A Mild and Efficient Asymmetric Hetero-Diels–Alder Reaction of the Brassard Diene with Aldehydes

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This paper describes the successful development of the hetero-Diels–Alder (HDA) reaction of the Brassard diene with aldehydes in the presence of a series of titanium(IV) tridentate Schiff-base complexes under mild conditions. The influence of the substituent of the chiral Schiff-base ligands on the enantioselectivities of the reaction was studied. It was found that ligand **L13** is a highly enantioselective ligand for the Ti-catalyzed HDA reaction, affording 6-substituted 4-ethoxy-5,6-dihydropyran-2-one in up to 99% *ee*. The mechanism of the HDA reaction between the Brassard diene and benzaldehyde in the presence of the (Schiff base)Ti^{IV} complex was investigated. The results indicate that the reaction pathway is influenced by reaction temperature: at higher temperature (0 °C), the reaction is mostly a Diels–Alder process, whereas at lower temperature (–78 °C) it is a Mukaiyama aldol process.

Introduction

The catalytic asymmetric synthesis of enantiomerically enriched products is of importance to modern synthetic and pharmaceutical chemistry.[1] The catalytic asymmetric hetero-Diels–Alder (HDA) reaction,[2] which is one of the most important asymmetric C–C bond-forming reactions, provides a highly effective protocol for preparing optically active six-membered ring compounds such as dihydropyrans, dihydropyranones, etc.[3] The chiral Lewis acid catalyzed HDA reaction is easy to perform. BINOL and its derivatives,[3d,3e,3i–3m,4] chiral C_2-symmetric bis(oxazolines),[5] and Schiff-base ligands,[3f,3g,6] such as salen, aminoindanol-derived Schiff-base ligands, and Nobin-derived Schiff-base ligands, complexed with suitable metals such as copper, aluminum, chromium, titanium, and other transition metals or nonmetals, such as boron, have been successfully applied to the enantioselective HDA reaction. Recently, organocatalytic enantioselective HDA reactions have been developed.[7] Rawal et al. have found that the enantioselective HDA reaction of a nitrogen-containing diene with aldehydes occurs smoothly with 52–97% yield and 86–98% *ee* in the presence of α,α,α′,α′-tetra(1-naphthyl)-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol (TADDOL) without any metals,[7a] and Jørgensen and co-workers have reported the first example of an inverse-electron-demand HDA reaction catalyzed by proline derivatives (up to 94% *ee*).[7b]

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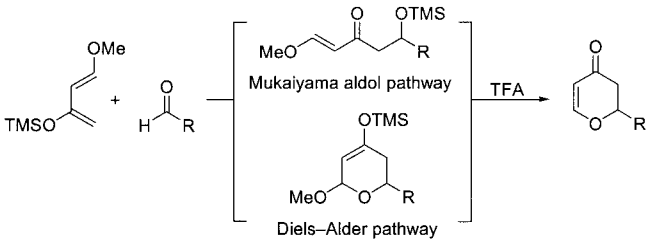
Two mechanistic pathways are generally taken into account for the HDA reaction when Lewis acid catalyzed reactions are considered. The two pathways (Scheme 1) are formulated as a Mukaiyama aldol reaction (stepwise mechanism) and a [4+2] Diels–Alder cycloaddition (concerted mechanism).[2c] The actual reaction mechanism is usually demonstrated by separation of the reaction intermediates[6a] or semiempirical calculations.[8]



Scheme 1. Two possible mechanisms of the hetero-Diels–Alder reaction.

Chiral 5,6-dihydropyran-2-one or α,β-unsaturated δ-lactone derivatives are key structural subunits of some natural products with a wide range of biological activity, such as antifungal and antitumor.[9] Thus, the synthesis of δ-lactones has been an area of intense research efforts. Many methods have been developed, such as the annulation of open-chained precursors,[10] the derivatization from a 2,3-dihydropyran-4-one,[9d,10e] and the two-step addition reaction of ene to dicarbonyl compounds.[10e] From the viewpoint of synthesis, one of the most convenient accesses to δ-lactones is based on the HDA reaction of the Brassard

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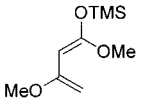
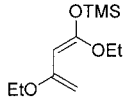
diene[11] (**1a**) with suitable aldehydes or ketones. The reaction of the Brassard diene with aliphatic aldehydes in the presence of $Eu(hfc)_3$ occurs smoothly with high enantioselectivity.[12a–12d] However, the enantioselective approach with the Brassard diene and aromatic aldehydes only gave a disappointing result, in which the enantiomeric excess value obtained was less than 5%.[12e] Very recently, we reported the first example of the highly enantioselective synthesis of optically active δ-lactones in the presence of chiral titanium(IV) tridentate Schiff-base complexes.[13] Ding and coworkers subsequently reported the same reaction with TADDOL.[14] This paper describes our studies of the relationships between catalyst structure and activity, substrate generality, mechanism, and limitations.



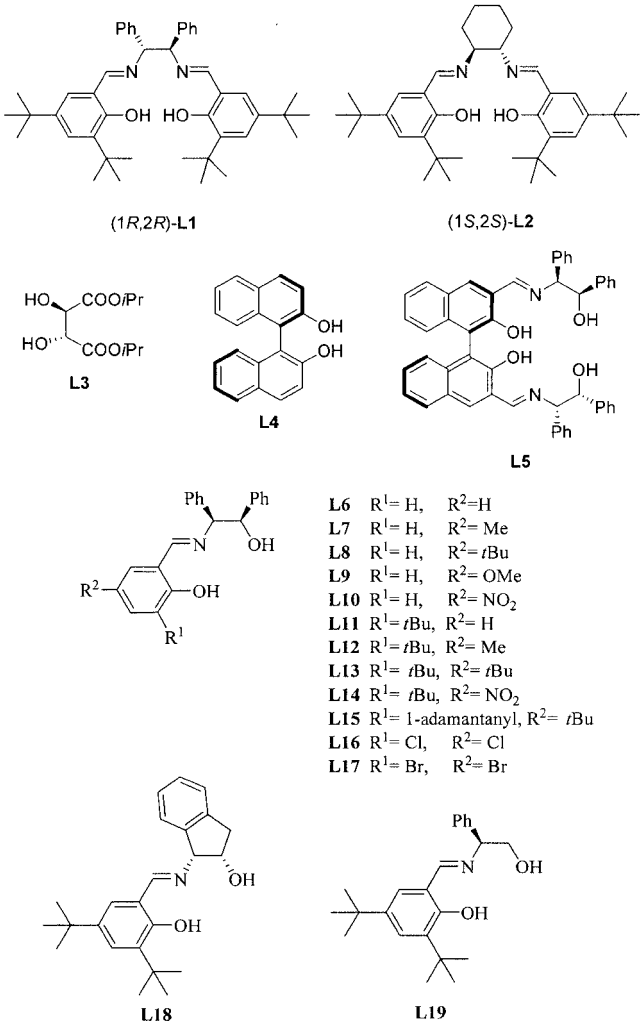
1a



1b

Results and Discussion

Considering the stability of the Brassard diene, the methoxy group of **1a** was replaced with an ethoxy group to give diene **1b**. Although this results in only a small change in the structure, diene **1b** is more stable and easier to purify than **1a**. Diene **1b** is easily synthesized according to Brassard's procedures.[11] As the ethyl group is larger than the methyl group, we speculated that the enantioselectivity of the product from diene **1b** would be higher than that from diene **1a**. In our initial attempts, diene **1a** gave the corresponding product with 86% *ee*, and diene **1b** gave the corresponding product with 90% *ee*, thus confirming our speculation.



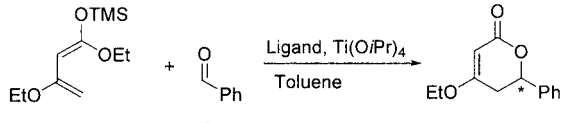
Scheme 2. Ligands used in this paper.

Preliminary Trials

A variety of different ligands complexed with $[Ti(OiPr)_4]$ were tested as catalysts for the HDA reaction of the Brassard diene **1b** with benzaldehyde in our initial attempts (Scheme 2). The ligands were prepared according to literature procedures.[15] The catalyst was prepared in situ by stirring a solution of the chiral ligand and $[Ti(OiPr)_4]$ in a molar ratio of 1:1 in toluene. The reaction procedure is as follows: benzaldehyde and the Brassard diene **1b** were successively added to the catalyst solution at 0 °C. After 72 h, the system was treated with trifluoroacetic acid (TFA), and the desired product was obtained by flash chromatography on silica gel. The enantiomeric excess of the product was assayed by HPLC with a Chiralpak AD-H column. The results are summarized in Table 1.

