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# Efficient Enantioselective Hetero-Diels–Alder Reaction of Brassard's Diene with Aliphatic Aldehydes: A One-Step Synthesis of (*R*)-(+)-Kavain and (*S*)-(+)-Dihydrokavain

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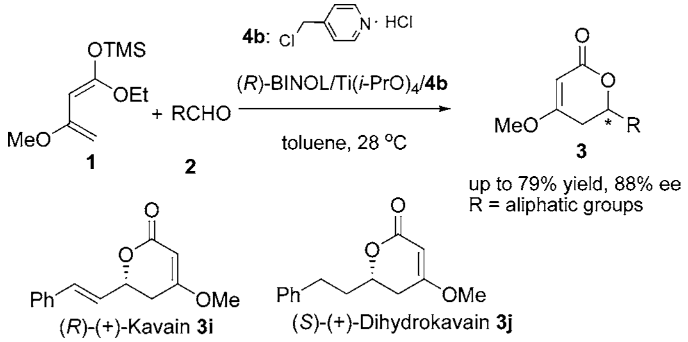
## ABSTRACT



**An efficient catalytic asymmetric hetero-Diels–Alder reaction of Brassard's diene with aliphatic aldehydes was reported. The catalyst, which was generated from (*R*)-BINOL, Ti(*i*-PrO)$_4$, and 4-picolyl chloride hydrochloride, promoted the reaction smoothly to afford the corresponding α,*β*-unsaturated *δ*-lactone derivatives in moderate-to-good yields (46–79%) with high enantioselectivities (up to 88% ee). Natural products (*R*)-(+)-kavain (70% ee, >99% ee after single recrystallization) and (*S*)-(+)-dihydrokavain (84% ee) were also prepared in one step by using this methodology.**

The α,*β*-unsaturated *δ*-lactones are key structural subunits of numerous natural and unnatural products with a wide range of biological activities.[1] Until now, numerous synthetic approaches have been examined to effect a facile synthesis of this core structure.[2] It is well-known that one of the most convenient methods is hetero-Diels−Alder (HDA) reaction[3] of Brassard's diene[4] with suitable aldehydes or ketones.[5] The scope of the methodology can also be limitlessly expanded when coupled with Winkler's transformation of 4-alkoxy-α,*β*-unsaturated *δ*-lactones to 2,3-dihydropyran-4-ones.[6] Although electron-rich as Danishefsky-type dienes,[3,7] the two-fold substitution at Brassard's diene terminus has a deleterious effect upon the enantioselectivity of HDA reac-

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(1) (a) Boger, D. L.; Weinreb, S. N. In *Hetero Diels-Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed.; Academic Press: San Diego, 1987. (b) Tietze, L. F.; Kettschau, G. In *Stereoselective Heterocyclic Synthesis 1*; Metz, P., Ed.; Springer: Berlin, 1997. (c) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793 and references therein. (d) Lucas, B. S.; Gopalsamuthiram, V.; Burke, S. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 769.

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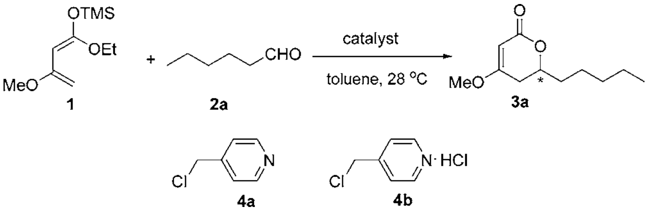
tions,[8] and less enantioselective catalytic examples were reported.[9,10] Up to now, only three highly enantioselective catalytic examples of Brassard's diene with aldehydes have been reported. Two of them are Schiff base−metal complex systems reported by our group,[11] and the other is a TADDOL system reported by Ding's group.[12] However, all of the examples are mainly restricted to aromatic aldehydes[13] and to the best of our knowledge, the major huddle in this area lies in a lack of high enantioselectivity for aliphatic aldehydes.[14] Herein, we reported our efforts on the development of the catalytic enantioselective HDA reaction of Brassard's diene with aliphatic aldehydes, as well as the one-step enantioselective synthesis of (*R*)-(+)-kavain and (*S*)-(+)-dihydrokavain.

