# Highly Enantioselective Hetero-Diels–Alder Reaction of Brassard Diene with Aromatic Aldehydes
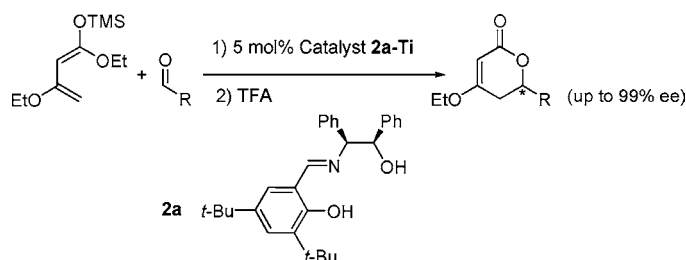
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## ABSTRACT



Hetero-Diels–Alder reactions of Brassard diene with aromatic aldehydes were carried out smoothly in the presence of titanium(IV) tridentate Schiff base complexes to give the corresponding chiral $\delta$-lactones in high enantioselectivities (up to 99% ee) under mild conditions.

As one of the most powerful reactions in organic synthesis, the catalytic asymmetric hetero-Diels−Alder (HDA) reaction[1] provides an effective protocol for preparing optically active six-membered ring compounds, dihydropyrans, dihydropyranones, etc.[2] Chiral 5,6-dihydropyran-2-one or $\alpha,\beta$-unsaturated $\delta$-lactone derivatives are key structural subunits of natural products with a wide range of biological activity,[3] such as antifungal and antitumor. Thus, synthetic methodology of $\delta$-lactones has been an area of intense research efforts. Many methods have been developed, such as the annulation of open-chained precursors,[4] the derivatization from a 2,3-dihydropyran-4-one,[2d,4e] and the two-step addition reaction of ene to dicarbonyl compounds.[4f] From the synthetic viewpoint, one of the most convenient ways to $\delta$-lactones is

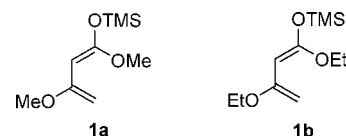based on a HDA reaction of Brassard diene[5] **1a** (Figure 1) with suitable aldehydes or ketones.



**Figure 1.** Structures of Brassard dienes **1a,b**.

The reactions of Brassard diene with aliphatic aldehydes in the presence of Eu(hfc)$_3$ were performed smoothly in high enantioselectivity.[6] However, the enantioselective approach of Brassard diene with aromatic aldehydes only gave a disappointing result; the enantiomeric excess (ee) value obtained was less than 5%.[6e] As the Brassard diene is prone to being destroyed by Lewis acids, recently a kind of polymer-supported Brassard diene[6f] was used in this reaction

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(1) For some recent reviews on the hetero-Diels−Alder reaction, see: (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (c) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

for a racemics library. As known, however, there is little research on Brassard diene in the HDA reaction, and no effective catalytic asymmetric system has been reported for the cycloaddition reaction of Brassard diene with aromatic aldehydes.

BINOL and its derivatives,[2d,e,i−m,7a−e] chiral $C_2$- symmetric bisoxazolines,[7f,g] and Schiff-base ligands[2f,g,4e,7h−l] such as salen ligands, aminoindanol-derived Schiff base ligand, and Nobin-derived Schiff base ligand, complexed with suitable metals such as aluminum, chromium, titanium, and other transition metals or nonmetals such as boron, have been successfully applied in the enantioselective HDA reaction. The tridentate Schiff base ligands derived from (1R,2S)-2-amino-1,2-diphenylethanol complexed with titanium have been used in the reactions of asymmetric cyanosilylation of aldehydes[8a] and asymmetric oxidation of *tert*-butyl disulfides.[8b]

**Figure 2.** Chiral ligands (**2a−f**) used in this paper.

Herein we describe an example of a highly enantioselective HDA reaction of Brassard diene with aromatic aldehydes catalyzed by titanium(IV) tridentate Schiff base complexes (Figure 2, Scheme 1).

**Scheme 1.** Hetero-Diels−Alder Reactions of Brassard Diene with Aldehydes

Considering the stability of Brassard diene, the methoxy group of Brassard diene **1a** was replaced with the ethoxy group to diene **1b**. Although there is only a small change in the structure, diene **1b** is more stable and easier to purify than **1a** and is synthesized easily through the Brassard procedure.[5]

Our studies started with benzaldehyde, **2a,** toluene, 0 °C, and 72 h as test substrate, ligand, solvent, reaction temperature, and reaction time, respectively. Several metals, such as Et$_2$Zn, AlEt$_3$, Et$_2$AlCl, TiCl$_4$, Zr(O$i$Pr)$_4$, Ti(O$i$Pr)$_2$Cl$_2$, and Ti(O$i$Pr)$_4$, were screened in the initial experiments. Most of them gave an ee value less than 33%. Only Ti(O$i$Pr)$_4$ can give a high ee, up to 93%. It was indicated that the counterions could decide the asymmetric induction capability of chiral catalysts in the HDA reaction.[9] Some additives, such as 4 Å MS[2k−m,7l] and acids[7l] applied successfully in the HDA

