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Highly Enantio- and Diastereoselective Brassard Type Hetero-Diels−Alder Approach to 5-Methyl-Containing α,*β*-Unsaturated *δ*-Lactones

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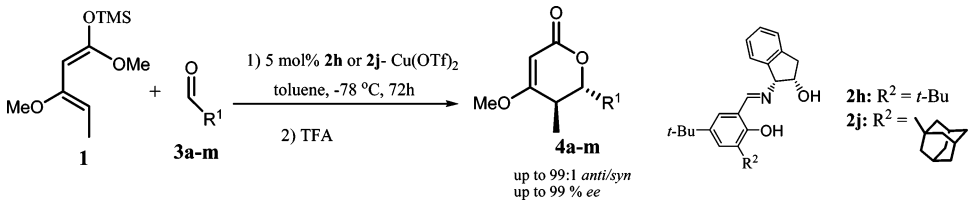

Two efficient new chiral copper (II) Schiff base complexes were developed for the highly enantio- and diastereoselective HDA reaction of Brassard type diene **1b** with aldehydes, to afford the corresponding 5-methyl-containing α,*β*-unsaturated *δ*-lactone derivatives in moderate yields, high enantioselectivities (up to 99% ee) and excellent diastereoselectivities (up to 99:1 anti/syn). On the basis of the absolute configuration of **4a**−**4j** disclosed by X-ray diffraction and CD analysis, a possible transition-state model for the enantio- and diastereoselective catalytic reaction has been proposed.

Introduction

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,[1] such as antifungal and antitumor activities. The synthesis of *δ*-lactones has attracted a lot of attention, and various methods have been developed to synthesize this core structure. In addition to annulation of open-chained precursors,[2] other methods such as the formation through vinylogous aldol reactions,[3] the oxidation of lactols[4a,b] or hexoses,[4c] the derivatization from dihydropyranones[5a] or dihydropyrans,[5b] and the two-step addition reaction of ene to dicarbonyl compounds[6] have also been developed. It is noteworthy that many natural products, including, for example, the prelactone series,[2h−k,5] have in common the 5-methyl-containing *δ*-lactone structural motif.[2d,e,3a,4c,7]

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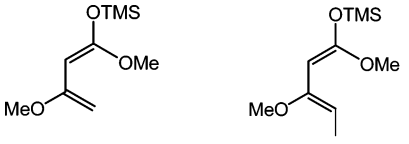

Brassard's diene **1a** Brassard type diene **1b**

FIGURE 1. Structures of Brassard's diene **1a** and Brassard type diene **1b**.

The catalytic asymmetric hetero-Diels−Alder (HDA) reaction[8] promoted by Lewis acids provides a highly effective protocol for preparing optically active six-membered ring compounds,[9] and some effective catalysts have been developed.[10] As one of the most convenient approaches to the α,β-unsaturated δ-lactones, the HDA reaction of electron-rich Brassard's diene[11] with suitable aldehydes or ketones provides an efficient method to synthesize this core structure in a single step. The synthesis of optically active δ-lactones through the reaction of Brassard's diene **1a** (Figure 1) with optically active aldehydes has been achieved in the presence of Lewis acid catalysts.[12] For the catalytic asymmetric HDA reaction of **1a** with aldehydes **3**, only two successful examples so far have been reported,[13] although the first example emerged in 1990 (5−13% enantiomeric excess (ee)).[14] The direct approach to form α,β-unsaturated δ-lactones has been successfully used to synthesize some natural products.[12a,13c] And also through Winkler's transformation,[15] the final cycloadducts can be converted to the corresponding 2,3-dihydro-pyran-4-ones. On the basis of the foregoing contributions, we expected that if **1a** was modified by an additional methyl group to Brassard type diene **1b**, then the HDA reaction could afford the 5-methyl-containing δ-lactone structure, an essential structural component of a large number of natural products. After preliminary trials, we found that **1b** was very different with **1a** in the HDA reaction; besides two stereogenic centers were formed in the final cycloadduct. Herein, we report on two efficient new chiral copper(II) Schiff base complexes to catalyze the highly enantio- and diastereoselective HDA reaction of **1b** with variety of aldehydes.

