JOC*Article*

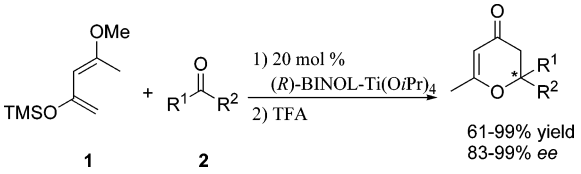
Highly Enantioselective Synthesis of 2,6-Disubstituted and 2,2,6-Trisubstituted Dihydropyrones: A One-Step Synthesis of (*R*)-(+)-Hepialone and Its Analogues

Weiqing Yang,[†] Deju Shang,[†] Yanling Liu,[†] Ying Du,[†] and Xiaoming Feng*,[†,‡]

Key Laboratory of Green Chemistry & Technology (Sichuan University), Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China, and State Key Laboratory of Applied Organic Chemistry, Lanzhou 730000, China

xmfeng@scu.edu.cn

Received July 14, 2005



An efficient enantioselective approach to chiral dihydropyrones has been developed by the hetero-Diels−Alder (HDA) reactions of (*E*)-4-methoxy-2-trimethylsiloxy-penta-1,3-diene (diene **1**) with aldehydes and pyruvates. It has been found that the readily accessible (*R*)-BINOL-Ti(O*i*Pr)$_4$ (1.1:1) complex was a very effective catalyst for this reaction. Aromatic, heteroaromatic, conjugated, and aliphatic aldehydes afforded the corresponding products in moderate to high isolated yields (up to 99%) with excellent enantioselectivities (up to 99% ee). The first example of highly enantioselective synthesis of 2,2,6-trisubstituted dihydropyrones by the catalytic reaction of diene **1** with pyruvates was reported. The isolated intermediates indicated that this asymmetric HDA reaction proceeded in a Mukaiyama aldol pathway. On the basis of the absolute configurations of the products, a possible mechanism was proposed. Moreover, the catalytic system could be used to synthesize a series of enantioenriched β-hydroxyketones **4**. Finally, this methodology was successfully applied for the one-step synthesis of the important natural product (*R*)-(+)-Hepialone with 88% isolated yield and 94% enantioselectivity.

Introduction

Chiral pyran derivatives are important intermediates for the synthesis of many biologically active compounds. Asymmetric reactions using a catalytic amount of a chiral catalyst are among the most useful and efficient methods for the syntheses of these compounds. HDA reactions of Danishefsky's diene with aldehydes promoted by Lewis acids, which provide 2,3-dihydro-4*H*-pyran-4-one derivatives, are promising tools for the construction of pyran ring systems.[1] Recently, some effective catalysts for HDA reactions have been developed and applied to the synthesis of natural products.[2] However, although high enantioselectivities were observed in some cases, the main products of the HDA reactions are 6-unsubstituted pyranone derivatives in most cases.

Asymmetric HDA reactions of Danishefsky's diene with aldehydes could only provide 2-substituted dihydropyrones. To date, there have been some examples of the synthesis of multisubstituted dihydropyrones,[2d,f,3] while the synthesis of 2,6-disubstituted dihydropyrones has not yet been fully studied. Low enantioselectivity (18% ee) was achieved by Togni using a chiral vanadium catalyst in the early 1990s.[3d] Very recently, the Gouverneur group reported the synthesis of enantioenriched 2-(4-methoxyphenyl)-6-methyl-2,3-dihydro-4*H*-pyran-4-one **3o** by a bioorganic route using aldolase ab84G3 or ab93F3.[4] There have not been reports about the asymmetric synthesis of 2,2,6-trisubstituted dihydropyrones, to the best of our knowledge. Recently, we reported our preliminary studies of the HDA reaction of (*E*)-4-methoxy-2-trimethylsiloxy-penta-1,3-diene (diene **1**) with aromatic aldehydes.[5] The

[†] Sichuan University.
[‡] State Key Laboratory of Applied Organic Chemistry.