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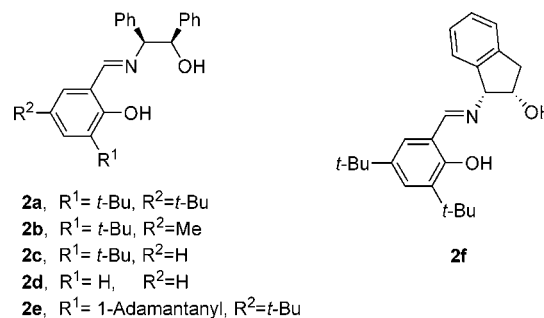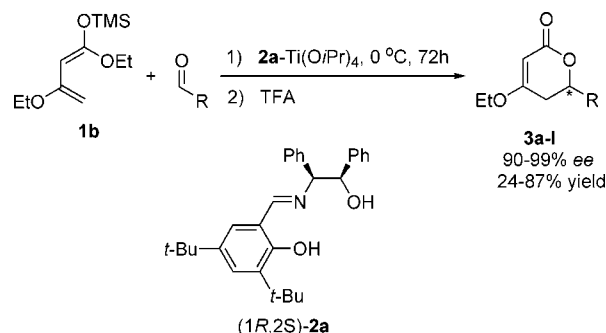
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reaction previously, were added to the system, but there followed much worse results. When 4 Å MS and benzoic acid were used, the ee decreased sharply from 93% to 76% and 74%, respectively. Perhaps the different structure of Brassard diene with Danishefsky's diene is the key reason. Togni speculated that double substitution at the terminus had deleterious consequences upon the enantioselectivity of this cycloaddition reaction.[6e]

By using the prescribed conditions to survey the chiral induction of these ligands (**2a**−**f**), the results (Table 1, entries

**Table 1.** Catalytic Enantioselective HDA Reactions of Brassard Diene with Benzaldehyde[a]

| entry | ligand | catalyst loading (mol %)[b] | $T$ (°C) | solvent | yield (%) | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **2a** | 20 | 0 | toluene | 58 | 92 |
| 2 | **2b** | 20 | 0 | toluene | 43 | 81 |
| 3 | **2c** | 20 | 0 | toluene | 45 | 76 |
| 4 | **2d** | 20 | 0 | toluene | 35 | 64 |
| 5 | **2e** | 20 | 0 | toluene | 54 | 85 |
| 6 | **2f** | 20 | 0 | toluene | 48 | 47[d] |
| 7 | **2a** | 20 | 0 | THF | 46 | 61 |
| 8 | **2a** | 20 | 0 | Et$_2$O | 42 | 89 |
| 9 | **2a** | 20 | 0 | CH$_2$Cl$_2$ | 76 | 93 |
| 10 | **2a** | 20 | 23 | CH$_2$Cl$_2$ | 74 | 81 |
| 11 | **2a** | 20 | −20 | CH$_2$Cl$_2$ | 48 | 94[e] |
| 12 | **2a** | 10 | 0 | CH$_2$Cl$_2$ | 73 | 93 |
| 13 | **2a** | 5 | 0 | CH$_2$Cl$_2$ | 71 | 93 |
| 14 | **2a** | 1 | 0 | CH$_2$Cl$_2$ | 20 | 78[e] |

[a] All reactions were performed with benzaldehyde (1 mmol) and Brassard diene (1.5 mmol) in 1 mL of solvent for 72 h. [b] Catalysts were composed of a 1.1:1 molar ratio of ligands to Ti(O$i$Pr)$_4$. [c] Enantioselectivities were determined by HPLC, using commercially Chiralpak AD-H column. [d] The product has a reverse configuration compared to the others. [e] Reaction time is 7 days.

1−6) showed that the *ortho* groups of phenol hydroxy in the ligand impact strongly the enantioselectivity of the catalyst. The bulkier *ortho* group, such as *tert*-butyl, can achieve a high ee value (Table 1, entry 1). However, adamantanyl resulted in a lower enantioselectivity (Table 1, entry 5). This can be attributed to its large steric hindrance. It was obvious that a suitable group in the ligand can enhance the match between substrate and catalyst and therefore result in higher enantioselectivity, but ligand **2f** would not perform the reaction with high enantioselectivity. It maybe partly attributed to the less flexible five-membered ring structure of **2f**; moreover, Ti was an inappropriate metal to the Jacobsen's catalyst[2f,g] in which the central metal was Cr.

