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Indium(III)-Catalyzed Asymmetric Hetero-Diels–Alder Reaction of Brassard-Type Diene with Aliphatic Aldehydes

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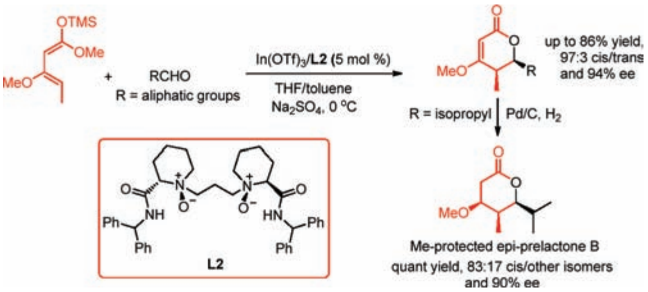
ABSTRACT



A highly diastereo- and enantioselective hetero-Diels–Alder (HDA) reaction of a Brassard-type diene with aliphatic aldehydes has been developed. The chiral *N,N'*-dioxide L2/In(OTf)$_3$ complex was efficient toward the obtention of the corresponding β-methoxy-γ-methyl α,β-unsaturated δ-lactones in good yields (up to 86%) as well as dr and ee values (up to 97:3 cis/trans and 94% ee). In addition, the product 4a could be easily transformed into the methyl-protected epi-prelactone B by hydrogenation.

δ-Lactones,[1,2] specifically β-hydroxy-γ-methyl-δ-lactones,[3] are found as essential structural motifs in many bioactive natural products, such as prelactones B, C, V;[4] leiodermatolide;[5] and discodermolide[6] (Figure 1). The hetero-Diels–Alder (HDA) reaction[7] of Brassard's dienes[8] **1** and **2** with aldehydes was an efficient method to synthesize δ-lactone structures (Scheme 1).[9] And also, combined with Winkler's transformation of 4-alkoxy-α,β-unsaturated δ-lactones to 2,3-dihydropyran-4-ones,[10] the scope of the methodology could be greatly expanded. However, the terminal 2-fold substitutions of Brassard's diene enhanced the difficulty of controlling the enantioselectivity of the HDA reaction.[11] As a result, though electron-rich as the well-developed

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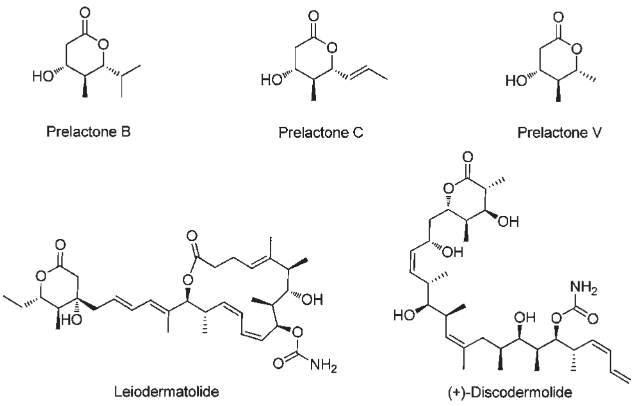
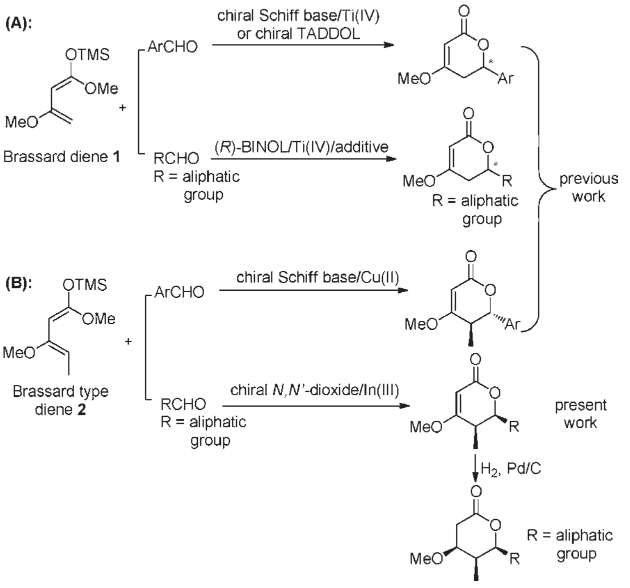


Figure 1. Natural products containing a β-hydroxy-γ-methyl-δ-lactone structure.