The initial studies revealed that the HDA reaction product, which is formed in high enantioselectivity, depends on the ligand structures. No product was obtained with tetradentate ligands (**L1**–**2**) complexed with $[Ti(OiPr)_4]$, probably because benzaldehyde coordinates to the catalyst to form an intermediate with greater steric hindrance, which

Table 1. Preliminary trials of the asymmetric HDA reaction between benzaldehyde and **1b** catalyzed by some easily accessible chiral ligands.[a]



1b **2a** **3a**

Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	**L1**	n.d.	–
2	**L2**	n.d.	–
3	**L3**	trace	–
4	**L4**	23	65
5	**L5**	trace	–
6	**L6**	32	63
7	**L13**	46	90

[a] All reactions were performed with benzaldehyde (1 mmol) and **1b** (1.2 mmol) in 1 mL of toluene at 0 °C for 48 h. Catalysts: 1:1 molar ratio of ligand/$[Ti(OiPr)_4]$. Catalyst loading was 20 mol-%. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC with a Chiralpak AD-H column.

prevents **1b** approaching benzaldehyde. Diisopropyl tartrate (**L3**) also has little catalytic capability. The bidentate ligand (*R*)-BINOL (**L4**) promotes this conversion with 23% yield and 65% *ee*. The multidentate ligand **L5**, with larger hindrance, also shows very little catalytic activity. Fortunately, tridentate ligands derived from (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**L6** and **L13**) exhibit better chiral induction for this reaction, especially **L13** (90% *ee*).

Ligand and Lewis Acid Effects

A group of tridentate Schiff-base ligands and Lewis acids was examined as catalysts for the HDA reaction of **1b** with benzaldehyde. The ligands were prepared according to literature procedures.[15] This ligand screening revealed that the HDA product is formed in diverse yields and enantioselectivities depending on the ligand's structure. Some representative results are shown in Table 2.

Table 2. Influence of different ligands on the hetero-Diels–Alder reaction of benzaldehyde with **1b**.[a]

Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	**L6**	35	64
2	**L7**	35	63
3	**L8**	42	71
4	**L9**	n.d.	–
5	**L10**	n.d.	–
6	**L11**	45	76
7	**L12**	43	81
8	**L13**	58	92
9	**L14**	trace	–
10	**L15**	54	85
11	**L16**	43	82
12	**L17**	31	90
13	**L18**	48	47
14	**L19**	trace	–

[a] All reactions were performed with benzaldehyde (1 mmol) and **1b** (1.2 mmol) in 1 mL of toluene at 0 °C for 48 h. Catalysts: 1:1 molar ratio of ligand/[Ti(O*i*Pr)$_4$]. Catalyst loading was 20 mol-%. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC with a Chiralpak AD-H column.

The chiral induction of ligands **L6**–**19** was surveyed. The results (Table 2) show that both electronic and steric effects of the substituents on the aromatic ring have an influence on the enantiomeric excess of the product. Substituents *ortho* to the phenol hydroxy group in the ligands influence the enantioselectivity more strongly than *para* substituents. When substituent R^1 was H and the R^2 group was varied from H and methyl to *tert*-butyl, the group's electron-donating capability and the reactivity increased slightly (Table 2, entries 1–3). However, when R^2 was methoxy or nitro, the reaction did not proceed (Table 2, Entries 4,5). When R^1 was *tert*-butyl and R^2 was changed from H and methyl to *tert*-butyl, the group's electron-donating capability and both the reactivity and the enantioselectivity improved (Table 2, Entries 6–8). When R^2 was nitro, the reaction hardly proceeded (Table 2, Entry 9). Thus, a rather strong electron-donating group or a rather strong electron-withdrawing group reduce the reactivity. A bulkier *ortho* group, like *tert*-butyl, gives a higher *ee* (Table 2, Entry 8). However, when the *ortho* group was adamantyl, the large steric hindrance resulted in a lower enantioselectivity (Table 2, Entry 10). When the two substituents were Cl or Br, the reactions afforded the products in good to excellent enantioselectivities with moderate yields (Table 2, Entries 11 and 12). It therefore became obvious that a suitable group on the phenol ring of the ligand can enhance the match between substrate and catalyst and result in higher enantioselectivity. Some other ligands with different chiral moieties were also examined, although the results were disappointing (Table 2, Entries 13 and 14). The **L18**–Ti(O*i*Pr)$_4$ complex, for instance, promoted the reaction with very low enantioselectivity. This may be partly attributed to its less flexible five-membered ring structure; moreover, Ti^{IV} is an inappropriate metal for the Jacobsen catalyst[3f,3g] in which the central metal is Cr. Ligand **L13** is therefore the optimal one.

Besides [Ti(O*i*Pr)$_4$], other Lewis acids were also screened in the HDA reaction of **1b** with benzaldehyde. The results are shown in Table 3. Among the Lewis acid complexes screened, the Al^{III}–**L13** complex afforded a racemic product (Table 3, Entries 1–3), the Zr^{IV}–**L13** complex provided the product in low yield with 29% *ee* (Table 3, Entry 7), and the Ti^{IV}–**L13** complex promoted the reaction to give a moderate yield (Table 3, Entries 4–6). However, only [Ti(O*i*Pr)$_4$] achieved a high enantioselectivity of up to 92% *ee* (Table 3, Entry 6).

Table 3. Influence of the Lewis acid on the hetero-Diels–Alder reaction of benzaldehyde with **1b**.[a]

Entry	Lewis acid	Yield [%][b]	*ee* [%][c]
1	Al(O*i*Pr)$_3$	trace	–
2	$AlEt_3$	43	0
3	$AlEt_2Cl$	52	0
4	$TiCl_4$	63	26
5	[$TiCl_2$(O*i*Pr)$_2$]	48	33
6	[Ti(O*i*Pr)$_4$]	58	92
7	[Zr(O*i*Pr)$_4$]	<5	29

[a] All reactions were performed with benzaldehyde (1 mmol) and **1b** (1.5 mmol) in 1 mL of toluene at 0 °C for 72 h. Catalysts: 1.1:1 molar ratio of ligand **L13**/Lewis acid, with a catalyst loading of 20 mol-%. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC with a Chiralpak AD-H column.

Solvent Effects

The performance of the Ti^{IV}–**L13** complex in various solvents was determined by applying the standard procedure. This solvent survey revealed that toluene, benzene, Et_2O, and CH_2Cl_2 gave the product of the HDA reaction with high enantioselectivity and 58%, 37%, 42%, and 76% yield, respectively (Table 4). THF showed a strong solvent effect in which a rather low *ee* was obtained. From these results, CH_2Cl_2 was determined to be the appropriate solvent for this reaction.

Table 4. Influence of solvent on the Ti^{IV}–**L13**-catalyzed hetero-Diels–Alder reaction of benzaldehyde with **1b**.[a]

Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	toluene	58	92
2	benzene	37	93
3	Et_2O	42	89
4	CH_2Cl_2	76	93
5	THF	46	61

[a] All reactions were performed with benzaldehyde (1 mmol) and **1b** (1.5 mmol) in 1 mL of solvent at 0 °C for 72 h. Catalysts: 1.1:1 molar ratio of ligand **L13**/[Ti(O*i*Pr)$_4$], with a catalyst loading of 20 mol-%. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC with a Chiralpak AD-H column.

Temperature Effect

The influence of the temperature of the HDA reaction of **1b** with benzaldehyde was investigated in the presence of Ti^{IV}–**L13** (Table 5). A temperature dependence on the yield and enantioselectivity was found. At 0 °C, both the yield and the enantioselectivity had the optimal values (Table 3, Entry 2). A higher temperature (23 °C) gave lower enantioselectivity (Table 3, Entry 1), and a lower temperature brought about a sharp drop in the reactivity and, at –40 and –78 °C, also a drop in the enantioselectivity (Table 3, Entries 3–5).

Table 5. Temperature effects on the asymmetric HDA reaction between **1b** and benzaldehyde.[a]

Entry	Temperature [°C]	Yield [%][b]	*ee* [%][c]
1	23	74	81
2	0	76	93
3	–20	48	94[d]
4	–40	38	51[d]
5	–78	41	43[d]

[a] All reactions were performed with benzaldehyde (1 mmol) and **1b** (1.5 mmol) in 1 mL of CH_2Cl_2 for 72 h. Catalysts: 1.1:1 molar ratio of ligand **L13**/[Ti(O*i*Pr)$_4$] with a catalyst loading of 20 mol-%. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC with a Chiralpak AD-H column. [d] The reaction time was prolonged to 7 d due to the lower reaction rate.

Additive Effects

To investigate the effect of an additive on the reaction, some representative additives, such as 4 Å molecular sieves (MS) and acids that have been applied successfully in the HDA reaction previously,[6d,6e] were added to the system, but gave much worse results (Table 6). With 4 Å MS, benzoic acid, and *p*-nitrobenzoic acid, the *ee* of the product decreased sharply from 93% to 76%, 74%, and 65%, respectively. Perhaps the structure discrimination of the Brassard diene with Danishefsky's diene is the key to explain these results, as Togni has speculated that double substitution at the terminus has deleterious consequences upon the enantioselectivity of this cycloaddition reaction.[12e]

Table 6. The effect of an additive on the asymmetric HDA reaction.[a]

Entry	Additive	Yield [%][b]	*ee* [%][c]
1	100 mg 4 Å MS	58	76
2	Benzoic acid	43	74
3	*p*-Nitrobenzoic acid	68	65
4	3,5-Dinitrosalicylic acid	trace	–

[a] All reactions were performed with benzaldehyde (1 mmol) and **1b** (1.5 mmol) in 1 mL of CH_2Cl_2 for 72 h. Catalysts: 1.1:1 molar ratio of ligand **L13**/[Ti(O*i*Pr)$_4$] with a catalyst loading of 20 mol-%. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC with a Chiralpak AD-H column.

