), 384 (8.15), 268 (93.51), 239 (22.13); elemental analysis calcd (%) for $C_{28}H_{21}NO_3$: C 80.17, H 5.05, N 3.34; found: C 79.77, H 5.12, N 3.30.

(*S*)-L10: Yield: 90%; m.p. 214 – 215 °C; $[\alpha]_D^{20} = -126.8°$ ($c = 0.545$, THF); IR (KBr): $\tilde{\nu} = 3422$, 3053, 1607, 1507, 1458, 1432, 1346, 1297, 1247, 1169, 1074, 977, 816, 752 cm^{-1}; ^{1}H NMR (DMSO/TMS): $\delta = 9.05$ (d, $J = 4.20$ Hz, 1H), 8.17 (d, $J = 9.00$ Hz, 1H), 8.05 (d, $J = 7.20$ Hz, 1H), 7.95 – 7.87 (m, 3H), 7.50 (t, $J = 7.20$ Hz, 1H), 7.38 – 7.08 (m, 10H), 6.79 (d, $J = 8.40$ Hz, 1H), 3.68 (s, 3H); EIMS: m/z (%): 419 (100.00) $[M]^+$, 402 (84.73), 390 (11.75), 268 (61.83), 239 (20.32); HRMS (EI): calcd for $C_{28}H_{21}NO_3$: 419.1521; found: 419.1530 $[M]^+$.

(*S*)-L11: Yield: 91%; m.p. 246 – 247 °C; $[\alpha]_D^{20} = -35.7°$ ($c = 0.49$, THF); IR (KBr): $\tilde{\nu} = 3422$, 1620, 1575, 1487, 1274, 1161, 1039, 982, 813, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.67$ (s, 1H), 8.12 (d, $J = 8.84$ Hz, 1H), 7.98 (d, $J = 8.47$ Hz, 1H), 7.95 (d, $J = 9.20$ Hz, 1H), 7.88 (d, $J = 7.99$ Hz, 1H), 7.68 (d, $J = 8.85$ Hz, 1H), 7.54 – 7.49 (m, 1H), 7.38 – 7.19 (m, 6H), 7.01 (d, $J =$ 8.36 Hz, 1H), 6.87 – 6.69 (m, 3H), 4.90 (s, 1H), 3.73 (s, 3H); EIMS: m/z (%): 419 (100.00) $[M]^+$, 402 (84.73), 390 (11.75), 268 (61.83), 239 (14.26); HRMS (EI): calcd for $C_{28}H_{21}NO_3$: 419.1521; found: 419.1493 $[M]^+$.

(*S*)-L12: Yield: 95%; m.p. 193 – 194 °C; $[\alpha]_D^{20} = +18.5°$ ($c = 0.50$, THF); IR (KBr): $\tilde{\nu} = 3426$, 1607, 1578, 1505, 1431, 1382, 1345, 1274, 1207, 1147, 1088, 819, 780, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.59$ (s, 1H), 8.07 (d, $J =$ 8.79 Hz, 1H), 7.95 (d, $J = 8.16$ Hz, 1H), 7.90 (d, $J = 8.93$ Hz, 1H), 7.84 (d, $J = 7.92$ Hz, 1H), 7.59 (d, $J = 8.81$ Hz, 1H), 7.50 – 7.47 (m, 1H), 7.36 – 7.19 (m, 6H), 7.09 – 6.92 (m, 3H), 6.67 (t, $J = 6.54$ Hz, 1H), 5.08 (s, 1H), 2.16 (s, 3H); EIMS: m/z (%): 403 (81.84) $[M]^+$, 386 (96.85), 374 (20.73), 268 (100.00), 239 (27.78); elemental analysis calcd (%) for $C_{28}H_{21}NO_2$: C 83.35, H 5.25, N 3.47; found: C 83.35, H 5.32, N 3.38.

***(R)*-L12**: Following the same procedure for the preparation of (*S*)-**7** by using (*R*)-**1** instead of (*S*)-**1**. $[\alpha]_D^{20} = -18.6°$ ($c = 0.50$, THF).