Danishefsky-type dienes,[7,12] Brassard's diene has been less efficiently developed in the catalytic asymmetric HDA reaction with aldehydes.[13,14] As a developing area, up to now, the HDA reactions of Brassard's diene **1** with aromatic[15] and aliphatic[16] aldehydes have been realized by chiral Ti(IV) complexes or a TADDOL organocatalyst (Scheme 1A). At the same time, the HDA reaction of Brassard-type diene **2** with aromatic aldehydes has also been achieved by Cu(II)/Schiff base complexes (Scheme 1B).[17] However, to the best of our knowledge, no efficient catalytic system has been developed for the asymmetric HDA reaction of Brassard-type diene **2** with aliphatic aldehydes,[18] although the corresponding adducts could be easily transformed to the building blocks existing in many natural products (Figure 1) by hydrogenation. So, it is highly meaningful to explore efficient catalytic systems for the asymmetric HDA reaction of Brassard-type diene **2** with aliphatic aldehydes.

Scheme 1. Construction of δ-Lactones through HDA Reactions of Brassard Dienes with Aldehydes



It is well-known that the indium, which is three times as abundant as silver, is particularly effective at activating carbonyl groups.[12b,19] On the other hand, the chiral *N*,*N*′-dioxide–metal complexes, which have a tunable chiral environment via modifying their electronic properties or steric hindrance, have been successfully applied in many asymmetric reactions.[20] Herein, we report our efforts in

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(18) 15% yield, 59/41 trans/cis, and 73% ee were obtained for *n*-butanal. 58% yield, 10/90 cis/trans, and 62% ee were obtained for (*E*)-but-2-enal.[17]

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applying the chiral *N*,*N*′-dioxide/In(OTf)$_3$ complex in the diastereo- and enantioselective HDA reaction of Brassard-type diene **2** with aliphatic aldehydes.

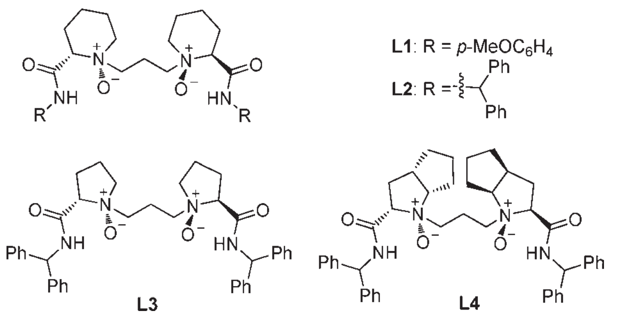
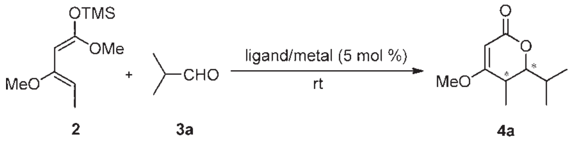


Figure 2. Representative chiral ligands used in this study.