Solvent survey revealed that toluene, Et$_2$O, and CH$_2$Cl$_2$ can provide products from the HDA reaction in high enantioselectivities (Table 1, entries 1, 8, and 9) with 58%, 42%, and 76% yield, respectively, but THF shows a strong solvent effect in which a rather low ee was found (Table 1, entry 7). Reaction temperature also influences the enantioselectivities of the HDA reaction of Brassard diene with aldehydes (Table 1, entries 9−11). Both enantioselectivity and yield can be achieved smoothly at 0 °C (Table 1, entry

9). The catalyst loading can be reduced to 5 mol % without loss of enantioselectivity, and the yields were decreased slightly, from 76% to 71% (Table 1, entries 9 and 13). However, when 1 mol % catalyst loading was used, the enantioselectivity was reduced to 78% and the yield was decreased sharply to 20%. Extensive screening showed the optimized catalytic system as 5 mol % **2a**-Ti(O$i$Pr)$_4$, 0.25 M aldehyde, 1.5 equiv of diene in 1 mL of CH$_2$Cl$_2$ at 0 °C.

Encouraged by the result obtained for the benzaldehyde, we investigated the enantioselective HDA reaction of Brassard diene with a variety of other aromatic aldehydes catalyzed by titanium(IV)-ligand **2a** complex, all of which gave rise to products with high enantioselectivities (up to 99% ee, Table 2). As can be seen from data for the reactions

**Table 2.** Asymmetric Hetero-Diels−Alder Reaction of Brassard Diene with Aromatic Aldehydes Promoted by Ligand **2a**[a]

| entry | aldehyde | yield (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | benzaldehyde | 71 | 93 |
| 2 | *m*-methoxy-benzaldehyde | 45 | 96 |
| 3 | *o*-methyl-benzaldehyde | 24 | 92 |
| 4 | *m*-methyl-benzaldehyde | 53 | 93 |
| 5 | *p*-methyl-benzaldehyde | 36 | 90 |
| 6 | *o*-chloro-benzaldehyde | 70 | 99 |
| 7 | *m*-chloro-benzaldehyde | 70 | 90 |
| 8 | *p*-chloro-benzaldehyde | 87 | 97 |
| 9 | *p*-fluoro-benzaldehyde | 53 | 93 |
| 10 | *p*-cyano-benzaldehyde | 61 | 90 |
| 11 | *p*-nitro-benzaldehyde | 56 | 91 |
| 12 | 2-naphthyl-aldehyde | 61 | 96 |

[a] All reactions were performed in 1 mL of CH$_2$Cl$_2$ with aldehyde (0.25 mmol) and Brassard diene (0.375 mmol), in the presence of 0.0125 mmol of Ti(O$i$Pr)$_4$ and 0.01375 mmol of **2a** at 0 °C for 72h. [b] Isolated yield. [c] Enantioselectivities were determined by HPLC, using commercially Chiralpak AD-H column or Chiralcel OJ column (entries 2 and 5).

of substituted benzaldehydes, there are significant electronic and steric effects of aromatic ring groups on reactivity. With the enhancement of a groups' electron-donating capability from Cl, CH$_3$, to OCH$_3$, the reactivity is reduced (Table 2, entries 7, 4, and 2). With the enhancement of a groups' electron-withdrawing capability from Cl, CN, to NO$_2$, the reactivity is also reduced (Table 2, entries 8, 10, and 11). Therefore, appropriate electron-withdrawing groups of substituted benzaldehydes can give higher enantioselectivities and yields (Table 2, entries 6 and 8); the stronger electron-withdrawing groups result in a drop in yield (Table 2, entries 9−11) and the electronic-donating groups generally show lower reactivity (Table 2, entries 2−5). The reactions of chlorine-substituted benzaldehydes with diene **1b** were carried out smoothly (Table 2, entries 6−8). Moreover, the *meta* position of substituted benzaldehydes has more influence on both reactivity and enantioselectivity than *ortho* or *para* position (Table 2, entries 2, 4, and 7). Condensed ring aldehyde also shows high enantioselectivity with moderate yield (Table 2, entry 12). In all cases, the reactions proceeded smoothly to give the desired lactones in high enantioselec-

tivities. It is noted that this is the first example of the highly enantioselective HDA reaction of Brassard diene with aromatic aldehydes.

In summary, we developed a kind of titanium(IV) tridentate Schiff base complex to promote the synthesis of δ-lactone by the HDA reaction. Titanium(IV)-ligand **2a** complex exhibits excellent chiral induction in the reaction of Brassard diene with aromatic aldehydes under mild conditions. Further studies are being directed toward elucidating the mechanism, as well as toward enlarging the substrate generality of this reaction.

**Supporting Information Available:** Experimental details and characterization data, including ^{1}H and ^{13}C NMR, HRMS spectra, and HPLC conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049364C