Ratio of Ligand/Metal

To further optimize the reaction conditions, the effects of the molar ratio of ligand **L13**/[Ti(O*i*Pr)$_4$] on yield and enantioselectivity were examined in detail. When the molar ratio of ligand **L13**/[Ti(O*i*Pr)$_4$] was 1.1:1, the optimal enantioselectivity and yield were obtained (Table 7, Entry 3). The yield varied appreciably with a change of the molar ratio. An insufficiency or excess of ligand both gave worse results (Table 7, Entries 1 and 5).

Table 7. The effect of the ratio of ligand/metal on the asymmetric HDA reaction.[a]

Entry	Ratio of ligand/metal	Yield [%][b]	*ee* [%][c]
1	0.8:1	48	89
2	1:1	63	90
3	1.1:1	76	93
4	1.5:1	68	92
5	2:1	52	94

[a] All reactions were performed with benzaldehyde (1 mmol) and **1b** (1.5 mmol) in 1 mL of CH_2Cl_2 at 0 °C for 72 h. Catalysts: ligand **L13**/[Ti(O*i*Pr)$_4$] with a catalyst loading of 20 mol-%. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC with a Chiralpak AD-H column.

Concentration of Substrate

The concentration of the substrate was examined to determine the optimal reaction conditions (Table 8). The solvent volume used in the reaction was changed and the other conditions were kept fixed. Maintaining a sufficient concentration is important for the HDA reaction, and a low concentration of catalyst and substrate leads to a sharp drop in the yield and enantioselectivity (Table 8, Entry 1). When the concentration of substrate was 0.25 M, the optimal yield and enantioselectivity were achieved (up to 78% yield and

Table 8. The effect of the catalyst concentration on the asymmetric HDA reaction.[a]

Entry	Solvent volume [mL]	Concentration of substrate [M]	Yield [%][b]	*ee* [%][c]
1	8	0.125	52	83
2	4	0.25	78	94
3	2	0.5	75	93
4	1	1	76	93
5	0.5	2	74	92

[a] All reactions were performed with benzaldehyde (1 mmol) and **1b** (1.5 mmol) in CH_2Cl_2 at 0 °C for 72 h. Catalysts: 1.1:1 molar ratio of ligand **L13** and [Ti(O*i*Pr)$_4$] with a catalyst loading of 20 mol-%. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC with a Chiralpak AD-H column.

94% *ee*, Table 8, Entry 2). The corresponding concentration of catalyst was 0.05 M.

Catalyst Loading

The amount of catalyst was found to be an important factor that influences the enantioselectivity and yield of the HDA reaction. The catalyst loading was changed from 40 mol-% to 1 mol-%; the results are listed in Table 9. A higher amount of catalyst gave a worse result, probably due to the high concentration causing aggregation of the catalyst (Table 9, Entry 1). There was no difference in the enantioselectivity and no significant loss in the yield with catalyst loadings between 20 mol-% and 5 mol-% (Table 9, Entries 2–4). However, when the catalyst loading was reduced to 2 mol-% and 1 mol-%, the enantioselectivities and yields decreased sharply (Table 9, Entries 5 and 6). The optimal catalyst loading was 5 mol-%, at this point, with a concentration of catalyst of 0.05 M, which is the same value determined earlier (Table 8, Entry 2). This extensive screening showed that the optimized catalytic system is 5 mol-% Ti^{IV}–**L13**, 0.25 M aldehyde with 1.5 equiv. of **1b** in 1 mL of CH_2Cl_2 at 0 °C for 72 h.

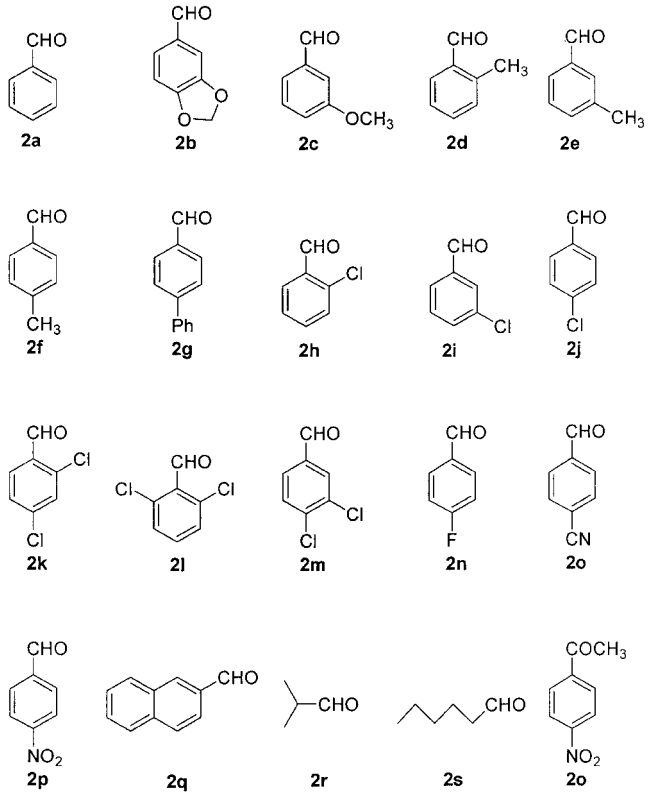
Table 9. The effect of catalyst loading on the asymmetric HDA reaction.[a]

Entry	Catalyst loading [mol-%]	Yield [%][b]	*ee* [%][c]
1	40	56	84
2	20	76	93
3	10	73	93
4	5	71	93
5	2	43	82
6	1	20	78

[a] All reactions were performed with benzaldehyde (0.25 mmol) and **1b** (0.375 mmol) in 1 mL of CH_2Cl_2 at 0 °C for 72 h. Catalysts: 1.1:1 molar ratio of ligand **L13** and [Ti(O*i*Pr)$_4$]. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC, using Chiralpak AD-H column.

Substrate Generality

Encouraged by the results obtained with benzaldehyde, we investigated the enantioselective HDA reaction of **1b** with a variety of other aldehydes (Scheme 3), most of which gave products with high enantioselectivities (up to 99% *ee*, Table 10). As can be seen from these data, there are significant electronic and steric effects of the aromatic ring's groups on the reactivity. With an enhancement of the groups' electron-donating capability from Cl to CH_3 and OCH_3, the reactivity was reduced (Table 10, Entries 9, 5, and 3), and with an enhancement of the groups' electron-withdrawing capability from Cl to CN and NO_2 the reactivity was also reduced (Table 10, Entries 10, 15, and 16). Appropriate electron-withdrawing groups on the substituted benzaldehydes did, however, give higher enantioselectivities and yields (Table 10, Entries 8 and 10), although the stronger electron-withdrawing and -donating groups generally show lower reactivity (Table 10, Entries 14–16 and Entries 2–7). The reactions of chloro-substituted benzaldehydes with diene **1b** occurred smoothly (Table 10, Entries 8–



Scheme 3. Substrates applied to the HDA reaction of the Brassard diene.

Table 10. Asymmetric hetero-Diels–Alder reaction of **1b** with aldehydes promoted by Ti–**L13**.[a]

Entry	Substrate	Yield [%] [b]	*ee* [%][c]
1	benzaldehyde (**2a**)	71	93
2	piperonal (**2b**)	21	88
3	*m*-anisaldehyde (**2c**)	45	96
4	*o*-tolualdehyde (**2d**)	24	92
5	*m*-tolualdehyde (**2e**)	53	93
6	*p*-tolualdehyde (**2f**)	36	90
7	*p*-phenylbenzaldehyde (**2g**)	46	95
8	*o*-chlorobenzaldehyde (**2h**)	70	99
9	*m*-chlorobenzaldehyde (**2i**)	70	90
10	*p*-chlorobenzaldehyde (**2j**)	87	97
11	2,4-dichlorobenzaldehyde (**2k**)	67	95
12	2,6-dichlorobenzaldehyde (**2l**)	N.D.	–
13	3,4-dichlorobenzaldehyde (**2m**)	54	87
14	*p*-fluorobenzaldehyde (**2n**)	53	93
15	*p*-cyanobenzaldehyde (**2o**)	61	90
16	*p*-nitrobenzaldehyde (**2p**)	56	91
17	2-naphthylbenzaldehyde (**2q**)	61	96
18	isobutyral (**2r**)	48(54)	21(75)[16]
19	*n*-hexanal (**2s**)	26	7
20	*p*-nitroacetophenone (**2t**)	66	7

[a] All reactions were performed with aldehyde (0.25 mmol) and **1b** (0.375 mmol) in 1 mL of toluene at 0 °C for 72 h. Catalysts: 1.1:1 molar ratio of ligand/[Ti(O*i*Pr)$_4$], with a catalyst loading of 5 mol-%. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC with a Chiralpak AD-H column.