The model reaction was initiated with Brassard-type diene **2** and isobutanal **3a** for structural similarity with the natural product prelactone B (Figure 1). Various chiral *N*,*N*′-dioxides (Figure 2) coordinated with In(OTf)$_3$ were investigated in THF at rt. The results showed that both the amide part and the amino acid backbone of the chiral ligand affected the reaction greatly. Unfortunately, the *N*,*N*′-dioxides derived from aromatic amines only gave racemic products, though they have exhibited great ability in many other asymmetric reactions. For example, the *N*,*N*′-dioxide **L1** derived from 4-methoxyaniline supported the racemic product in 52% yield (Table 1, entry 1). Comparatively, the *N*,*N*′-dioxides derived from aliphatic amines could give the desired products in a variety of dr and ee values (for details, see the Supporting Information). The *N*,*N*′-dioxide **L2** derived from diphenylmethanamine with L-pipecolic acid backbone could give 89% yield, 87:13 cis/trans, and 79% ee (Table 1, entry 2). Surprisingly, the cis-product was in the majority, determined by ^{1}H NMR analysis, while the trans-product was mainly obtained from aromatic aldehydes in the Cu(II)/Schiff base catalytic system.[17] When **L3** derived from L-proline or **L4** derived from L-ramipril acid was used, the ee values sharply decreased to 4% and 29%, respectively (Table 1, entries 3–4). Besides, the counterion was another parameter strongly affected the reactivity and selectivity. When In(OAc)$_3$ was applied, a trace amount of product was obtained (Table 1, entry 5). InBr$_3$ and InCl$_3$, which showed great ability in carbon–carbon bond-forming reactions,[21] resulted in very low yields and ee values with the dr even reversed (Table 1, entries 6–7). When the reaction temperature was lowered to 0 °C, the ee could be enhanced to 90%, while the yield decreased to 41% and the ratio of cis/trans slightly declined to 81:19 (Table 1, entry 2 vs 8). To our delight, using mixed solvents (toluene/THF = 2:1), meanwhile prolonging the reaction time, could improve the yield to 84% with a slightly increased ratio of cis/trans and maintained ee values (90% ee) (Table 1, entry 9). It is noteworthy that adding anhydrous Na$_2$SO$_4$ to the system could prevent the system from instability caused by In(OTf)$_3$ absorbing moisture in air.

Table 1. Evaluation of Reaction Parameters[a]



entry	ligand	metal	yield[b] (%)	cis/trans[c]	cis ee[c] (%)
1	**L1**	In(OTf)$_3$	52	71:29	0
2	**L2**	In(OTf)$_3$	89	87:13	79
3	**L3**	In(OTf)$_3$	67	74:26	4
4	**L4**	In(OTf)$_3$	54	71:29	29
5	**L2**	In(OAc)$_3$	trace	ND	ND
6	**L2**	InBr$_3$	15	29:71	5[f]
7	**L2**	InCl$_3$	11	32:68	4[f]
8[d]	**L2**	In(OTf)$_3$	41	81:19	90
9[d,e]	**L2**	In(OTf)$_3$	84	85:15	90

[a] Unless otherwise noted, all reactions were performed with isobutanal (0.25 mmol) and diene **2** (0.3 mmol) in the presence of 5 mol % catalyst loading in 1.0 mL of THF at rt for 72 h. [b] Isolated yield. [c] Determined by GC analysis. ND = Not determined. [d] The reaction was performed at 0 °C. [e] The reaction was performed in 0.5 mL of THF and 1.0 mL of toluene for 96 h. Anhydrous Na$_2$SO$_4$ (30 mg) was added. [f] The ee value of trans-product.

With the optimal reaction conditions in hand, the substrate scope was then examined (Scheme 2). Obviously, α-branched aliphatic aldehydes were beneficial for the results (Scheme 2, **4a**–**4d**). Linear *n*-butanal gave **4c** with only a 65:35 ratio of cis/trans and 72% ee. Monosubstituted 2-ethyl butanal and isobutanal provided **4a** and **4b** with better selectivities (82:18 and 85:15 cis/trans, 84% ee and 90% ee, respectively). Bulkyl pivaldehyde yielded **4d** with the best results (86% yield, 97:3 cis/trans and 94% ee). Cyclohexanal also reacted smoothly with Brassard-type diene **2** to afford the corresponding **4e** in 82% yield, 81:19 cis/trans, and 91% ee. After a single recrystallization, **4e** with 98:2 cis/trans and 99% ee could be achieved. Besides,

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(20) For selected examples of our recent work, see: (a) Li, W.; Wang, J.; Hu, X. L.; Shen, K.; Wang, W. T.; Chu, Y. Y.; Liu, X. H.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2010**, *132*, 8532. (b) Xie, M. S.; Chen, X. H.; Zhu, Y.; Gao, B.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799. (c) Shang, D. J.; Xin, J. G.; Liu, Y. L.; Zhou, X.; Liu, X. H.; Feng, X. M. *J. Org. Chem.* **2008**, *73*, 630. (d) Liu, Y. L.; Shang, D. J.; Zhou, X.; Zhu, Y.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Org. Lett.* **2010**, *12*, 180. (e) Cai, Y. F.; Liu, X. H.; Hui, Y. H.; Jiang, J.; Wang, W. T.; Chen, W. L.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160. (f) Zheng, K.; Shi, J.; Liu, X. H.; Feng, X. M. *J. Am. Chem. Soc.* **2008**, *130*, 15770. (g) Cao, W. D.; Liu, X. H.; Wang, W. T.; Lin, L. L.; Feng, X. M. *Org. Lett.* **2011**, *13*, 600.