(1) Reviews: (a) Kagan, H. B. *Comprehensive Organic Chemistry*; Pergamon: Oxford, 1992; Vol. 8. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Lin, G.; Li, Y.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*, Wiley: New York, 2001. (d) Carmona, D.; Lamata, M. P.; Oro, L. A. *Coord. Chem. Rev.* **2000**, *200*−*202*, 717−772. (e) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (f) Jørgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093−2102. (g) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558−3588 and references therein.

10.1021/jo051458s CCC: $30.25
Published on Web 09/21/2005

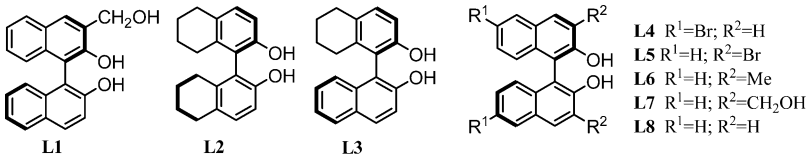


FIGURE 1. Ligands applied to the HDA reaction of benzaldehyde with diene **1**.

present paper describes our detailed studies of the relationship between catalyst structure and activity, substrate generality, the absolute configuration of products, reaction mechanism, and application to the synthesis of the natural product (*R*)-(+)-Hepialone.

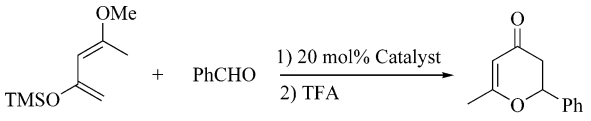
Results and Discussion

Various ligands (Figure 1) and Lewis acids were examined as catalysts for the HDA reaction of benzaldehyde with diene **1**. Some representative results are listed in Table 1. The Ti(IV) complex of (*R*)-BINOL (**L8**) gave the desired product in highest yield and with highest ee (Table 1, entry 8). The derivatives of BINOL were also screened. Our results demonstrated that steric hindrance at 3,3′-positions was disadvantageous (Table 1, entries 1 and 5−7). (*R*)-6,6′-Br_2-BINOL produced almost the same results as (*R*)-BINOL (Table 1, entries 4 vs 8). The catalysts derived from hydrogenated (*R*)-BINOL both had high enantioselectivities (Table 1, entries 2 and 3), unfortunately the catalytic activity decreased with the increase of dihedral angle of the axial biaryl group in the BINOL series. Besides the Ti(IV)-BINOL complex, other metal-BINOL complexes were also examined. Al(III)-BINOL complexes could catalyze the reaction but gave low enantioselectivities (Table 1, entries 11 and 12). The (*R*)-BINOL-Ti(O*i*Pr)$_4$ complex afforded better results than (*R*)-BINOL-Ti(O*i*Pr)$_2$Cl$_2$ and (*R*)-BINOL-$TiCl_4$ (Table 1, entries 8 vs 9 and 10). The (*R*)-BINOL-Ti(O*i*Pr)$_4$ (1:1) complex was selected as catalyst for screening the following parameters: the ratio of BINOL to Ti(O*i*Pr)$_4$, solvent, catalyst loading, substrate concentration, and temperature. The optimal conditions are listed in Table 2, footnote a.

To obtain better results, 4 Å MS were added to the reaction mixtures (Table 2). Both the isolated yields and enantioselectivities acquired in the presence of 4 Å MS (Table 2, entries 2−4) were higher than those obtained in the absence of MS (Table 2, entry 1). The best result was obtained when 120 mg of 4 Å MS was used (Table 2, entry 3).