TABLE 1. Hetero-Diels−Alder Reaction of 1b with Benzaldehyde Catalyzed by 2e−Ti(O*i*Pr)$_4$ and TADDOL[a]

entry	catalyst (mol %)	yield[b] (%)	anti/syn[c]	ee[c] (%)
1	**2e**−Ti(O*i*Pr)$_4$ (10)	55	59:41	43
2	TADDOL (20)	50	76:24	2

[a] All reactions were performed with benzaldehyde (0.25 mmol) and diene **1b** (0.3 mmol) at 0 °C for 72 h. [b] Isolated yield. [c] Diastereoselectivities and enantioselectivities were determined by HPLC, with a chiralpak AD-H column.

Results and Discussion

We have recently shown that the tridentate Schiff base ligand **2e** complexed with titanium is an effective catalyst for the HDA reaction of Brassard's diene **1a** with aromatic aldehydes (24−87% yield, 90−99% ee),[13a,b] while Ding's group has used TADDOL to catalyze the same reaction (45−85% yield, 68−91% ee).[13c] However, when both of the systems were employed to the reaction of diene **1b** with benzaldehyde, disappointing results were obtained (Table 1).

The initial studies showed that Cu(OTf)$_2$ was more efficient than other metals in this reaction (see the Supporting Information for details). Then, tridentate Schiff base ligands derived from various chiral β-amino alcohols (Figure 2) complexed with Cu(OTf)$_2$ were examined (Table 2). These ligands were prepared according to literature procedures.[10q,16] The data suggested that the structure of β-amino alcohols affected the enantioselectivity greatly (Table 2, entries 1−8), and the ligand derived from (1*R*,2*S*)-1-amino-2-indanol was found to be the most efficient for enantioselectivity (Table 2, entries 8 and 10). Meanwhile, the presence of the larger adamantanyl group at the 3-position of the phenolic ring increased the diastereoselectivity greatly (Table 2, entry 9), but the enantioselectivity decreased significantly (Table 2, entry 5 vs entry 9, entry 8 vs entry 10). Thus, both **2h** and **2j** had the potential to be the optimal ligand and were examined in the next step. Interestingly, the less flexible

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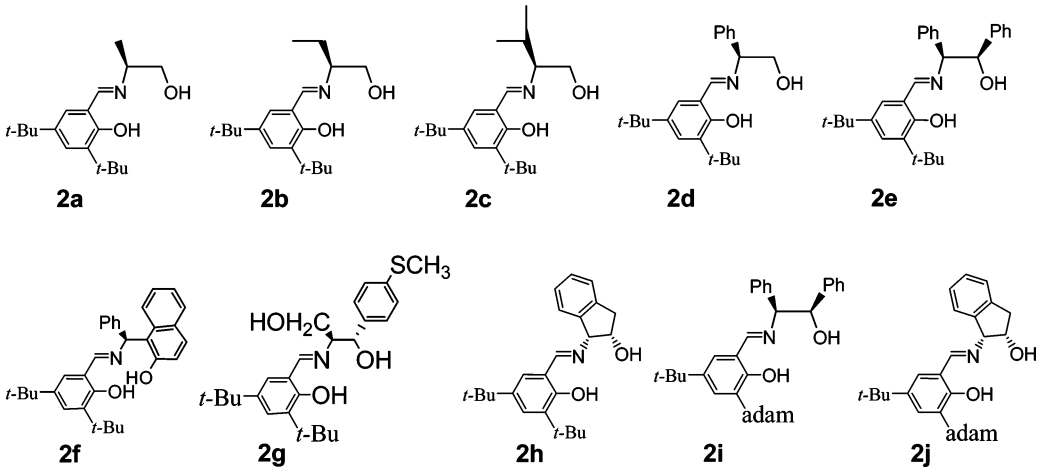
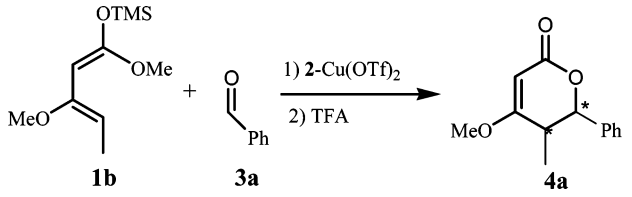


FIGURE 2. Chiral ligands employed for asymmetric induction.