10). Dichloro-substituted benzaldehydes were also used in this reaction: 2,4- and 3,4-substituted benzaldehydes gave good results (Table 10, Entries 11 and 13), but the 2,6-substituted benzaldehyde gave no product (Table 10, Entry 12). This could be due to larger steric hindrance than in the others, as the carbon atom of the carbonyl moiety is surrounded by the two chlorine atoms and catalyst. Moreover, the *meta* position of the substituted benzaldehydes has more influence on both reactivity and enantioselectivity than the *ortho* or *para* position (Table 10, Entries 3, 5, and 9). A condensed-ring aldehyde also gives high enantioselectivity (Table 10, Entriy 17). All in all, the reactions of **1b** with aromatic aldehydes proceed smoothly to give the desired lactones in high enantioselectivities. However, when isobutyral, *n*-hexanal, and *p*-nitroacetophenone were examined in this HDA reaction, the results were disappointing, with very low enantioselective excess (Table 10, Entries 18–20). The HDA reaction between isobutyral and the Brassard diene was promoted by (*R*)-BINOL–Ti(O*i*Pr)$_4$, and an enantiomeric excess of 75% could be achieved.[16] This shows that the Ti^{IV}–**L13** complex is an excellent catalyst for the conversion of the Brassard diene with aromatic aldehydes but not with aliphatic aldehydes.

Mechanism Studies

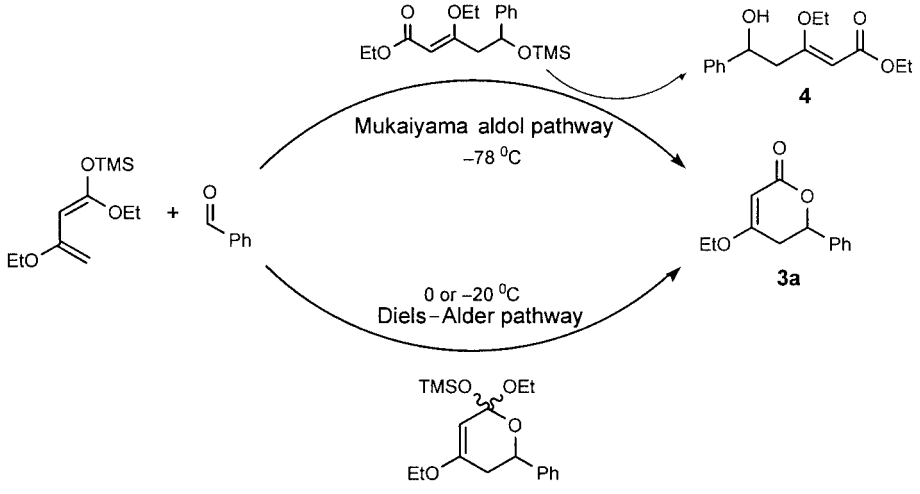
Finally, to determine the mechanism of this kind of HDA reaction, we performed some experiments to clarify whether the reaction proceeds by the Mukaiyama aldol pathway or the Diels–Alder pathway (Scheme 4). When the reaction was performed at 0 or –20 °C, **3a** (94% *ee*) and a trace of **4** could be directly obtained by purification through a silica gel column at the end of the reaction without treatment with TFA or other workup. However, when the reaction was carried out at –78 °C, most of the product obtained by the same procedure was **4** in 35% yield and 30% *ee*. Its structure was confirmed by NMR as the aldol product. The enantiomeric excess of **3a** was up to 99% with 12% yield. When the reaction mixture above was treated with TFA, which transforms **4** into **3a** by a cyclization reaction, the final enantiomeric excess of **3a** was reduced sharply to 43%. These results indicate that the reaction temperature has an influence on the reaction pathway: at higher temperature (0 °C), the reaction mostly follows the Diels–Alder pathway, and at lower temperature (–78 °C) it follows the Mukaiyama aldol pathway.

Conclusions

In conclusion, we have developed a series of titanium(IV) tridentate Schiff-base complexes that promote the synthesis of δ-lactones by the HDA reaction. The titanium(IV) complex with ligand **L13** exhibits excellent chiral induction in the reaction of **1b** with aromatic aldehydes under mild conditions. However, this complex gives worse enantioselectivities with aliphatic aldehydes. The substituents on the chiral Schiff-base ligands have a strong influence on the yield and enantioselectivity of the reaction. Ligand **L13** exhibits a high chiral induction in the Ti^{IV}-catalyzed HDA reaction, affording 6-substituted 4-ethoxy-5,6-dihydropyran-2-one in up to 99% *ee*. The mechanism of the HDA reaction between the Brassard diene and benzaldehyde in the presence of the (Schiff base)Ti^{IV} complex was studied. The results indicate that the reaction temperature influences the reaction pathway: at higher temperature (0 °C), the reaction mostly follows the Diels–Alder pathway, and at lower temperature (–78 °C) it follows the Mukaiyama aldol pathway. Further efforts will be devoted to the understanding of the difference between the Brassard diene and Brassard diene-type derivatives, and searching for effective catalysts for aliphatic aldehydes.

Experimental Section

General Method: Unless otherwise noted, all non-aqueous reactions were carried out under dry nitrogen in dried glassware. All manipulations involving [Ti(O*i*Pr)$_4$] were performed using standard Schlenk techniques. The ^{1}H and ^{13}C NMR spectra were recorded



Scheme 4. Mechanism of HDA reaction between **1b** and aldehyde.

at 600 MHz and 150 MHz (Bruker Avance), respectively. The chemical shifts are reported in ppm downfield from $CDCl_3$ (δ = 7.27 ppm) for ^1H NMR and relative to the the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Coupling constants in ^1H NMR are given in Hz. HR mass spectra were recorded with a BRUKER-APEX-2 (SIMS). Optical rotation data were recorded with a Perkin–Elmer Polarimeter-341. The enantiomeric excess (*ee*) of the products was determined by HPLC using Chiralpak AD-H or Chiralcel OJ columns with hexane/2-propanol as eluent, and the retention times were compared to corresponding racemic samples.

Materials: Toluene, THF, and Et_2O were freshly distilled from sodium/benzophenone ketyl. CH_2Cl_2 was distilled freshly from CaH_2. Brassard diene **1b** was prepared from ethyl 3-ethoxybut-2-enoate[17] according to a literature procedure.[11] Ligands **L5**–**19** were prepared[15] from aminoethanol and substituted salicylaldehydes, purchased from Aldrich, or prepared from the corresponding phenols. [Ti(O*i*Pr)$_4$] was distilled and stored as a 1.0 M solution in toluene. All aldehydes were purchased from Acros, Aldrich, or Fluka. Liquid aldehydes were distilled in vacuo prior to use, and solid aldehydes were used directly without further purification. Racemic samples of **3a**–**t** were prepared with anhydrous $ZnCl_2$ or Et_2AlCl as the catalyst.

Typical Procedure: [Ti(O*i*Pr)$_4$] (12.5 μL, 1 M in toluene, 0.0125 mmol) was stirred with **2a** (5.9 mg, 0.01375 mmol) in CH_2Cl_2 (0.5 mL) at 35 °C for 1 h under nitrogen. The mixture was then cooled to room temperature, and benzaldehyde (25 μL, 0.25 mmol) and 0.5 mL of dry CH_2Cl_2 were added. The reaction solution was stirred for 0.5 h, then cooled to –20 °C, and Brassard diene **1b** (85 μL, 0.375 mmol) added. The reaction mixture was stirred at 0 °C for 72 h before quenched with five drops of TFA. After stirring for an additional 2 h, the mixture was neutralized with saturated $NaHCO_3$ (2 mL) and partitioned between Et_2O and water twice. The combined organic layers were washed with saturated brine and then dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent 3:1 petroleum ether/ethyl acetate) to afford the cycloadduct **3a** in 71% yield with 93% *ee* [determined by HPLC on Chiralpak AD-H Column, hexane/2-propanol (95:5), flow rate 1.0 mL min^{-1}, t_{major} = 19.83 min, t_{minor} = 23.11 min]. $[\alpha]_D^{20}$ = +160 (c = 0.16, CH_2Cl_2).

4-Ethoxy-6-phenyl-5,6-dihydropyran-2-one (3a): The *ee* was determined by HPLC using a Chiralpak AD-H column (95:5 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 19.8 min, t_{minor} = 23.1 min). Colorless needle crystals (after recrystallization from ethyl acetate/hexane); m.p. 76–77 °C. $[\alpha]_D^{20}$ = +160.0 (c = 0.160, CH_2Cl_2, 93% *ee*; 71% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.43–7.35 (m, 5 H, Ph-H), 5.44 (dd, J = 12.2, 3.8 Hz, 1 H, PhCH-O), 5.23 (d, J = 1.4 Hz, 1 H, =CH), 4.01 (m, 2 H, OCH_2), 2.83 (ddd, J = 17.2, 12.2, 1.4 Hz, 1 H, CH_AH_B), 2.60 (dd, J = 17.2, 4.0 Hz, 1 H, CH_AH_B), 1.41 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.0, 167.3, 138.5, 128.9, 128.8, 126.2, 91.0, 77.4, 65.2, 35.5, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 219.1016; found 219.1018.