Our studies started with the reaction of Brassard's diene **1** with hexanal **2a** as a model reaction. After some experimentation, we focused our attention on the well-known BINOL−Ti(IV) complexes,[15] which have been extensively studied as effective chiral Lewis acid catalysts. The first trial by simple mixing (*R*)-BINOL and Ti(*i*-PrO)$_4$ in situ in the ratio of 1:1 and 2:1 gave the results of 35% yield and 26% ee (Table 1, entry 1) and 10% yield and 66% ee (Table 1, entry 2), respectively. Although a modest improvement, the BINOL−Ti(IV) system showed the potential for asymmetric HDA reaction of Brassard's diene. In order to improve the yield and enantioselectivity, additives were introduced into the (*R*)-BINOL−Ti(IV) system (for details, see Supporting Information). To our delight, when 4-pycolyl chloride **4a** was added to the BINOL−Ti(IV) (1:1) complex, both the yield and enantioselectivity improved drastically (Table 1, entry 3 vs entry 1). Considering the stability, **4a** was replaced by commercially available 4-pycolyl chloride hydrochloride **4b** with results maintained (57% yield and 71% ee, Table 1, entry 4). However, when **4b** was added to the BINOL−Ti(IV) (2:1) complex, the enantioselectivity sharply dropped (Table 1, entry 5 vs entry 2). Further improvement of the ee (83% ee) was achieved after increasing the catalyst loading from 10 to 15 mol % (Table 1, entry 6), and the yield was also improved to 74% by prolonging the reaction time to 115 h (Table 1, entry 7).

**Table 1.** HDA Reaction of Brassard's Diene with Hexanal Catalyzed by (*R*)-BINOL−Ti(IV) Complexes[a]



| entry | (*R*)-BINOL: Ti(*i*-PrO)$_4$:**4b** | catalyst loading (mol %) | reaction time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | 1:1:0 | 10 | 48 | 35 | 26 |
| 2 | 2:1:0 | 10 | 48 | 10 | 66 |
| 3[d] | 1:1:1 (**4a**) | 10 | 48 | 51 | 72 |
| 4 | 1:1:1 | 10 | 48 | 57 | 71 |
| 5 | 2:1:1 | 10 | 48 | 20 | 23 |
| 6 | 1:1:1 | 15 | 48 | 55 | 83 |
| 7 | 1:1:1 | 15 | 115 | 74 | 83 |

[a] All reactions were performed with hexanal (0.25 mmol) and diene **1** (0.375 mmol) in 1.0 mL toluene at 28 °C. [b] Isolated yield. [c] Enantioselectivities were determined by GC analysis. [d] Additive was **4a**.

Under the optimized conditions, the substrate scope of this reaction system was then examined with other aliphatic aldehydes. As shown in Table 2, this catalyst system was efficient for a majority of aliphatic aldehydes, including nonbranched (Table 2, entries 1−4), branched (Table 2, entry 5), cyclo- (Table 2, entry 6), and α,*β*-unsaturated (Table 2, entry 7) aliphatic aldehydes, leading to the corresponding 6-substituted 4-methoxy-5,6-dihydropyran-2-ones in 46−79% yields with 81−88% ee. For aromatic aldehydes, such as benzaldehyde, 87% ee was also obtained when the reaction was performed at 0 °C.

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(2) For a review, see: (a) Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 225. (b) Dieter, R. K.; Guo, F. *Org. Lett.* **2006**, *8*, 4779. (c) Tiseni, P. S.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 5325. (d) D'Annibale, A.; Ciaralli, L.; Bassetti, M.; Pasquini, C. *J. Org. Chem.* **2007**, *72*, 6067. (e) You, Z. W.; Jiang, Z. X.; Wang, B. L.; Qing, F. L. *J. Org. Chem.* **2006**, *71*, 7261. (f) Creech, G. S.; Kwon, O. *Org. Lett.* **2008**, *10*, 429. (g) Esteban, J.; Costa, A. M.; Gómez, À.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 65. (h) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2. (i) Bonazzi, S.; Güttinger, S.; Zemp, I.; Kutay, U.; Gademann, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 8707.

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(8) Togni, A. *Organometallics* **1990**, *9*, 3106.

(9) For examples of Danishefsky-type diene with two-fold substitution at terminus, see: (a) Danishefsky, S.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256. (b) Danishefsky, S.; Harvey, D. F.; Quallich, G.; Uang, B. J. *J. Org. Chem.* **1984**, *49*, 392. (c) Huang, Y. Z.; Feng, X. M.; Wang, B.; Zhang, G. L.; Jiang, Y. Z. *Synlett* **2002**, 2122. (d) Yang, W. Q.; Shang, D. J.; Liu, Y. L.; Du, Y.; Feng, X. M. *J. Org. Chem.* **2005**, *70*, 8533.