TABLE 2. Effects of Ligands on the HDA Reaction of Benzaldehyde with Brassard Type Diene 1b[a]



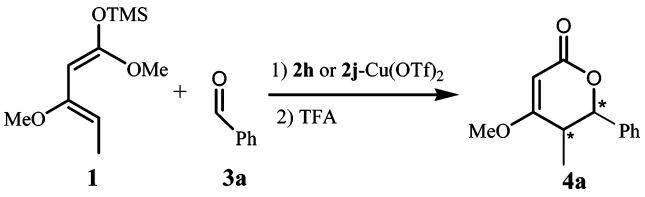
entry	ligand	yield[b] (%)	anti/syn[c]	ee[c] (%)
1	**2a**	75	68:32	24
2	**2b**	53	63:37	24
3	**2c**	18	68:32	73
4	**2d**	59	72:28	14
5	**2e**	26	77:23	48
6	**2f**	13	79:21	0
7	**2g**	35	69:31	10
8	**2h**	46	72:28	80
9	**2i**	15	90:10	12
10	**2j**	46	89:11	75

[a] All reactions were performed with benzaldehyde (0.25 mmol) and diene **1b** (0.3 mmol) in 1.0 mL of toluene at 0 °C for 72 h. Catalysts were composed of a 1.1:1 molar ratio of ligands to $Cu(OTf)_2$; catalyst loading was 10 mol %. [b] Isolated yield. [c] Diastereoselectivities and enantioselectivities were determined by HPLC, with a chiralpak AD-H column.

five-membered ring of the indanyl structure as well as the adamantanyl group gave only poor results in our previous work about the HDA reaction of **1a** with aldehydes.[13a,b]

Further improvement was achieved after optimization of the reaction conditions, with the representative results listed in Table 3. The reaction temperature was found to be one of the crucial factors in this reaction. Either catalyzed by **2h**−$Cu(OTf)_2$ or **2j**−$Cu(OTf)_2$, the ee and yield were increased with the temperature lowering (Table 3, entries 1−7). The diastereoselectivity was improved significantly in the **2j**−$Cu(OTf)_2$ system (Table 3, entries 4−7); however, it was not improved at all in the **2h**−$Cu(OTf)_2$ system (Table 3, entries 1−3). So, the **2j**−$Cu(OTf)_2$ complex was temporarily chosen to be the optimal one. At −78 °C, it could give 70% yield, 94:6 anti/syn, and 97% ee. In addition, when the catalyst loading was reduced to 5 mol %, there was not any loss in yield, diastereoselectivity, and enantioselectivity (Table 3, entries 11 and 13). Yield increased with the temperature lowering, which was probably due to the fact that the Brassard type diene was destroyed in the presence of Lewis acid before it reacted with

TABLE 3. Hetero-Diels−Alder Reaction of Benzaldehyde with Brassard Type Diene 1b Catalyzed by 2h− or 2j−Cu(OTf)$_2$ under Various Conditions[a]



entry	ligand	catalyst loading (%)	temp (°C)	solvent	yield[b] (%)	anti/syn[c]	ee[c] (%)
1	**2h**	10	0	toluene	46	72:28	80
2	**2h**	10	−20	toluene	48	63:37	88
3	**2h**	10	−45	toluene	68	71:29	92
4	**2j**	10	0	toluene	46	89:11	75
5	**2j**	10	−20	toluene	47	88:12	80
6	**2j**	10	−45	toluene	66	93:7	94
7	**2j**	10	−78	toluene	70	94:6	97
8	**2j**	10	−45	CH_2Cl_2	35	76:24	0
9	**2j**	10	−45	Et_2O	18	87:13	92
10	**2j**	10	−45	THF	trace	87:13	86
11	**2j**	5	−45	toluene	55	92:8	94
12	**2j**	2	−45	toluene	25	88:12	41
13	**2j**	5	−78	toluene	70	95:5	98

[a] All reactions were performed with benzaldehyde (0.25 mmol) and diene **1b** (0.3 mmol) in 1.0 mL of solvent for 72 h. Catalysts were composed of a 1.1:1 molar ratio of ligand to $Cu(OTf)_2$. [b] Isolated yield. [c] Diastereoselectivities and enantioselectivities were determined by HPLC, with a chiralpak AD-H column.

aldehyde,[13,17] while the lowered temperature could slow the speed of the decomposition.