6-(Benzo[*d*][1,3]dioxol-5-yl)-4-ethoxy-5,6-dihydropyran-2-one (3b): The *ee* was determined by HPLC using a Chiralcel OJ column (90:10 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{minor} = 43.3 min, t_{major} = 47.4 min). White solid; m.p. 128–129 °C. $[\alpha]_D^{20}$ = +114.7 (c = 0.068, CH_2Cl_2, 88% *ee*; 21% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 6.92 (d, J = 1.5 Hz, 1 H, Ph-H), 6.86 (dd, J = 8.0, 1.1 Hz, 1 H, Ph-H), 6.81 (d, J = 8.0 Hz, 1 H, Ph-H), 5.98 (s, 2 H, OCH_2O), 5.33 (dd, J = 12.2, 3.8 Hz, 1 H, PhCH-O), 5.20 (d, J = 1.4 Hz, 1 H, =CH), 4.00 (m, 2 H, OCH_2), 2.80 (ddd, J = 17.1, 12.2, 1.4 Hz, 1 H, CH_AH_B), 2.53 (dd, J = 17.1, 3.8 Hz, 1 H, CH_AH_B), 1.40 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.9, 167.2, 148.2, 148.0, 132.4, 120.0, 108.5, 106.9, 101.5, 90.9, 77.3, 65.2, 35.6, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 263.0914; found 263.0918.

4-Ethoxy-6-(3-methoxyphenyl)-5,6-dihydropyran-2-one (3c): The *ee* was determined by HPLC using a Chiralcel OJ column (90:10 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{minor} = 23.7 min, t_{major} = 27.0 min). Pale-yellow solid; m.p. 78–80 °C. $[\alpha]_D^{20}$ = +142.9 (c = 0.112, CH_2Cl_2, 96% *ee*; 45% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.32–6.89 (m, 5 H, Ph-H), 5.42 (dd, J = 12.2, 3.8 Hz, 1 H, PhCH-O), 5.22 (s, 1 H, =CH), 4.00 (m, 2 H, OCH_2), 3.83 (s, 3 H, OCH_3), 2.82 (dd, J = 17.2, 12.2 Hz, 1 H, CH_AH_B), 2.60 (dd, J = 17.2, 3.8 Hz, 1 H, CH_AH_B), 1.41 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.0, 167.3, 160.1, 140.1, 129.9, 118.3, 114.4, 111.6, 91.0, 65.2, 55.5, 35.5, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 249.1121; found 249.1125.

4-Ethoxy-6-(2-methylphenyl)-5,6-dihydropyran-2-one (3d): The *ee* was determined by HPLC using a Chiralpak AD-H column (96:4 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 20.3 min, t_{minor} = 23.0 min). Pale-yellow solid; m.p. 59–60 °C. $[\alpha]_D^{20}$ = +169.6 (c = 0.112, CH_2Cl_2, 92% *ee*; 24% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.53–7.19 (m, 5 H, Ph-H), 5.63 (dd, J = 12.6, 3.6 Hz, 1 H, PhCH-O), 5.24 (d, J = 1.3 Hz, 1 H, =CH), 4.02 (m, 2 H, OCH_2), 2.82 (ddd, J = 17.2, 12.7, 1.4 Hz, 1 H, CH_AH_B), 2.52 (dd, J = 17.3, 3.6 Hz, 1 H, CH_AH_B), 2.38 (s, 3 H, $PhCH_3$), 1.42 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.2, 167.5, 136.5, 135.0, 130.9, 128.7, 126.7, 126.3, 90.9, 74.8, 65.2, 34.4, 19.3, 14.3 ppm. HRMS: calcd. for $[M + H]^+$ 233.1172; found 233.1175.

4-Ethoxy-6-(3-methylphenyl)-5,6-dihydropyran-2-one (3e): The *ee* was determined by HPLC using a Chiralpak AD-H column (95:5 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 15.6 min, t_{minor} = 18.0 min). Pale-yellow solid; m.p. 87–88 °C. $[\alpha]_D^{20}$ = +173.2 (c = 0.112, CH_2Cl_2, 93% *ee*; 53% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2 H, Ph-H), 7.20–7.17 (m, 2 H, Ph-H), 5.40 (dd, J = 12.2, 3.8 Hz, 1 H, PhCH-O), 5.22 (d, J = 1.2 Hz, 1 H, =CH), 4.00 (m, 2 H, OCH_2), 2.82 (ddd, J = 17.2, 12.3, 1.3 Hz, 1 H, CH_AH_B), 2.59 (dd, J = 17.2, 3.8 Hz, 1 H, CH_AH_B), 2.38 (s, 3 H, $PhCH_3$), 1.41 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.0, 167.4, 138.7, 138.5, 129.5, 128.7, 126.9, 123.2, 91.0, 77.4, 65.1, 35.5, 21.6, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 233.1172; found 233.1171.

4-Ethoxy-6-(4-methylphenyl)-5,6-dihydropyran-2-one (3f): The *ee* was determined by HPLC using a Chiralcel OJ column (94:6 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 30.0 min, t_{minor} = 36.8 min). Pale-yellow solid; m.p. 58–60 °C. $[\alpha]_D^{20}$ = +154.6 (c = 0.126, CH_2Cl_2, 90% *ee*; 36% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.31–7.20 (m, 4 H, Ph-H), 5.40 (dd, J = 12.2, 3.8 Hz, 1 H, PhCH-O), 5.22 (s, 1 H, =CH), 4.00 (m, 2 H, OCH_2), 2.82 (dd, J = 17.2, 12.3 Hz, 1 H, CH_AH_B), 2.57 (dd, J = 17.2, 3.8 Hz, 1 H, CH_AH_B), 2.37 (s, 3 H, $PhCH_3$), 1.42 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.0, 167.5, 138.6, 135.6, 129.5, 126.2, 91.0, 77.4, 65.1, 35.5, 21.4, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 233.1172; found 233.1176.

4-Ethoxy-6-(4-phenylphenyl)-5,6-dihydropyran-2-one (3g): The *ee* was determined by HPLC using a Chiralcel OJ column (80:20 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{minor} = 30.5 min, t_{major} = 36.0 min). Yellow solid; m.p. 123–124 °C. $[\alpha]_D^{20}$ = +148.1 (c = 0.104, CH_2Cl_2, 95% *ee*; 46% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.64–7.60 (m, 4 H, Ph-H), 7.51–7.45 (m, 4 H, Ph-H), 7.37 (m, 1 H, Ph-H), 5.49 (dd, J = 12.1, 3.8 Hz, 1 H, PhCH-O), 5.24 (d, J =

1.4 Hz, 1 H, =CH), 4.01 (m, 2 H, OCH_2), 2.87 (ddd, J = 17.1, 12.2, 1.4 Hz, 1 H, CH_AH_B), 2.64 (dd, J = 17.2, 3.8 Hz, 1 H, CH_AH_B), 1.42 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.9, 167.2, 141.7, 140.7, 137.5, 129.0, 127.7, 127.6, 127.3, 126.7, 91.0, 77.4, 65.2, 35.4, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 295.1329; found 295.1325.

6-(2-Chlorophenyl)-4-ethoxy-5,6-dihydropyran-2-one (3h): The *ee* was determined by HPLC using a Chiralpak AD-H column (98:2 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 26.1 min, t_{minor} = 29.9 min). Pale-yellow solid; m.p. 85–86 °C. $[\alpha]_D^{20}$ = +270.2 (c = 0.124, CH_2Cl_2, 99% *ee*; 70% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.69–7.67 (m, 1 H, Ph-H), 7.39–7.35 (m, 2 H, Ph-H), 7.32–7.29 (m, 1 H, Ph-H), 5.80 (dd, J = 12.3, 3.8 Hz, 1 H, PhCH-O), 5.24 (d, J = 1.3 Hz, 1 H, =CH), 4.02 (m, 2 H, OCH_2), 2.78 (ddd, J = 17.2, 12.2, 3.8 Hz, 2 H, CH_AH_B), 2.62 (ddd, J = 17.2, 12.2, 1.4 Hz, 1 H, CH_AH_B), 1.42 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.0, 167.2, 136.5, 131.5, 129.8, 127.7, 127.6, 90.8, 74.4, 65.3, 34.1, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 253.0626; found 253.0632.