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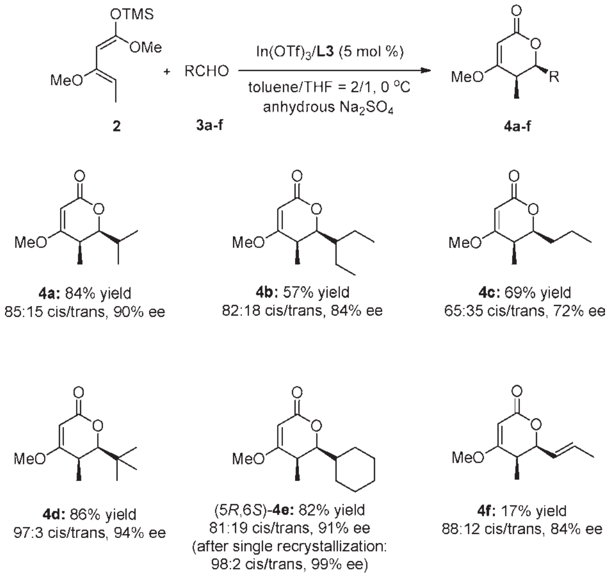
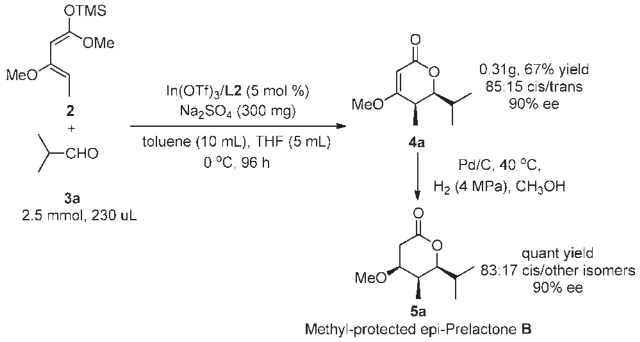
the absolute configuration of **4e** was unambiguously determined to be 5*R*,6*S* by single-crystal X-ray diffraction analysis.[22] (*E*)-But-2-enal was also examined, but a poor yield was obtained with 88:12 cis/trans and 84% ee.[23]

Scheme 2. Substrate Scope for the Catalytic Asymmetric HDA Reaction of Brassard-Type Diene **2** with Aliphatic Aldehydes



To further evaluate the synthetic potential of the catalytic system, a scaled-up synthesis of chiral **4a** was performed. As shown in Scheme 3, by treatment of 2.5 mmol of isobutanal **3a** under the optimized reaction conditions, 0.31 g of the correspoinding **4a** was obtained without any loss in dr and ee values. Meanwhile, by hydrogenation in the presence of Pd/C at 40 °C under 4 MPa pressure, the product **4a** could be readily transformed into the methyl-protected epi-prelactone B[24] in quantitative yield and with basically maintained dr and ee values (Scheme 3).

Scheme 3. Scaled-up Version of HDA Reaction of Brassard-Type Diene **2** with Isobutanal **3a** and Hydrogenation of the Product **4a**



In summary, a highly diastereo- and enantioselective hetero-Diels–Alder reaction of Brassard-type diene **2** with aliphatic aldehydes catalyzed by the chiral *N*,*N'*-dioxide **L2**/In(OTf)$_3$ complex has been developed. The corresponding β-methoxy-γ-methyl-α,β-unsaturated-δ-lactones were obtained in good yields as well as dr and ee values. The cycloadducts could be easily transformed into useful building blocks by hydrogenation. Further efforts will be devoted to understanding the reaction mechanism and applying this methodology to synthesize other natural products.

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Supporting Information Available. Experimental procedures, effects of ligand, metal, reaction temperature, and spectral and analytical data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) CCDC 825023 (**4e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(23) The low reactivity led to the poor yield of **4f**. In addition, aromatic benzaldehyde also showed low reactivity in this catalytic system, and the dr and ee value were not determined.

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