(10) For example of highly enantioselective aza-Diels−Alder reaction of Brassard's diene with imines, see: Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796.

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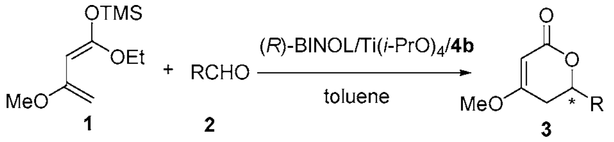
(12) Du, H. F.; Zhao, D. B.; Ding, K. L. *Chem. Eur. J.* **2004**, *10*, 5964.

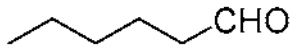
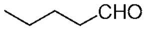
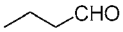
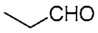
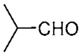
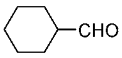
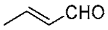
(13) A 69% ee was obtained for 3-phenylpropionaldehyde in the TADDOL system.[12].

(14) Less than 10% ee was obtained by Feng's catalyst, (+)-Eu(hfc)$_3$, or Jacobsen's catalyst.[6]

(15) For reviews, see: (a) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. (b) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (c) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807. (d) Ramón, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126.

**Table 2.** HDA Reaction of Brassard's Diene with Aliphatic Aldehydes Catalyzed by ($R$)-BINOL/Ti(IV)/**4b**[a]



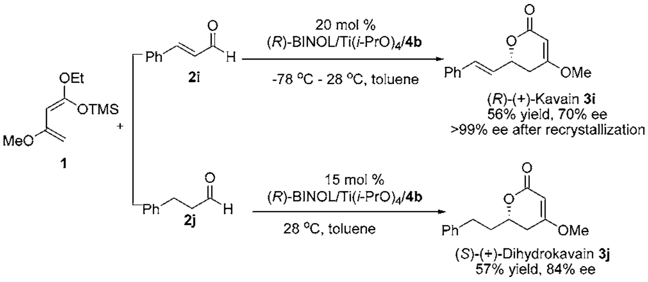
| entry | aldehyde | | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 |  | **2a** | 74 | 83 |
| 2 |  | **2b** | 46 | 82 |
| 3 |  | **2c** | 79 | 84 |
| 4 |  | **2d** | 72 | 88 |
| 5 |  | **2e** | 54 | 83 |
| 6 |  | **2f** | 65 | 81 |
| 7 |  | **2g** | 79 | 85 |
| 8[d] | PhCHO | **2h** | 56 | 87 ($R$) |

[a] Unless noted otherwise, the reactions were performed with aldehydes (0.25 mmol) and diene **1** (0.375 mmol) in 1.0 mL toluene at 28 °C for 115 h. ($R$)-BINOL:Ti($i$-PrO)$_4$:**4b** = 1:1:1; catalyst loading was 15 mol %. [b] Isolated yield. [c] Enantioselectivities were determined by GC or HPLC analysis. [d] Performed at 0 °C. The absolute configuration was determined by comparison with literature data.[12]

Kavain and dihydrokavain are lactones isolated from the kava plant *Piper methysticum* (Piperaceae).[16] Much attention has been attracted to synthesize the kava lactones.[17−19] For enantioselective syntheses of kavain and dihydrokavain, most approaches gave less than 32% overall yield in more than five steps.[18a−f] Smith completed the chiral-auxiliay-based synthesis of (+)-kavain (64% overall yield) and (+)-dihydrokavain (40% overall yield) in three steps.[18g]

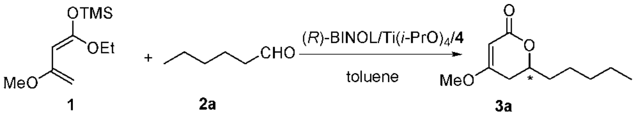
The HDA reaction of Brassard's diene with cinnamaldehyde and 3-phenylpropionaldehyde can afford the kavain and dihydrokavain in one step.[20,8,12] However, up to now, this approach only produced kavain in 13% ee[8] and dihydrokavain in 69% ee.[12] In our catalytic system, ($R$)-(+)-kavain was obtained in 56% yield with 70% ee[21] and ($S$)-(+)-dihydrokavain was obtained in 57% isolated yield with 84% ee. After a single recrystallization, enantiopure ($R$)-(+)-kavain (>99% ee) could be obtained. The absolute configurations of the natural products were determined by comparison with literature data.[18,12]