6-(3-Chlorophenyl)-4-ethoxy-5,6-dihydropyran-2-one (3i): The *ee* was determined by HPLC using a Chiralpak AD-H column (95:5 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 17.9 min, t_{minor} = 21.7 min). Pale-yellow solid; m.p. 114–116 °C. $[\alpha]_D^{20}$ = +161.0 (c = 0.118, CH_2Cl_2, 90% *ee*; 70% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.44 (s, 1 H, Ph-H), 7.34–7.29 (m, 3 H, Ph-H), 5.41 (dd, J = 12.2, 3.9 Hz, 1 H, PhCH-O), 5.22 (d, J = 1.5 Hz, 1 H, =CH), 4.01 (m, 2 H, OCH_2), 2.79 (ddd, J = 17.2, 12.2, 1.4 Hz, 1 H, CH_AH_B), 2.61 (dd, J = 17.1, 4.0 Hz, 1 H, CH_AH_B), 1.41 (t, J = 7.1 Hz, 1 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.7, 166.8, 140.6, 134.9, 130.2, 128.9, 126.4, 124.2, 91.0, 76.4, 65.3, 35.4, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 253.0626; found 253.0624.

6-(4-Chlorophenyl)-4-ethoxy-5,6-dihydropyran-2-one (3j): The *ee* was determined by HPLC using a Chiralpak AD-H column (95:5 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 23.9 min, t_{minor} = 29.1 min). Pale-yellow solid; m.p. 103–104 °C. $[\alpha]_D^{20}$ = +151.9 (c = 0.104, CH_2Cl_2, 97% *ee*; 87% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 4 H, Ph-H), 5.41 (dd, J = 12.1, 3.8 Hz, 1 H, PhCH-O), 5.22 (s, 1 H, =CH), 4.00 (m, 2 H, OCH_2), 2.77 (dd, J = 17.2, 12.1 Hz, 1 H, CH_AH_B), 2.59 (dd, J = 17.2, 3.9 Hz, 1 H, CH_AH_B), 1.40 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.7, 167.0, 137.1, 134.6, 129.1, 127.6, 91.0, 76.6, 65.3, 35.4, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 253.0626; found 253.0630.

6-(2,4-Dichlorophenyl)-4-ethoxy-5,6-dihydropyran-2-one (3k): The *ee* was determined by HPLC using a Chiralpak AD-H column (98:2 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 26.6 min, t_{minor} = 30.8 min). White solid; m.p. 100–101 °C. $[\alpha]_D^{20}$ = +243.4 (c = 0.12, CH_2Cl_2, 95% *ee*, 67% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.5 Hz, 1 H, Ph-H), 7.41 (d, J = 2.1 Hz, 1 H, Ph-H), 7.35 (dd, J = 8.5, 2.0 Hz, 1 H, Ph-H), 5.74 (dd, J = 12.4, 3.8 Hz, 1 H, PhCH-O), 5.23 (d, J = 1.4 Hz, 1 H, =CH), 4.02 (m, 2 H, OCH_2), 2.76 (dd, J = 17.2, 3.8 Hz, 1 H, CH_AH_B), 2.58 (ddd, J = 17.2, 12.4, 1.4 Hz, 1 H, CH_AH_B), 1.42 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.8, 166.8, 135.1, 135.0, 132.2, 129.6, 128.7, 128.0, 90.8, 73.9, 65.4, 34.1, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 287.0236; found 287.0235.

6-(2,6-Dichlorophenyl)-4-ethoxy-5,6-dihydropyran-2-one (3l): The racemic mixture of enantiomers was separated by HPLC using a Chiralpak AD-H column (90:10 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_1 = 13.0 min, t_2 = 13.7 min). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.0 Hz, 2 H, Ph-H), 7.24 (t, J = 8.0 Hz, 1 H, Ph-H), 6.21 (dd, J = 13.5, 4.6 Hz, 1 H, PhCH-O), 5.24 (d, J = 1.7 Hz, 1 H, =CH), 4.03 (m, 2 H, OCH_2), 3.46 (ddd, J = 17.3, 13.5, 1.6 Hz, 1 H, CH_AH_B), 2.40 (dd, J = 17.3, 4.6 Hz, 1 H, CH_AH_B), 1.42 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.6, 166.6, 135.5, 132.3, 130.5, 129.7, 90.9, 73.7, 65.2, 30.6, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 287.0236; found 287.0240.

6-(3,4-Dichlorophenyl)-4-ethoxy-5,6-dihydropyran-2-one (3m): The *ee* was determined by HPLC using a Chiralpak AD-H column (95:5 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 20.0 min, t_{minor} = 28.9 min). White solid; m.p. 74–75 °C. $[\alpha]_D^{20}$ = +139.1 (c = 0.11, CH_2Cl_2, 87% *ee*, 54% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.54 (d, J = 2.0 Hz, 1 H, Ph-H), 7.47 (d, J = 8.4 Hz, 1 H, Ph-H), 7.25 (dd, J = 8.4, 2.0 Hz, 1 H, Ph-H), 5.39 (dd, J = 12.1, 3.9 Hz, 1 H, PhCH-O), 5.21 (d, J = 1.3 Hz, 1 H, =CH), 4.00 (m, 2 H, OCH_2), 2.75 (ddd, J = 17.1, 12.1, 1.3 Hz, 1 H, CH_AH_B), 2.60 (dd, J = 17.1, 3.9 Hz, 1 H, CH_AH_B), 1.41 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.5, 166.6, 138.8, 133.2, 132.9, 130.9, 128.2, 125.4, 91.0, 75.8, 65.3, 35.3, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 287.0236; found 287.0240.

4-Ethoxy-6-(4-fluorophenyl)-5,6-dihydropyran-2-one (3n): The *ee* was determined by HPLC using a Chiralpak AD-H column (93:7 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 16.8 min, t_{minor} = 20.3 min). Pale-yellow solid; m.p. 64–65 °C. $[\alpha]_D^{20}$ = +164.5 (c = 0.104, CH_2Cl_2, 93% *ee*; 53% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.39 (m, 2 H, Ph-H), 7.10–7.07 (m, 2 H, Ph-H), 5.41 (dd, J = 12.2, 3.8 Hz, 1 H, PhCH-O), 5.21 (d, J = 1.5 Hz, 1 H, =CH), 4.00 (m, 2 H, OCH_2), 2.79 (ddd, J = 17.1, 12.2, 1.5 Hz, 1 H, CH_AH_B), 2.57 (dd, J = 17.1, 3.8 Hz, 1 H, CH_AH_B), 1.40 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.83, 167.08, 163.75, 162.11, 134.41, 134.38, 128.10, 128.76, 115.91, 115.76, 90.96, 76.72, 65.22, 35.51, 14.21 ppm. HRMS: calcd. for $[M + H]^+$ 237.0921; found 237.0916.

6-(4-Cyanophenyl)-4-ethoxy-5,6-dihydropyran-2-one (3o): The *ee* was determined by HPLC using a Chiralpak AD-H column (85:15 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 19.2 min, t_{minor} = 22.8 min). Pale-yellow solid; m.p. 71–72 °C. $[\alpha]_D^{20}$ = +181.9 (c = 0.116, CH_2Cl_2, 90% *ee*; 61% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.72, (d, J = 8.4 Hz, 2 H, Ph-H), 7.56 (d, J = 8.2 Hz, 2 H, Ph-H), 5.49 (dd, J = 12.0 Hz, 3.9, 1 H, PhCH-O), 5.24 (d, J = 1.3 Hz, 1 H, =CH), 4.02 (m, 2 H, OCH_2), 2.76 (ddd, J = 17.1, 12.0, 1.3 Hz, 1 H, CH_AH_B), 2.64 (dd, J = 17.1, 3.9 Hz, 1 H, CH_AH_B), 1.42 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.4, 166.4, 143.7, 132.8, 126.8, 118.5, 112.7, 91.0, 76.2, 65.4, 35.3, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 244.0968; found 244.0976.

4-Ethoxy-6-(4-nitrophenyl)-5,6-dihydropyran-2-one (3p): The *ee* was determined by HPLC using a Chiralpak AD-H column (85:15 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 20.2 min, t_{minor} = 26.1 min). Yellow solid; m.p. 92–93 °C. $[\alpha]_D^{20}$ = +159.3 (c = 0.108, CH_2Cl_2, 91% *ee*; 56% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 8.28 (d, J = 8.8 Hz, 2 H, Ph-H), 7.63 (d, J = 8.7 Hz, 2 H, Ph-H), 5.55 (dd, J = 12.1, 4.1 Hz, 1 H, PhCH-O), 5.25 (d, J = 1.1 Hz, 1 H, =CH), 4.03 (m, 2 H, OCH_2), 2.78 (ddd, J = 17.1, 12.1, 1.2 Hz, 1 H, CH_AH_B), 2.67 (dd, J = 17.1, 4.1 Hz, 1 H, CH_AH_B), 1.42 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.3, 166.3, 148.2, 145.5, 126.9, 124.2, 91.0, 76.0, 65.5, 35.3, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 264.0866; found 264.0874.