(*S*)-L13: Yield: 91%; m.p. 224 – 225 °C; $[\alpha]_D^{20} = -43.2°$ ($c = 0.54$, THF); IR (KBr): $\tilde{\nu} = 3394$, 3052, 1622, 1576, 1488, 1431, 1378, 1345, 1282, 1218, 1157, 1074, 982, 816, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.64$ (s, 1H), 8.11 (d, $J = 8.82$ Hz, 1H), 7.97 (d, $J = 9.12$ Hz, 1H), 7.94 (d, $J = 9.24$ Hz, 1H), 7.86 (d, $J = 8.04$ Hz, 1H), 7.65 (d, $J = 8.82$ Hz, 1H), 7.52 – 7.49 (m, 1H), 7.37 – 7.17 (m, 6H), 7.04 – 6.99 (m, 3H), 6.66 (d, $J = 8.30$ Hz, 1H), 4.94 (s, 1H), 2.22 (s, 3H); EIMS: m/z (%): 403 (100) $[M]^+$, 386 (94), 374 (20), 268 (76), 239 (20); elemental analysis calcd (%) for $C_{28}H_{21}NO_2$: C 83.35, H 5.25, N 3.47; found: C 83.05, H 5.26, N 3.40.

(*S*)-L14: Yield: 99%; m.p. 180 – 181 °C; $[\alpha]_D^{20} = -89.5°$ ($c = 0.525$, THF); IR (KBr): $\tilde{\nu} = 3422$, 3053, 1905, 1808, 1617, 1587, 1465, 1432, 1389, 1348, 1272, 1175, 1073, 978, 819, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.53$ (s, 1H), 8.11 (d, $J = 8.80$ Hz, 1H), 7.97 – 7.84 (m, 5H), 7.66 (d, $J = 8.80$ Hz, 1H), 7.51 – 7.04 (m, 9H), 6.72 (t, $J = 8.60$ Hz, 1H), 1.21 (s, 9H); EIMS: m/z (%): 445 (86.33) $[M]^+$, 430 (66.75), 428 (42.00), 402 (46.18), 285 (100.00), 268 (80.61); HRMS (EI): calcd for $C_{31}H_{27}NO_2$: 445.2042; found: 445.2071 $[M]^+$.

(*S*)-L15:[12a] Yield: 58%; m.p. 148 – 149 °C; $[\alpha]_D^{20} = +28.7°$ ($c = 0.51$, THF); IR (KBr): $\tilde{\nu} = 3366$, 3055, 2958, 2870, 1622, 1576, 1487, 1431, 1380, 1346, 1266, 1181, 1071, 982, 819, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.71$ (s, 1H), 8.11 (d, $J = 8.86$ Hz, 1H), 7.98 – 7.84 (m, 3H), 7.66 (d, $J = 8.70$ Hz, 1H), 7.51 – 7.50 (m, 1H), 7.36 – 7.19 (m, 8H), 7.00 (d, $J = 8.49$ Hz, 1H), 6.71 (d, $J =$ 8.40 Hz, 1H), 1.25 (s, 9H); EIMS: m/z (%): 445 (71.99) $[M]^+$, 428 (100.00), 268 (52.77), 239 (12.35), 211 (9.26), 158 (12.29).

(*S*)-L16: Yield: 99%; m.p. 98 – 100 °C; $[\alpha]_D^{20} = -45.0°$ ($c = 0.515$, THF); IR (KBr): $\tilde{\nu} = 3426$, 3054, 1617, 1578, 1502, 1465, 1436, 1382, 1361, 1273, 1207, 1172, 1073, 978, 820, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.67$ (s, 1H), 8.11 (d, $J = 8.78$ Hz, 1H), 7.98 (d, $J = 8.14$ Hz, 1H), 7.90 (d, $J = 8.85$ Hz, 1H), 7.84 (d, $J = 7.83$ Hz, 1H), 7.66 (d, $J = 8.80$ Hz, 1H), 7.51 – 7.19 (m, 8H), 7.07 – 7.04 (m, 2H), 1.25 (s, 9H), 1.22 (s, 9H); EIMS: m/z (%): 501 (91.49) $[M]^+$, 486 (100.00), 458 (36.40), 268 (26.56); elemental analysis calcd (%) for $C_{35}H_{35}NO_2$: C 83.80, H 7.03, N 2.79; found: C 83.54, H 7.05, N 2.88.