Encouraged by the results obtained with benzaldehyde as a starting material, a variety of other aldehydes were investigated under the optimized reaction conditions (Table 3). Aromatic, heteroaromatic, conjugated, and aliphatic aldehydes and pyruvates afforded the corre-

TABLE 1. Effects of the Ligands on the HDA Reaction of Diene 1



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

entry[a]	ligand	metal compounds	yield (%)[b]	ee (%)[c]
1	L1	Ti(O*i*Pr)$_4$	33	26
2	L2	Ti(O*i*Pr)$_4$	15	85
3	L3	Ti(O*i*Pr)$_4$	37	82
4	L4	Ti(O*i*Pr)$_4$	51	84
5	L5	Ti(O*i*Pr)$_4$	35	43
6	L6	Ti(O*i*Pr)$_4$	46	46
7	L7	Ti(O*i*Pr)$_4$	7	12
8	L8	Ti(O*i*Pr)$_4$	58	86
9	L8	Ti(O*i*Pr)$_2$Cl$_2$	34	59
10	L8	$TiCl_4$	29	37
11	L8	Al(O*i*Pr)$_3$	52	17
12	L8	$AlEt_3$	33	23

[a] All reactions were carried out on a 0.25 mmol scale in 1.0 mL of toluene with 20 mol % catalyst loading (ligand/metal = 1.1) at 0 °C for 48 h. [b] Isolated yield of **3a**. [c] The ee values of **3a** were determined by HPLC using chiralcel OD.

TABLE 2. Effects of 4 Å MS on the HDA Reaction of Benzaldehyde with Diene 1

entry	amount of 4 Å MS (mg)	yield (%)[b]	ee (%)[c]
1	0	54	90
2	60	62	98
3	120	70	99
4	180	68	99

[a] All reactions were carried out on a 0.25 mmol scale in 1.0 mL of toluene with 20 mol % catalyst loading [(*R*)-BINOL/Ti(O*i*Pr)$_4$ = 1.1:1] at 0 °C for 48 h. [b] Isolated yield of **3a**. [c] The ee values of **3a** were determined by HPLC using chiralcel OD.

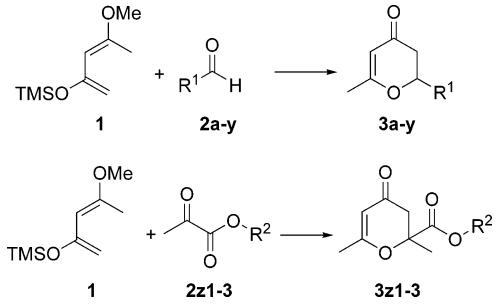
(2) For recent reports, see: (a) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336−1337. (b) Fan, Q.; Lin, L.; Liu, J.; Huang, Y.; Feng, X.; Zhang, G. *Org. Lett.* **2004**, *6*, 2185−2188. (c) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846−5850. (d) Fu, Z.; Gao, B.; Yu, Z.; Yu, L.; Huang, Y.; Feng, X.; Zhang, G. *Synlett* **2004**, 1772−1775. (e) Du, H.; Zhao, D.; Ding, K. *Chem. Eur. J.* **2004**, *10*, 5964−5970. (f) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793−3798. (g) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (h) Du, H.; Long, J.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 4349−4352. (i) Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* **2002**, *67*, 2175−2178. (j) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10−11. (k) Kii, S.; Hashimoto, T.; Maruoka, K. *Synlett* **2002**, 931−932. (l) Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1333−1336. (m) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772−10773. (n) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974−9983. (o) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366−5367. (p) Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, *57*, 845−851. (q) Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2000**, 824−825. (r) Leveque, L.; Le Blanc, M.; Pastor, R. *Tetrahedron Lett.* **2000**, *41*, 5043−5046. (s) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649. (t) Simonsen, K. B.; Svenstrup, N.; Roberson, M.; Jørgensen, K. A. *Chem.−Eur. J.* **2000**, *6*, 123−128. (u) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400. (v) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−405. (w) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 118−121. (x) Wang B.; Feng, X.; Cui, X.; Liu, H.; Jiang, Y. *Chem. Commun.* **2000**, 1605−1606.

(3) (a) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599−8605. (b) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757−5762. (c) Gong, L.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 2327−2331. (d) Togni, A. *Organometallics* **1990**, *9*, 3106−3113.