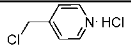
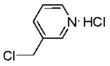
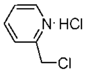
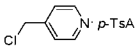
**Scheme 1.** One-Step Synthesis of ($R$)-(+)-Kavain and ($S$)-(+)-Dihydrokavain



Though the precise role of the additive **4b** is still unclear, it can be confirmed that the substituted position of the chloromethyl group on the pyridine ring as well as the acid part are essential for the successful asymmetric HDA reaction with aliphatic aldehydes. As shown in Table 3, when the substituted position changed from $p$, $m$, to $o$, the ee of the product decreased from 71% to 64% to 28% (Table 3, entries 1−3). The replacement of HCl with $p$-toluenesulphonic acid ($p$-TsA) only led to racemic product (Table 3, entry 4).

**Table 3.** Additive Effects on the HDA Reaction of Brassard's Diene with Hexanal Catalyzed by ($R$)-BINOL/Ti(IV)/**4**[a]



| entry | additive | | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 |  | **4b** | 57 | 71 |
| 2 |  | **4c** | 54 | 64 |
| 3 |  | **4d** | 42 | 28 |
| 4 |  | **4e** | 53 | 0 |

[a] All reactions were performed with hexanal (0.25 mmol) and diene **1** (0.375 mmol) in 1.0 mL toluene for 48 h. ($R$)-BINOL:Ti($i$-PrO)$_4$:**4** = 1:1:1; catalyst loading was 10 mol %. [b] Isolated yield. [c] Enantioselectivities were determined by GC analysis.

Nonlinear effect (NLE)[22] for the present system was investigated by varying ee's of the chiral BINOL while

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(19) For synthesis of dihydrokavain-5-ol, see: (a) Friesen, R. W.; Vanderwal, C. *J. Org. Chem.* **1996**, *61*, 9103. (b) Arai, Y.; Masuda, T.; Yoneda, S.; Masaki, Y.; Shiro, M. *J. Org. Chem.* **2000**, *65*, 258. (c) Singh, R. P.; Singh, V. K. *J. Org. Chem.* **2004**, *69*, 3425.

(20) (a) Castellino, S.; Sims, J. J. *Tetrahedron Lett.* **1984**, *25*, 4059. (b) Pierres, C.; George, P.; Hijfte, L.; Ducep, J. B.; Hibert, M.; Mann, A. *Tetrahedron Lett.* **2003**, *44*, 3645.

(21) A 20 mol % catalyst loading was employed, and the diene **1** was added at −78 °C (for details, see Supporting Information).

(22) For a review of nonlinear effects, see: Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922.

keeping the other reaction conditions the same as above. As shown in Figure 1, a strong positive nonlinear effect was observed, which implied that the reaction occurred in the presence of a polymeric titanium active species.

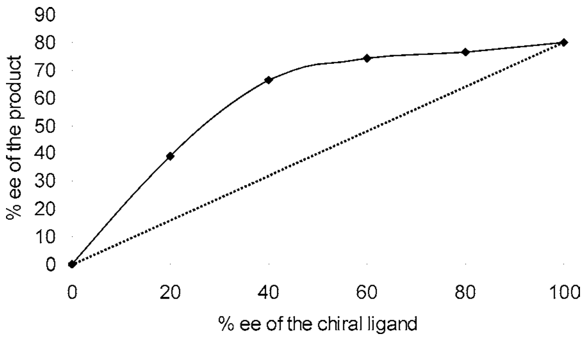

**Figure 1.** Nonlinear effect in the HDA reaction of Brassard's diene **1** with hexanal **2a**.

In conclusion, the catalytic enantioselective hetero-Diels−Alder reaction of Brassard's diene with aliphatic aldehydes has been achieved by a (*R*)-BINOL/Ti(*i*-PrO)$_4$/**4b** system to afford the corresponding $\delta$-lactone derivatives in moderate-to-good yields (46−79%) with high enantioselectivities (up to 88% ee). By using this methodology, natural products, (*R*)-(+)-kavain (70% ee, >99% ee after single recrystallization) and (*S*)-(+)-dihydrokavain (84% ee) were prepared in one step starting from cinnamaldehyde and 3-phenylpropionaldehyde. Further efforts will be devoted to understanding the mechanism, searching for more efficient catalyst system, and applying this methodology to synthesize other natural products.

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**Supporting Information Available:** Experimental procedures, effects of additive, temperature, solvent and other catalysts, and spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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