(*S*)-L17: Yield: 97%; m.p. 78 – 80 °C; $[\alpha]_D^{20} = -68.1°$ ($c = 0.475$, THF); IR (KBr): $\tilde{\nu} = 3422$, 3053, 1617, 1596, 1465, 1432, 1382, 1349, 1267, 1210, 1167, 1073, 978, 814, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.58$ (s, 1H), 8.09 (d, $J = 9.00$ Hz, 1H), 7.97 (d, $J = 8.70$ Hz, 1H), 7.89 (d, $J = 7.80$ Hz, 1H), 7.84 (d, $J = 7.80$ Hz, 1H), 7.63 (d, $J = 8.70$ Hz, 1H), 7.50 – 7.18 (m, 8H), 7.03 – 7.00 (m, 2H), 6.86 (d, $J = 1.71$ Hz, 1H), 2.21 (s, 3H), 1.03 (s, 9H); EIMS: m/z (%): 458 (4.43) $[M]^+$, 446 (33.56), 285 (100.00), 268 (42.01), 239 (15.65), 44 (24.80); HRMS (EI): calcd for $C_{32}H_{29}NO_2$: 459.2198 $[M]^+$; found: 459.2153.

(*S*)-L18: Yield: 84%; m.p. 237 – 238 °C; $[\alpha]_D^{20} = +64.9°$ ($c = 0.615$, THF); IR (KBr): $\tilde{\nu} = 3446$, 3053, 2828, 1797, 1620, 1557, 1456, 1431, 1378, 1346, 1274, 1147, 1074, 977, 817, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.45$ (s, 1H), 8.06 (d, $J = 8.84$ Hz, 1H), 7.94 (d, $J = 7.74$ Hz, 1H), 7.91 (d, $J = 8.69$ Hz, 1H), 7.85 (d, $J = 8.03$ Hz, 1H), 7.54 (d, $J = 8.88$ Hz, 1H), 7.52 – 7.46 (m, 1H), 7.36 – 7.16 (m, 7H), 6.97 (d, $J = 8.42$ Hz, 1H), 6.88 (s, 1H), 5.18 (s, 1H), 2.17 (s, 3H); EIMS: m/z (%): 481 (30.33) $[M]^+$, 466 (72.41), 285 (12.33), 268 (100), 239 (18.85), 86 (12.84); HRMS (EI): calcd for $C_{28}H_{20}BrNO_2$: 481.0677; found: 466.0444 $[M - CH_3]^+$.

(*S*)-L19: Yield: 93%; m.p. 260 – 262 °C; $[\alpha]_D^{20} = +68.7°$ ($c = 0.54$, THF); IR (KBr): $\tilde{\nu} = 3426$, 3056, 1618, 1505, 1458, 1431, 1381, 1345, 1274, 1222, 1178, 1075, 983, 867, 819, 778 cm^{-1}; ^{1}H NMR (DMSO/TMS): $\delta = 9.05$ (d, $J =$ 3.78 Hz, 1H), 8.18 (d, $J = 8.90$ Hz, 1H), 8.06 (d, $J = 8.10$ Hz, 1H), 7.96 – 7.88 (m, 3H), 7.51 – 7.40 (m, 1H), 7.37 – 7.01 (m, 9H), 6.80 (d, $J = 8.36$ Hz, 1H), 3.71 (s, 3H); EIMS: m/z: (%): 497 (50.57) $[M]^+$, 482 (100.00), 268 (65.87); HRMS (EI): calcd for $C_{28}H_{20}BrNO_3$: 497.0627; found: 497.0610 $[M]^+$.

(*S*)-L20:[12a] Yield: 97%; m.p. 137 – 139 °C; $[\alpha]_D^{20} = +76.4°$ ($c = 0.43$, THF); IR (KBr): $\tilde{\nu} = 3426$, 3054, 2958, 1618, 1502, 1457, 1431, 1381, 1347, 1266, 1167, 1074, 982, 818, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.57$ (s, 1H), 8.10 (d, $J = 8.90$ Hz, 1H), 7.94 – 7.81 (m, 4H), 7.60 (d, $J = 8.80$ Hz, 1H), 7.52 – 7.50 (m, 2H), 7.40 – 7.11 (m, 8H), 1.25 (s, 9H); EIMS: m/z (%): 525 (28.96) $[M]^+$, 508 (100.00), 268 (70.37), 239 (20.91), 43 (27.72); elemental analysis calcd (%) for $C_{31}H_{26}BrNO_2$: C 71.00, H 5.00, N 2.67; found: C 70.71, H 5.44, N 2.55.