(4) Baker-Glenn, C.; Hodnett, N.; Reiter, M.; Ropp, S.; Ancliff, R.; Gouverneur, V.; *J. Am. Chem. Soc.* **2005**, *127*, 1481−1486.

(5) Huang, Y.; Feng, X.; Wang, B.; Zhang, G.; Jiang, Y. *Synlett* **2002**, 2122−2124

TABLE 3. Asymmetric HDA Reactions of Carbonyl Compounds with Diene 1

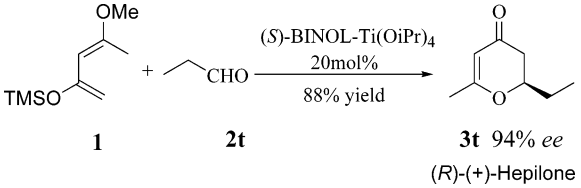


entry[a]	substrate	yield (%)[c]	ee (%)[d]
1	benzaldehyde (**2a**)	70	99
2	2-methylbenzaldehye (**2b**)	66	89
3	3-methylbenzaldehye (**2c**)	73	>99
4	4-methylbenzaldehye (**2d**)	93	99
5	2-chlorobenzaldehyde (**2e**)	90	83
6	3-chlorobenzaldehyde (**2f**)	83	98
7	4-chlorobenzaldehyde (**2g**)	81	99
8	1-naphthaldehyde (**2h**)	78	>99
9	2-naphthaldehyde (**2i**)	82	97
10	4-phenylbenzaldehye (**2j**)	93	98
11	4-fluorobenzaldehyde (**2k**)	89	94[e]
12	4-cyanobenzaldehyde (**2l**)	86	94
13	4-nitrobenzaldehyde (**2m**)	99	>99
14	3-methoxybenzaldehye (**2n**)	61	98
15	4-methoxybenzaldehye (**2o**)	83	>99 (*R*)
16	4-bromobenzaldehye (**2p**)	73	93 (*R*)
17	3-pyridinecarboxaldehyde (**2q**)	65	98
18	(*E*)-cinnamaldehyde (**2r**)	64	92[f]
19	3,4-dichlorobenzaldehyde (**2s**)	77	98
20	Propionaldehyde (**2t**)	88	94[e] (*S*)
21	*n*-butyraldehyde (**2u**)	70	92[e]
22	isobutyraldehyde (**2v**)	84	91[e]
23	*n*-pentanal (**2w**)	89	91[e]
24	*n*-hexanal (**2x**)	77	91[e]
25	cyclohexanecarboxaldehyde (**2y**)	61	85[e]
26[b]	ethyl pyruvate (**2z1**)	85	99[g]
27[b]	methyl pyruvate (**2z2**)	82	94[e]
28[b]	isopropyl pyruvate (**2z3**)	76	96[g]

[a] Entries 1−25 were carried out in the presence of 120 mg of 4 Å MS on a 0.25 mmol scale in 1.0 mL of toluene with 20 mol % catalyst loading [(*R*)-BINOL/Ti(O*i*Pr)$_4$ = 1.1:1] at 0 °C for 48 h. [b] Entries 26−28 were carried out on a 0.25 mmol scale in 1.0 mL THF with 10 mol % catalyst loading [(*R*)-BINOL/Ti(O*i*Pr)$_4$ = 2:1] at 0 °C for 72 h. [c] Isolated yield of **3**. [d] Determined by HPLC using a chiralcel OD column, unless otherwise stated. [e] Determined by HPLC using a chiralcel OBH column. [f] Determined by HPLC using a chiralpak AD column. [g] Determined by HPLC using a chiralcel OJ column.