4-Ethoxy-6-(naphthalen-3-yl)-5,6-dihydropyran-2-one (3q): The *ee* was determined by HPLC using a Chiralpak AD-H column (92:8 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 19.5 min, t_{minor} = 24.5 min). White solid; m.p. 125–126 °C. $[\alpha]_D^{20}$ = +145.5 (c = 0.176, CH_2Cl_2, 96% *ee*; 61% yield). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.91–7.86 (m, 4 H, Ar-H), 7.63 (m, 3 H, Ar-H), 5.61 (dd, J =

12.1, 3.8 Hz, 1 H, ArCH-O), 5.26 (s, 1 H, =CH), 4.02 (m, 2 H, OCH_2), 2.91 (dd, J = 17.2, 12.1 Hz, 1 H, CH_AH_B), 2.70 (dd, J = 17.2, 3.8 Hz, 1 H, CH_AH_B), 1.42 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.92, 167.27, 135.92, 133.46, 133.32, 128.79, 128.35, 127.93, 126.69, 126.66, 125.32, 123.69, 91.04, 65.18, 35.53, 14.23 ppm. HRMS: calcd. for $[M + H]^+$ 269.1172; found 269.1165.

4-Ethoxy-6-isopropyl-5,6-dihydropyran-2-one (3r): The *ee* was determined by GC using a Chiralsil DEX CB column (150 °C; t_{major} = 24.2 min, t_{minor} = 25.3 min). Yellow oil; 21% *ee*; 48% yield. ^1H NMR (600 MHz, $CDCl_3$): δ = 5.11 (d, J = 1.7 Hz, 1 H, =CH), 4.13 (m, 1 H, -CH-O), 3.95 (m, 2 H, OCH_2), 2.51 (ddd, J = 17.0, 12.8, 1.6 Hz, 1 H, CH_AH_B), 2.26 (dd, J = 17.0, 3.6 Hz, 1 H, CH_AH_B), 1.97 (m, 1 H, CH), 1.38 (t, J = 7.0 Hz, 3 H, CH_3), 1.04 (d, J = 6.7 Hz, 3 H, isopropyl-CH_3), 1.00 (d, J = 6.87 Hz, 3 H, isopropyl-CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.5, 168.0, 90.7, 80.7, 64.9, 32.1, 30.6, 18.2, 18.0, 14.2 ppm. HRMS: calcd. for $[M + H]^+$ 185.1178; found 185.1017.

4-Ethoxy-6-pentyl-5,6-dihydropyran-2-one (3s): The *ee* was determined by GC using a Chiralsil DEX CB column (170 °C; t_{minor} = 29.3 min, t_{major} = 29.9 min). Yellow oil; 7% *ee*; 26% yield. ^1H NMR (600 MHz, $CDCl_3$): δ = 5.09 (d, J = 1.2 Hz, 1 H, =CH), 4.36 (m, 1 H, -CH-O), 3.95 (m, 2 H, OCH_2), 2.46 (ddd, J = 17.0, 12.0, 1.2 Hz, 1 H, CH_AH_B), 2.31 (dd, J = 17.0, 3.7 Hz, 1 H, CH_AH_B), 1.79 (m, 1 H, pentyl-H), 1.62 (m, 1 H, pentyl-H), 1.51 (m, 1 H, pentyl-H), 1.40 (m, 1 H, pentyl-H), 1.38 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.32 (m, 4 H, pentyl-H), 0.89 (t, J = 6.7 Hz, 3 H, pentyl-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.2, 167.9, 90.7, 76.1, 64.9, 34.9, 33.4, 31.7, 24.7, 22.7, 14.21, 14.16.

4-Ethoxy-6-methyl-6-(4-nitrophenyl)-5,6-dihydropyran-2-one (3t): The *ee* was determined by HPLC using a Chiralcel OD column (80:20 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{minor} = 13.6 min, t_{major} = 21.5 min). Yellow solid; m.p. 144–145 °C; 7% *ee*; 66% yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.8 Hz, 2 H, Ph-H), 7.59 (d, J = 8.8 Hz, 2 H, Ph-H), 5.09 (s, 1 H, =CH), 3.90 (m, 2 H, OCH_2), 2.98 (m, 2 H, cyclic-CH_2), 1.73 (s, 3 H, CH_3), 1.35 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm. HRMS: calcd. for $[M + H]^+$ 278.1023; found 278.1024.

Ethyl 3-Ethoxy-5-hydroxy-5-phenylpent-2-enoate (4): The *ee* was determined by HPLC using a Chiralpak AD-H column (92:8 hexane/2-propanol; flow rate: 1.0 mL min^{-1}; t_{major} = 19.5 min, t_{minor} = 24.5 min). Colorless oil; 30% *ee*; 35% yield.^1H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.37 (m, 4 H, Ph-H), 7.31 (m, 1 H, Ph-H), 5.10 (s, =CH), 4.96 (m, 1 H, HOC-H), 4.21 (m, 2 H, $=COCH_2$), 4.13 (q, J = 7.1 Hz, 2 H, $COOCH_2$), 2.59 (m, 2 H, $=CCH_2$), 2.35 (d, J = 2.9 Hz, 1 H, CO-H), 1.35 (t, J = 7.0 Hz, 3 H, $=COCH_2CH_3$), 1.27 (t, J = 7.1 Hz, 3 H, $COOCH_2CH_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.2, 165.1, 143.2, 128.6, 127.9, 125.6, 99.0, 72.2, 67.8, 59.6, 45.2, 15.4, 14.3 ppm.

(*R*)-3-{(*E*)-[(1*S*,2*R*)-2-Hydroxy-1,2-diphenylethylimino]methyl}-1-(2-{(*E*)-[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethylimino]methyl}-3-hydroxynaphth-4-yl)naphthalen-2-ol (L5): M.p. 104–105 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 2 H, N=CH), 7.81 (m, 4 H, Ph-H), 7.4–7.42 (m, 4 H, Ph-H), 7.36–7.20 (m, 20 H, Ph-H), 7.07 (d, J = 8.0 Hz, 2 H, Ph-H), 5.06 (d, 7.2 hz, 2 H, HOC-H), 4.55 (d, J = 7.2 Hz, 2 H, C=NC-H), 2.10 (br., 2 H, CO-H) ppm.

2-{[(1*S*,2*R*)-2-Hydroxy-1,2-diphenylethylimino]methyl}phenol (L6): M.p. 82–84 °C. ^1H NMR (600 MHz, $CDCl_3$): δ = 13.15 (s, 1 H, PhO-H), 8.08 (s, 1 H, N=CH), 7.40–7.26 (m, 10 H, Ph-H), 7.09 (d, J = 7.9 Hz,1 H, Ph-H), 6.95 (d, J = 7.9 Hz, 1 H, Ph-H), 6.82 (s, 1 H, Ph-H), 5.06 (d, J = 7.0 Hz, 1 H, HOC-H), 4.53 (d, J = 7.0 Hz, 1 H, C=NC-H), 2.06 (d, J = 2.0 Hz, 1 H, CO-H) ppm.

2-{[(1*S*,2*R*)-2-Hydroxy-1,2-diphenylethylimino]methyl}-4-methylphenol (L7): M.p. 123–124 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.92 (s, 1 H, PhO-H), 8.02 (s, 1 H, N=CH), 7.38–7.25 (m, 10 H, Ph-H), 7.09 (d, 8 Hz, 1 H, Ph-H), 6.85 (m, 2 H, Ph-H), 5.04 (dd, 7.2 Hz, 2 Hz, 1 H, HOC-H), 4.49 (d, J = 7.2 Hz, 1 H, C=NC-H), 2.22 (s, 3 H, Me), 2.11 (d, 2 Hz, 1 H, CO-H) ppm.

4-*tert*-Butyl-2-{[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethylimino]-methyl}phenol (L8): M.p. 168–170 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H, N=CH), 7.37–7.25 (m, 11 H, Ph-H), 7.07 (d, J = 2.4 Hz, 1 H, Ph-H), 6.88 (d, J = 8.8 Hz, 1 H, Ph-H), 5.06 (dd, J = 7.2, 2.8 Hz, 1 H, HOC-H), 4.53 (d, J = 7.2 Hz, 1 H, C=NC-H), 2.04 (d, J = 2.8 Hz, 1 H, CO-H), 1.24 (s, 9 H, *t*Bu) ppm.

2-{[(1*S*,2*R*)-2-Hydroxy-1,2-diphenylethylimino]methyl}-4-methoxyphenol (L9): M.p. 98–99 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.65 (s, 1 H, PhO-H), 8.03 (S, 1 H, N=CH), 7.40–7.27 (m, 10 H, Ph-H), 6.89 (m, 2 H, Ph-H), 6.59 (d, J = 1.6 Hz, 1 H, Ph-H), 5.05 (dd, J = 7.2, 2.8 Hz, 1 H, HOC-H), 4.50 (d, J = 7.2 Hz, 1 H, C=NC-H), 3.72 (s, 3 H, OMe), 2.04 (d, J = 2.8 Hz, 1 H, CO-H) ppm.

2-{[(1*S*,2*R*)-2-Hydroxy-1,2-diphenylethylimino]methyl}-4-nitrophenol (L10): M.p. 188–190 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 14.40 (s, 1 H, Ph-H), 8.19 (dd, J = 9.2, 5.6 Hz, 1 H, Ph-H), 8.10 (s, 1 H, N=CH), 8.07 (d, J = 2.8 Hz, 1 H, Ph-H), 7.42–7.23 (m, 10 H, Ph-H), 6.99 (d, J = 9.2 Hz, 1 H, Ph-H), 5.06 (dd, J = 7.2, 2.4 Hz, 1 H, HOC-H), 4.61 (d, J = 7.2 Hz, 1 H, C=NC-H), 2.08 (d, J = 2.4 Hz, 1 H, CO-H) ppm.