(*S*)-L21: Yield: 84%; m.p. 286 – 288 °C; $[\alpha]_D^{20} = +19.5°$ ($c = 0.485$, THF); IR (KBr): $\tilde{\nu} = 3446$, 1623, 1507, 1465, 1438, 1254, 979, 819, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): $\delta = 8.59$ (s, 1H), 8.08 (d, $J = 8.80$ Hz, 1H), 7.96 – 7.92 (m, 2H), 7.86 (d, $J = 7.70$ Hz, 1H), 7.65 (d, $J = 8.80$ Hz, 1H), 7.52 – 7.46 (m, 1H), 7.37 – 7.17 (m, 6H), 7.10 (d, $J = 8.70$ Hz, 1H), 7.00 (d, $J = 8.30$ Hz, 1H), 6.36 (d, $J = 2.3$ Hz, 1H), 6.22 (d, $J = 2.20$ Hz, 1H), 3.68 (s, 3H); EIMS: m/z (%):

0947-6539/02/0821-5040 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 21

498 (36.57) $[M]^+$, 480 (100.00), 285 (7.06), 268 (90.82), 239 (24.24); HRMS (EI): calcd for $C_{28}H_{20}BrNO_3$: 497.0627; found: 497.0602 $[M]^+$.

(*S*)-L22: Yield: 91%; m.p. 291–293 °C; $[\alpha]_D^{20} = +60.6°$ ($c = 0.500$, THF); IR (KBr): $\tilde{\nu} = 3450, 3050, 1630, 1610, 1550, 1490, 1440, 1360, 1310, 1280, 1180, 1150, 1075, 980, 820, 800, 750\ cm^{-1}$; ^1H NMR (DMSO/TMS): $\delta = 9.70–9.80$ (m, 2H), 8.50–8.48 (m, 2H), 8.29 (d, $J = 8.8$ Hz, 1H), 8.16 (d, $J = 8.0$ Hz, 1H), 8.07 (d, $J = 8.8$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.76 (d, $J = 7.2$ Hz, 1H), 7.59–7.32 (m, 6H), 7.26 (t, $J = 8.0$ Hz, 1H), 7.17 (d, $J = 8.4$ Hz, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 6.73–6.70 (m, 1H); elemental analysis calcd (%) for $C_{31}H_{21}NO_2$: C 68.58, H 4.32, N 2.86; found: C 68.91, H 4.19, N 2.87.

X-ray Crystallographic data for (*R*)-L1:[23] $C_{27}H_{19}NO_2$, orthorhombic crystals, space group $P2_12_12_1$; $a = 9.2152(6)$, $b = 11.4160(8)$, $c = 19.0345(13)$ Å; $V = 2002.4(2)$ Å^3, $\rho_{calcd} = 1.292\ g\,cm^{-3}$, $Z = 4$. A total of 1600 reflections were measured on a Bruker SMART CCD-APEX at 20 °C using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), 11530 reflections were collected and 4149 were unique. The structure was solved by direct methods (SHELX-97) and refined by full matrix least squares to $R = 0.0495$, $R_w = 0.0684$.

X-ray Crystallographic data for (*R*)-L7:[23] $C_{27}H_{18}NO_2Br$, orthorhombic crystals, space group $P2_12_12_1$; $a = 12.978(3)$, $b = 18.512(4)$, $c = 9.039(2)$ Å; $V = 2171.6(9)$ Å^3; $\rho_{calcd} = 1.43\ g\,cm^{-3}$, $Z = 4$. A total of 2852 reflections were measured on a Rigaku AFC7R diffractometer at 20 °C using $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å) with $2\theta_{max} = 55.0°$, 1250 independent reflections have $I > 1.5\sigma I$. The structure was solved by direct methods (SHELXS86) and refined by full matrix least squares to $R = 0.042$, $R_w = 0.045$.

X-ray Crystallographic data for (*R*)-L12:[23] $C_{28}H_{21}NO_2$, monoclinic crystals, space group $P2_1$; $a = 11.104(3)$, $b = 9.086(2)$, $c = 11.139(2)$ Å; $\beta = 110.51(2)°$, $V = 1052.5(4)$ Å^3; $\rho_{calcd} = 1.273\ g\,cm^{-3}$, $Z = 2$. A total of 2706 reflections were measured on a Rigaku AFC7R diffractometer at 20 °C using $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å) with $2\theta_{max} = 55.0°$, giving 2582 independent reflections of which 2244 have $I > 2.00\sigma I$, $R_{int} = 0.011$. The structure was solved by direct methods (SHELXS86) and refined by full matrix least squares to $R = 0.038$, $R_w = 0.046$.