sponding products in moderate to high isolated yields with considerably high ee values. A comparison of the experimental results (Table 3, entries 1−7) revealed the negative effect of *o*-substitution on benzaldehyde on the reaction enantioselectivity. The reactions of *o*-methyl- and *o*-chlorobenzaldehydes afforded the products with 89% and 83% ee, respectively (Table 3, entries 2 and 5), which were lower than those obtained from *m*- or *p*-substituted benzaldehydes (98−99% ee, Table 3, entries 3, 4, 6, and 7). It seemed that the electronic effect of substrates (Table 3, entries 11−15) was not so significant as the steric effect. The reason better results were obtained with acyclic aliphatic aldehydes (Table 3, entries 20−24) compared to cyclic aliphatic aldehyde (Table 3, entry 25) may be attributable to the steric hindrance of the cyclic aldehyde. A few pyruvates were also explored under the same reaction conditions as benzaldehyde, but

SCHEME 1. One-Step Synthesis of (*R*)-(+)-Hepialone



the results were not very good. There is only one hapto when benzaldehyde coordinates to the center metal Ti-(IV); however, two haptoes[1f] may exist when a pyruvate coordinates to the Ti(IV). Therefore, the reaction condition was reoptimized. When the reactions of the pyruvates were carried out under reoptimized conditions, good results were obtained (Table 3, entries 26−28).

(*R*)-(+)-2-Ethyl-6-methyl-2,3-dihydro-4*H*-pyran-4-one **3t** (Scheme 1) is a male moth sex pheromone that has been isolated from *Hepialus hecta L.* and *Hepialus californicus Bdv.*[6] It has already been the target of several synthetic studies.[7] In 1985, the Kamikawa group reported the multistep synthesis of optically pure **3t** from (*R*)-1,2-Epoxybutane.[7b] Applying our methodology, the propionaldehyde **2t** was used as the substrate in the asymmetric HDA reaction with diene **1** catalyzed by (*R*)-BINOL-Ti(O*i*Pr)$_4$ complex, and then (*S*)-(−)-Hepialone (Table 3, entry 20) was acquired in 88% yield and with 94% ee. As expected, the opposite optical isomer, the natural product (*R*)-(+)-Hepialone, was easily obtained in one step with the similar results (Scheme 1) when (*R*)-BINOL was replaced by (*S*)-BINOL.[8] Therefore, this catalytic system has provided one of the most direct and convenient approaches to the synthesis of (*R*)-(+)-Hepialone.

The absolute configuration of dihydropyrone **3p** was determined unambiguously by the Bijvoet method to be *R* with an absolute structure parameter of −0.031(17) on the basis of the anomalous dispersion of the bromine heavy atom (for details see Supporting Information). The absolute configuration of dihydropyrone **3o** was determined to be *R* by comparison of HPLC retention time with that reported.[4] Accordingly, it can be concluded that the reactions of the aromatic aldehydes **2o**, **2p** afforded dihydropyrones (*R*)-**3o**, **3p** when the (*R*)-BINOL-Ti(O*i*Pr)$_4$ complex was used, whereas the reaction of the aliphatic aldehyde **2t** gave dihydropyrone (*S*)-**3t** with the same catalyst.

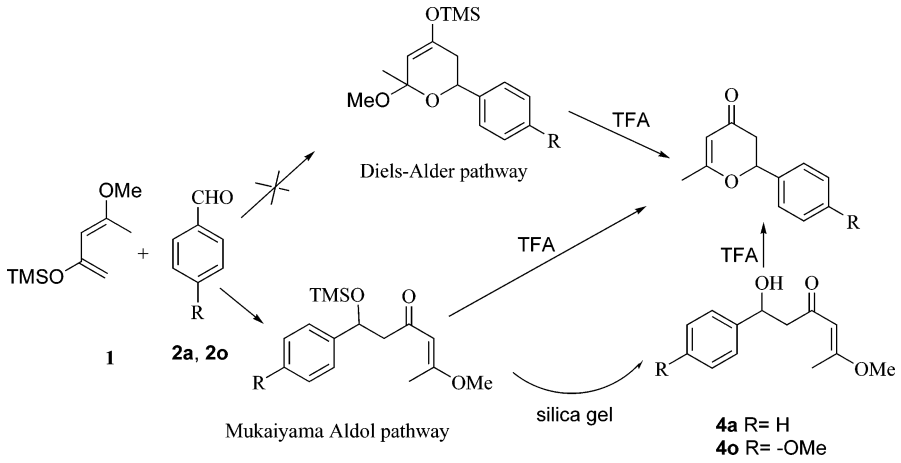
Two mechanistic pathways have been considered for HDA reactions of carbonyl compounds with Danishefsky's diene catalyzed by Lewis acids (Scheme 2). Utilizing B(III),[9] Ti(IV),[2r,10] and Zr(IV)[2f] catalysts frequently leads to a stepwise mechanism involving an initial Mukaiyama aldol addition, followed by cyclization. However, the