When the solvent effect was studied (Table 3, entry 6 and entries 8−10), it was surprising that CH_2Cl_2, which was previously determined to be the appropriate solvent for the reaction of diene **1a** with aldehydes,[13a,b] gave a racemic product (Table 3, entry 8). The best result was obtained in toluene. Although the similar enantioselectivity could be found in Et_2O, the diastereoselectivity and the yield were obviously inferior to that in toluene (Table 3, entry 9 vs entry 6).

The complexes of ligand **2j** with various Lewis acids were examined under the optimized conditions, with the results summarized in Table 4. It was obvious that $Cu(OTf)_2$ was the

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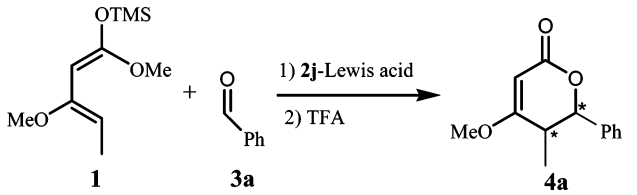
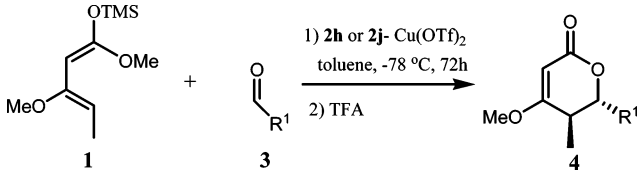
TABLE 4. Lewis Acid Effects on the HDA Reaction of Benzaldehyde with Brassard Type Diene 1b[a]



entry	metal	yield[b] (%)	anti/syn[c]	ee[c] (%)
1	$Ti(OiPr)_4$	9	69:31	56
2	$Al(OC_3H_7)_3$	ND		
3	$Sc(OTf)_3$	7	76:24	0
4	$Zn(OTf)_2$	39	53:47	34
5	$Yb(OTf)_3$	4	75:25	0
6	$Sn(OTf)_2$	trace	70:30	6
7	$Cu(OTf)_2$	66	93:7	94

[a] All reactions were performed with benzaldehyde (0.25 mmol) and diene **1b** (0.3 mmol) in 1.0 mL of toluene at −45 °C for 72 h. Catalysts were composed of a 1.1:1 molar ratio of ligand **2j** to metals; catalyst loading was 10 mol %. [b] Isolated yield. [c] Diastereoselectivities and enantioselectivities were determined by HPLC, with a chiralpak AD-H column.

TABLE 5. Asymmetric HDA Reaction of Brassard Type Diene 1b with Aldehydes Catalyzed by Ligand 2h− or 2j−Cu(OTf)$_2$ Complexes[a]



entry	aldehyde	ligand	yield[b] (%)	anti/syn[c]	anti ee[c] (%)
1	PhCHO **3a**	**2j**	70	95:5	98 (5*R*,6*S*)
2	*o*-MeC_6H_4CHO **3b**	**2j**	35	92:8	54 (5*R*,6*S*)
3	*o*-MeC_6H_4CHO **3b**	**2h**	52	99:1	94 (5*R*,6*S*)
4	*p*-MeC_6H_4CHO **3c**	**2j**	40	98:2	96 (5*R*,6*S*)
5	*p*-FC_6H_4CHO **3d**	**2j**	60	97:3	97 (5*R*,6*S*)
6	*p*-ClC_6H_4CHO **3e**	**2j**	55	>95:5	>94 (5*R*,6*S*)
7	*p*-BrC_6H_4CHO 3f	**2j**	65	>94:6	>91 (5*R*,6*S*)[d]
8	*m*-$O_2NC_6H_4CHO$ **3g**	**2j**	53	88:12	90 (5*R*,6*S*)
9	*p*-$O_2NC_6H_4CHO$ **3h**	**2j**	64	89:11	94 (5*R*,6*S*)
10	1-naphthylaldehyde **3i**	**2j**	30	92:8	24 (5*R*,6*S*)
11	1-naphthylaldehyde **3i**	**2h**	57	98:2	92 (5*R*,6*S*)
12	2-naphthylaldehyde **3j**	**2j**	63	>97:3	>97 (5*R*,6*S*)
13	2-furaldehyde **3k**	**2j**	40	98:2	99
14	(*E*)-MeCH═CHCHO **3l**	**2j**	58	90:10	62
15	*n*-butyraldehyde **3m**	**2j**	15	59:41	73