General procedure for catalytic enantioselctive hetero-Diels–Alder reaction: A mixture of (*S*)-Schiff Base (0.05 mmol), Ti(O*i*Pr)$_4$ in CH_2Cl_2 (0.5 M, 50 μL, 0.025 mmol) and activated powdered 4 Å MS (30 mg) in toluene (1 mL) was stirred for 2 h at 50 °C. The red solution was cooled to room temperature and the carboxylic acid (0.025 mmol), aldehyde (0.25 mmol) and Danishefsky's diene (60 μL, 0.3 mmol) were added sequentially. The mixture was stirred for 20 h before quenched with 10 drops of TFA. After stirring for additional 5 min, the mixture was neutralized with saturated $NaHCO_3$ (3 mL). After filtration through a plug of Celite, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography to give the cycloadduct. Full characterization data for products **3a–k** are included in Supporting Information.

Preparation of titanium complex ((±)-6) of racemic L1: A 10 mL Schlenk tube, equipped with a magnetic stirrer, was charged with (±)-**L1** (105 mg, 0.27 mmol). The air in the tube was replaced by argon, and absolute toluene (4 mL) was added. Titanium tetraisopropoxide in dichloromethane (0.5 M, 0.27 mL, 0.135 mmol) was injected and the solution was heated to 50 °C for 2 h. The solvent was removed in vacuo and the solid residue was submitted to recrystallization in dichloromethane (1.5 mL). The yellow crystals were collected by filtration (94 mg, 80%). M.p. 275–277 °C; IR (KBr): $\tilde{\nu} = 3053, 1614, 1590, 1549, 1504, 1463, 1446, 1369, 1325, 1239, 1150, 1072, 953, 754\ cm^{-1}$; ^1H NMR ($CDCl_3$/TMS): $\delta = 7.95$ (d, $J = 7.94$ Hz, 1H), 7.83 (s, 1H), 6.79–7.67 (m, 29H), 6.05–6.07 (m, 2H), 5.06 (d, $J = 7.95$, 1H), 1.57 (s, 4H); EIMS: *m*/*z* (%): 822 (2.08) $[M]^+$, 687 (81.17), 625 (78.85), 199 (100); elemental analysis calcd (%) for $C_{54}H_{34}N_2O_4Ti$: C 78.83, H 4.17, N 3.40; found: C 78.35, H 4.50, N 3.60.

Quantitative study of A21 on the reaction rate: A mixture of (*S*)-**L1** (20 mg, 0.051 mmol), Ti(O*i*Pr)$_4$ in CH_2Cl_2 (0.5 M, 50 μL, 0.05 mmol) and activated powdered 4 Å MS (30 mg) (or without addition of 4 Å MS) in toluene (1 mL) was stirred for 2 h at 50 °C. The red solution was cooled to 25 °C and **A21** (2.7 mg, 0.025 mmol), benzaldehyde (25 μL, 0.25 mmol) and Danishefsky's diene (60 μL, 0.3 mmol) were added sequentially. The reaction mixture was stirred at 25 °C for 30 min and then quenched with 10 drops of TFA, following by adding 25 mg (0.16 mmol) of biphenyl as an internal standard. After stirring for additional 5 min, the mixture was neutralized with saturated $NaHCO_3$ (3 mL). After filtration through a plug of Celite, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was submitted to HPLC analysis on a Intersil CN-3 column, hexane/isopropanol 95:5, flow rate 0.7 mL min^{-1}, UV detection at $\lambda = 254$ nm, t_R (biphenyl) = 7.2 min (factor 1.000); t_R (**3a**) = 16.3 min (factor 2.055).

Search for nonlinear effect in the catalytic system: A typical experiment was exemplified in the system catalyzed by 30% *ee* of (*S*)-**L1**/Ti complex. A solution of partially resolved (*S*)-**L1** (20 mg, 0.051 mmol) with 30% *ee*, Ti(O*i*Pr)$_4$ in CH_2Cl_2 (0.5 M, 50 μL, 0.05 mmol) and activated powdered 4 Å MS (30 mg) in toluene (1 mL) was stirred for 2 h at 50 °C. The solution was cooled to 25 °C and then **A21** (2.7 mg, 0.025 mmol), benzaldehyde (25 μL, 0.25 mmol) and Danishefsky's diene (60 μL, 0.3 mmol) were added sequentially. The mixture was stirred for 20 h at 25 °C before quenched with 10 drops of TFA. After stirring for additional 5 min, the mixture was neutralized with saturated $NaHCO_3$ (3 mL). After filtration through a plug of Celite, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography on silica gel to give the cycloadduct **3a** in 75% yield with 87% *ee* (determined by HPLC on Chiralcel OD column, hexane/isopropanol 90:10, flow rate 1.0 mL min^{-1}, $t_{R1} = 11.450$ min (*S*) (major), $t_{R2} = 13.467$ min (*R*) (minor)).

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