(6) (a) Francke, W.; Mackenroth, W.; Schröder, W.; Schulz, S.; Tengö, J.; Engels, E.; Engels, W.; Kittmann, R.; D. Schneider, *Z. Naturforsch.* **1985**, *40c*, 145−147. (b) Sinnwell, V.; Schulz, S.; Francke, W.; Kittmann, R.; Schneider, D. *Tetrahedron Lett.* **1985**, *26*, 1707−1710. (c) Kubo, I.; Matsumoto, T.; Wagner, D. L.; Shoolery, J. N. *Tetrahedron Lett.* **1985**, *26*, 563−566.

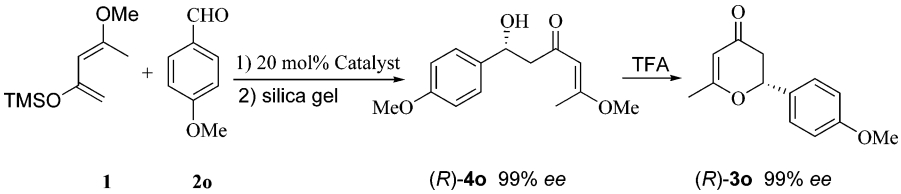
(7) (a) Dreessen, S.; Schabbert, S.; Schaumann, E. *Eur. J. Org. Chem.* **2001**, 245−251 and references therein. (b) Uchino, K.; Yamagiwa, Y.; Kamikawa, T.; Kubo, I. *Tetrahedron Lett.* **1985**, *26*, 1319−1320.

(8) The absolute configuration of **3t** was determined according to ref 7b.

SCHEME 2. Two Possible Pathways for the HDA Reaction of Diene 1 with Aldehyde



SCHEME 3. Synthesis of Enantioenriched β-Hydroxy Ketones and Cyclization to Dihydropyrones



concerted Diels−Alder pathway has been positively identified in reactions catalyzed by Lewis acids based on Zn(II),[11] Cu(II),[2w,3a,b,12] Rh(II),[2o,13] Al(III),[3c,14] Cr(III),[2p,u,v] Ce(III),[15] and Eu(III).[16]

In almost all reactions using (*R*)-BINOL-Ti(O*i*Pr)$_4$ (1.1:1.0) complexes, only one new product was observed by TLC detection. In the reactions of **2a** and **2o** with diene **1,** the products were carefully isolated using pretreated silica gel[17] column chromatography before treatment with TFA. The isolated intermediates **4a** and **4o** were β-hydroxy ketones[18] (Scheme 2). These facts indicated that the HDA reactions catalyzed by the chiral Ti(IV) complex proceeded via the Mukaiyama aldol pathway. In addition, the aldol adducts easily cyclized quantitatively to afford the desired products with no loss of enantioselectivity.[19] Therefore, the catalytic system could be used to synthesize a series of enantioenriched β-hydroxy ketones, because compound **4** could be easily acquired and was stable enough to exist (Scheme 3).

On the basis of the observed absolute configurations of the products (**3o**, **3p**, **3t**) and the structures of intermediates, a possible mechanism for asymmetric induction in this catalytic system could be outlined as in Figure 2. When the (*R*)-BINOL-Ti(O*i*Pr)$_4$ complex is used as the catalyst, the steric hindrance of the binaphthyl moiety shields the *si* face of the aldehyde, while the *re* face is available to accept the attacking diene to give the products as expected. On the other hand, the aldehyde cannot bond to Ti(IV) by the other face of the C═O, which is caused by the large steric hindrance between the binaphthyl moiety and aldehyde R group.