[a] All reactions were performed on a 0.25 mmol scale with 5 mol % of catalyst in 1.0 mL of toluene at −78 °C for 72 h. [b] Isolated yield. [c] Diastereoselectivities and enantioselectivities were determined either by HPLC or GC analysis. The absolute configurations were assigned by comparing the Cotton effect of the CD spectra with that of **4f**. [d] The absolute configuration was determined by X-ray crystal structural analysis of **4f** on the basis of the anomalous dispersion of the heavy bromine atom.

optimum Lewis acid for the reaction, giving much higher yield, diastereoselectivity, and enantioselectivity.

Encouraged by the results obtained from benzaldehyde under the optimized conditions, the substrate scope of this reaction was then examined. Ligand **2j** was very efficient for a majority of aromatic aldehydes, including electron-donating substituted (Table 5, entry 4), electron-withdrawing substituted (Table 5, entries 5−9), condensed ring (Table 5, entry 12), and heterocyclic (Table 5, entry 13) aldehydes, leading to the corresponding 5-methyl-containing α,β-unsaturated δ-lactones with high diastereoselectivities (88:12−99:1 anti/syn) and excellent enantioselectivities (91−99% ee). However, **3b** and **3i** with the ortho substituent gave poor ee (54% and 24%, respectively), though the ratio of anti/syn was excellent (Table 5, entries 2 and 10). For ortho-substituted aldehydes, the adamantyl group of the catalyst may be too large to allow for coordination of the aldehyde to the catalyst complex. Interestingly, **2h** with the smaller group, which was not so successful as **2j** in many cases, was very efficient for **3b** and **3i** under the same conditions (>98:2 anti/syn, >92% ee, Table 5, entry 3 vs entry 2, entry 11 vs entry 10). For α,β-unsaturated aliphatic aldehyde **3l**, it could give a moderate result (Table 5, entry 14). When *n*-butyraldehyde (**3m**) was examined, the enantioselectivity was moderate, and both the yield and diastereoselectivity were disappointing.

The absolute configuration of **4f**[18] was determined unambiguously by the Bijivoet method to be (5*R*,6*S*) with a Flack parameter of −0.019(12) on the basis of the anomalous dispersion of the bromine heavy atom. To determine the absolute configurations of the other products, the circular dichroism (CD) spectra of **4a**−**4j** were measured in methanol. Compounds (−)-**4a**−**4j** exhibited a similar (−) Cotton effect in their CD spectra. It can be deduced that these compounds possess the same (5*R*,6*S*) configuration as (−)-**4f**. (for details see the Supporting Information)

Two mechanistic pathways are generally taken into account when a given Lewis acid catalyzes the HDA reaction, which are formulated as a traditional Diels−Alder type cycloaddition reaction and a Mukaiyama aldol pathway, and have been studied in detail in the reaction of Danishefsky's diene with benzaldehyde.[19,20] In our previous work on the HDA reaction of **1a** with aromatic aldehydes catalyzed by the **2e**−Ti(IV) complex,[13b] the reaction temperature was found to influence the reaction pathway: at 0 °C, the reaction was mostly carried out by the Diels−Alder process and at −78 °C by Mukaiyama aldol process. The Mukaiyama aldol product could be clearly observed by TLC detection before treatment with TFA and be isolated through a silica gel column. When the reaction of **1a** with benzaldehyde proceeded under the optimized Cu(II)−**2j** or **2h** reaction conditions, most of the product obtained was racemic aldol product **5a** and a trace of cycloadduct **6a** in 82% ee by purification through a silica gel column without treatment with TFA or other workup. When the reaction mixture above was treated with TFA, which transforms the aldol product into cycloproduct by a cyclyzation reaction, the final enantiomeric excess of cycloproduct was reduced sharply to 6%. The aldol product was determined by NMR, which was identical with the literature.[13b] These results indicated that the reaction of **1a** with

(18) CCDC-279872 ((5*S*,6*R*)-(−)-**4f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, U.K.; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

(19) Some examples for a stepwise mechanism, see: (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907−6910. (b) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998−5999. (c) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793−3798. (d) Gao, B.; Fu, Z.-Y.; Yu, Z.-P.; Yu, L.; Huang, Y.-Z.; Feng, X.-M.; Zhang, G.-L. *Synlett* **2004**, 1772−1775. (e) Yang, W.-Q.; Shang, D.-J.; Liu, Y.-L.; Du, Y.; Feng, X.-M. *J. Org. Chem.* **2005**, *70*, 8533−8537.