6-*tert*-Butyl-2-{[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethylimino]methyl}phenol (L11): M.p. 47–49 °C. ^1H NMR (600 MHz, $CDCl_3$): δ = 13.66 (s, 1 H, PhO-H), 8.09 (s, 1 H, N=CH), 7.43–7.25 (m,11 H), 6.95 (dd, J = 7.6, 1.4 Hz, 1 H, Ph-H), 6.75 (t, J = 7.6 Hz, 1 H, Ph-H), 5.08 (d, J = 7.2 Hz, 1 H, HOC-H), 4.50 (d, J = 7.2 Hz, 1 H, C=NC-H), 2.08 (d, J = 2.0 Hz, 1 H, CO-H), 1.45 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.8, 160.4, 140.4, 139.6, 137.5, 130.2, 129.9, 128.9, 128.3, 128.2, 127.4, 118.8, 118.0, 80.4, 78.6, 76.8, 35.0, 29.5 ppm. HRMS: calcd. for $[M + H]^+$ 374.2115; found 374.2122.

6-*tert*-Butyl-2-{[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethylimino]methyl}-4-methylphenol (L12): M.p. 47–48 °C. ^1H NMR (600 MHz, $CDCl_3$): δ = 13.40 (s, 1 H, PhO-H), 8.05 (s, 1 H, N=CH), 7.42–7.26 (m, 10 H, Ph-H), 7.11 (s, 1 H, Ph-H), 6.75 (s, 1 H, Ph-H), 5.06 (d, J = 7.0 Hz, 1 H, HOC-H), 4.49 (d, J = 7.0 Hz, 1 H, C=NC-H), 2.23 (s, 3 H, Me), 1.45 (s, 9 H, *t*Bu) ppm. HRMS: calcd. for $[M + H]^+$ 388.2271; found 388.2275.

4,6-Di-*tert*-butyl-2-{[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethylimino]methyl}phenol (L13): M.p. 59–61 °C. ^1H NMR (600 MHz, $CDCl_3$): δ = 13.40 (s, 1 H, PhO-H), 8.15 (s, 1 H, N=CH), 7.37–7.25 (m, 11 H, Ph-H), 6.92 (d, J = 2.4 Hz, 1 H, Ph-H), 5.08 (dd, J = 6.7, 3.0 Hz, 1 H, HOC-H), 4.51 (d, J = 6.7 Hz, 1 H, C=NC-H), 2.06 (d, J = 3.0 Hz, 1 H, CO-H), 1.44 (s, 9 H, *t*Bu), 1.25 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.3,158.1, 140.4, 140.3, 139.8, 136.8, 128.9, 128.3, 128.2, 128.1, 127.4, 126.5, 118.0, 80.2, 78.6, 35.2, 34.3, 31.6, 29.6 ppm. HRMS: calcd. for $[M + H]^+$ 430.2741; found 430.2742.

6-*tert*-Butyl-2-{[(1*S*,2*R*)-2-Hydroxy-1,2-diphenylethylimino]methyl}-4-nitrophenol (L14): M.p. 66–67 °C. ^1H NMR (600 MHz, $CDCl_3$): δ = 15.03 (s, 1 H, PhO-H), 8.20 (d, J = 2.7 Hz, 1 H, Ph-H), 8.12 (s, 1 H, N=CH)7.95 (d, J = 2.7 Hz, 1 H, Ph-H), 7.45–7.23 (m, 10 H, Ph-H), 5.10 (d, J = 6.7 Hz, 1 H, HOC-H), 4.61 (d, J = 6.7 Hz, 1 H, C=NC-H), 2.10 (d, J = 2.2 Hz, 1 H, CO-H), 1.47 (s, 9 H, *t*Bu) ppm. HRMS: calcd. for $[M + H]^+$ 419.1965; found 419.1976.

6-Adamantyl-4-*tert*-butyl-2-{[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethylimino]methyl}phenol (L15): M.p. 101–103 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 13.37 (s, 1 H, PhO-H), 8.14 (s, 1 H, N=C-H), 7.44–7.27 (m, 11 H, Ph-H), 6.90 (d, 2.2HZ, 1 H, Ph-H), 5.09 (dd, J = 6.8, 3.0 Hz, 1 H, HOC-H), 4.50 (d, J = 6.8 Hz, 1 H, C=NC-H), 2.30–2.11 (m, 9 H, adamantyl-H), 2.06 (d, J = 3.0 Hz, 1 H, CO-H), 1.82 (m, 6 H, adamantyl-H), 1.25 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.4, 158.4, 140.5, 140.3, 139.8, 137.1, 128.9, 128.4, 128.3, 128.1, 127.4, 126.4, 118.0, 80.4, 78.5, 40.5, 37.45, 37.40, 34.3, 31.7, 29.4 ppm. HRMS: calcd. for $[M + H]^+$ 508.3210; found 508.3203.

4,6-Dichloro-2-{[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethylimino]-methyl}phenol (L16): M.p. 59–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1 H, N=CH), 7.40–7.23 (m, 11 H, Ph-H), 6.96 (d, J = 2.4 Hz, 1 H, Ph-H), 5.03 (d, J = 7.2 Hz, 1 H, HOC-H), 4.51 (d, J = 7.2 Hz, 1 H, C=NC-H), 2.04 (br., 1 H, CO-H) ppm. HRMS: calcd. for $[M + H]^+$ 386.0709; found 386.0718.

4,6-Dibromo-2-{[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethylimino]-methyl}phenol (L17): M.p. 70–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H, N=CH), 7.66 (d, J = 2.4 Hz, 1 H, Ph-H), 7.41–7.24 (m, 10 H, Ph-H), 7.14 (d, J = 2.4 Hz, 1 H, Ph-H), 5.03 (d, J = 7.2 Hz, 1 H, HOC-H), 4.51 (d, J = 7.2 Hz, 1 H, C=NC-H), 2.04 (s, 1 H, CO-H) ppm. HRMS: calcd. for $[M + H]^+$ 473.9699; found 473.9702.

(1*R*,2*S*)-1-(3,5-Di-*tert*-butyl-2-hydroxybenzylideneamino)-2,3-dihydro-1*H*-inden-2-ol (L18): M.p. 62–63 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 13.12 (s, 1 H, PhO-H), 8.64 (s, 1 H, N=C-H), 7.43–7.19 (m, 6 H, Ph-H), 4.81 (d, J = 5.1 Hz, 1 H, C=NC-H), 4.70 (m, 1 H, HOC-H), 3.26 (dd, 15.8, 5.8 Hz, 1 H, CH_2), 3.14 (dd, 15.8, 4.8 Hz, 1 H, CH_2), 2.17 (d, J = 7.0 Hz, 1 H, CO-H), 1.42 (s, 9 H, *t*Bu), 1.33 (s, 9 H, *t*Bu) ppm. HRMS: calcd. for $[M + H]^+$ 366.2428; found 366.2436.

4,6-Di-*tert*-butyl-2-{[(*S*)-2-hydroxy-1-phenylethylimino]-methyl}phenol (L19): M.p. 48–49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.51 (s, 1 H, PhO-H), 8.51 (s, 1 H, N=CH), 7.43–7.29 (m, 6 H, Ph-H), 7.12(d, J = 2.0 Hz, 1 H, Ph-H), 4.47 (dd, J = 7.6, 5.6 Hz, 1 H, C=NC-H), 3.93 (m, 2 H, HOC-H), 2.17 (s, 1 H, CO-H), 1.46 (s, 9 H, *t*Bu), 1.30 (s, 9 H, *t*Bu) ppm. HRMS: calcd. for $[M + H]^+$ 354.2428; found 354.2434.

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[16] The reaction procedure is as follows: [Ti(O*i*Pr)$_4$] (50 μL, 1 M in toluene, 0.05 mmol) was stirred with (*R*)-BINOL (28.6 mg, 0.1 mmol) in TBME (0.5 mL) at 35 °C under nitrogen for 1 h. The mixture was then cooled to room temperature, and isobutyral (22 μL, 0.25 mmol) and 0.5 mL of dry TBME were added. The reaction solution was stirred for 0.5 h, then cooled to –20 °C, and Brassard diene **1b** (85 μL, 0.375 mmol) added. The reaction mixture was then stirred at 0 °C for 72 h before being quenched with five drops of TFA. After stirring for an additional 2 h, the mixture was neutralized with saturated $NaHCO_3$ (2 mL), and partitioned between Et_2O and water twice. The combined organic layers were washed with saturated brine and then dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent 3:1 petroleum ether/ethyl acetate) to afford the cycloadduct **3r** in 54% yield with 75% *ee* [determined by GC using a Chiralsil DEX CB column (150 °C; t_{major} = 24.2 min, t_{minor} = 25.3 min)].

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