(20) Some examples for the concerted Diels−Alder pathway, see: (a) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−405. (b) Larson, E. R.; Danishefsky, S. *J. Am. Chem. Soc.* **1982**, *104*, 6458−6460. (c) Molander, G. A.; Rzasa, R. M. *J. Org. Chem.* **2000**, *65*, 1215−1217. (d) Yuan, Y.; Long, J.; Sun, J.; Ding, K.-L. *Chem. Eur. J.* **2002**, *8*, 5033−5042.

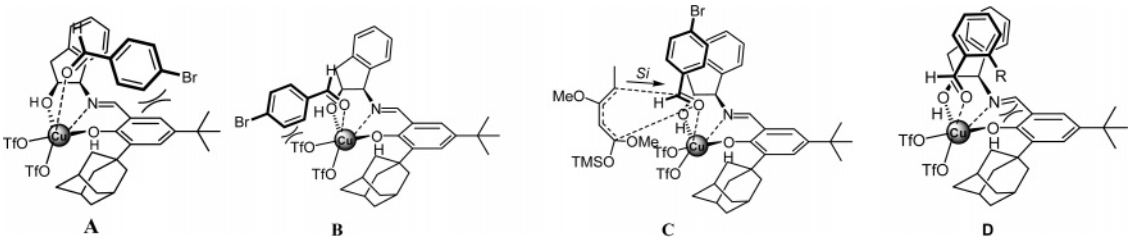
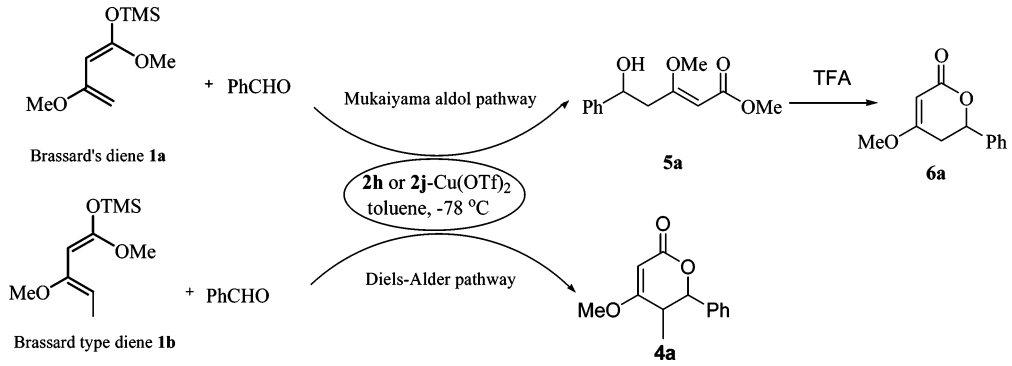


FIGURE 3. Proposed working model for the HDA reaction of diene **1b** with aldehyde.

SCHEME 1. Mechanistic Pathways of HDA Reaction between 1a or 1b with Aldehyde Catalyzed by 2h− or 2j−Cu(OTf)$_2$ Complexes



benzaldehyde under the optimized Cu(II) catalyst reaction conditions also follows the Mukaiyama aldol pathway (Scheme 1).

In the reaction of **1b** with aldehydes catalyzed by the **2h**− or **2j**−Cu(II) complex, when the reaction temperature was varied from 0 to −78 °C, only one new product could be detected by TLC before treating the reaction with TFA. Isolated through a silica gel column at the end of the reaction, **4a** was obtained in 71% yield, 95:5 anti/syn, 98.5% ee. Its structure was confirmed by NMR. The results were almost the same with those after treatment with TFA. The facts indicated that the reaction of **1b** with aldehydes catalyzed by the chiral **2h**− or **2j**−Cu(II) complex might proceed via the Diels−Alder pathway (Scheme 1).

Reference to chiral C_2-symmetric bisoxazoline−copper(II) complexes[8a,21] and Jacobsen's chromium−Schiff base complexes,[5b,10o] we think the copper(II) also coordinates with the tridentate Schiff base ligand, which is visually evident in the dissolvability and color change of the catalyst solution from the cloudy heterogeneous mixture of the bright yellow Schiff base and pale blue Cu(OTf)$_2$ in solvent at the beginning to a clear dark green homogeneous solution after 0.5 h of stirring. On the basis of the hypothesis above and the observed absolute configurations of products **4a**−**4j**, a possible transition-state model for asymmetric induction in this catalytic system could be outlined (Figure 3). The aldehyde carbonyl is prevented from binding to the Cu(II) center via the coordination shown in models A and B of Figure 3 due to the large steric hindrance between two phenyl subunits (model A, Figure 3) or between phenyl and OTf groups (model B, Figure 3). The favored one is suggested as model C. In this transition state, the steric hindrance of the indanyl subunit shields the Re face of the aldehyde, while the Si face of the aldehyde is much more available to accept the attacking diene to give the products with the (5*R*,6*S*) configuration as expected. On the other hand, the ortho substituent of the aldehyde could cause larger stereohindrance with the adamantyl group (model D), while the *t*Bu group was suitable. This model could well explain the absolute configuration and the phenomenon that ligand **2h** was efficient for ortho-substituted substrates, while **2j** was more successful for the others.

In summary, two efficient new chiral catalysts were developed for the first highly enantio- and diastereoselective HDA reaction of Brassard type diene **1b** with aldehydes. On the basis of the absolute configuration of **4** disclosed by X-ray diffraction and CD analysis, a possible transition-state model for the enantio- and diastereoselective catalytic reaction has been proposed. This catalyst system provided one of the most convenient approaches for the construction of 5-methyl-containing δ-lactone units, which will make the methodology more attractive for the synthesis of a variety of natural products. Further efforts should be devoted to the optimization of the catalyst to enhance the reactivity and the ability to catalyze aliphatic aldehydes, as well as the application of this methodology to the synthesis of bioactive 5-methyl-containing δ-lactones.

Experimental Section

(5*R*,6*S*)-6-Phenyl-4-methoxy-5-methyl-5,6-dihydropyran-2-one (4a): A mixture of Cu(OTf)$_2$ (0.0125 mmol) and **2j** (0.01375 mmol) in toluene (1 mL) was stirred at room temperature for 0.5 h under N_2 atmosphere. To the green mixture was added benzaldehyde (25 μL, 0.25 mmol), cooled to −78 °C, followed by addition of Brassard type diene **1b** (80 μL, 0.3 mmol). The reaction mixture was stirred for 72 h at −78 °C before being quenched with five drops of TFA. After stirring for additional 15 min, the mixture was

(21) For examples of the application of C_2-symmetric bisoxazoline−copper(II) in Mukaiyama aldol reactions, see: (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699 and references therein. For examples in hetero-Diels−Alder reactions, see: (c) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649 and references therein. Example of octahedral Cu(II) catalyst system, see: (d) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824−5825.

neutralized with saturated $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to afford the white solid **4a** in 70% yield, 98% ee, and 95:5 anti/syn (determined by HPLC on an AD-H column, hexane/2-propanol 90:10, flow rate 1.0 mL/min, $t_{major} = 17.7$ min, $t_{minor} = 13.3$ min). Mp 55−56 °C; $[\alpha]^{20}_D = -86.9$ ($c = 0.252$ in CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.33 (m, 5H), 5.20 (s, 1H), 5.01 (d, $J = 9.3$ Hz, 1H), 3.75 (s, 3H), 2.93−2.87 (m, 1H), 1.08 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 166.4, 137.6, 128.7, 128.5, 127.2, 89.9, 83.6, 56.3, 38.1, 12.8. HRMS: $(M + H)^+$; calcd 219.1016, found 219.1014.

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Supporting Information Available: Experimental procedures, initial results of Lewis acid effects study, spectral and analytical data for the products (PDF), and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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