In conclusion, an efficient catalytic enantioselective HDA reaction of (*E*)-4-methoxy-2-trimethylsiloxy-penta-1,3-diene and aldehydes using a Ti(IV)-(*R*)-BINOL complex has been documented. A wide range of aldehydes were employed and provided the products with high yields (61−99%) and excellent enantioselectivities (83−99% ee) under mild conditions. All of the surveyed pyruvates afforded 2,2,6-trisubstituted dihydropyrones in good yields (76−85%) and high ee values (94−99%). This is the first example of highly enantioselective syntheses of 2,2,6-trisubstituted dihydropyrones. On the basis of the intermediates isolated, a Mukaiyama aldol pathway was confirmed. A possible TS model was proposed according to the observed absolute configurations of the products. In addition, a series of chiral β-hydroxy-ketones could be easily synthesized using this catalytic

(9) (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907−6910. (b) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951−1952. (c)Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246−1255.

(10) (a) Matsukawa, S.; Mikami, K. *Tetrahedron: Asymmetry* **1997**, *8*, 815−816. (b) Keck, G. E.; Li, X.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998−5999.

(11) (a) Yao, S.; Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin. Trans. 1* **1997**, 2345−2349. (b) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807−7808.

(12) (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427−2430. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2165−2168.

(13) (a) Motoyama, Y.; Koga, Y.; Nishiyama, H. *Tetrahedron* **2001**, *57*, 853−860. (b) Faller, J. W.; Smart, C. J. *Tetrahedron Lett.* **1989**, *30*, 1189−1192.

(14) (a) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3501−3504. (b) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc*. **1988**, *110*, 310−312.

(15) Molander, G. A.; Rzasa. R. M. *J. Org. Chem.* **2000**, *65*, 1215−1217.

(16) (a) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451−3454. (c) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060−7067.

(17) Silica gel was pretreated by 0.3% NEt_3 in petroleum ether.

(18) The isolated intermediates **4a** and **4o** were a hydroxy-free form. A similar example can be seen in ref 2f. Compounds **4a** and **4o** were confirmed by ^{1}H and ^{13}C NMR and HRMS data; for details see Supporting Information.

(19) The ee values was determined by HPLC using a chiralcel OJ column, and the racemate of **4o** was acquired by the reaction of **2o** with diene **1** catalized by (±)-BINOL; for details see Supporting Information.

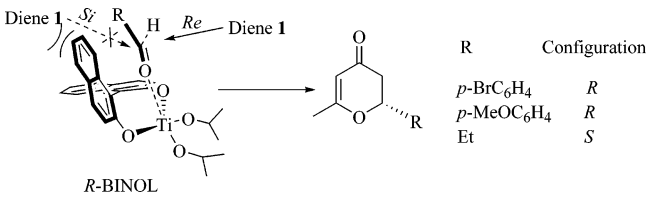


FIGURE 2. Proposed TS model of the HDA reaction of diene **1** with aldehydes catalyzed by (*R*)-BINOL-Ti(O*i*Pr)$_4$.

system. Finally, a natural product, (*R*)-(+)-Hepialone, has also been prepared in one step using this methodology from simple achiral materials. Future efforts will be devoted to understanding the effects of different substituents on Danishefsky's diene and to searching for effective catalysts for ketones.

Experimental Section

6-Methyl-2-phenyl-2,3-dihydro-4*H*-pyran-4-one (3a). A mixture of (*R*)-BINOL (15.8 mg, 0.055 mmol), Ti(O*i*Pr)$_4$ (1 M in toluene, 50 μL, 0.050 mmol), and 4 Å molecular sieves (120 mg) in toluene (1.0 mL) was heated at 35 °C for 1 h. The red mixture was cooled to room temperature, and benzaldehyde (26 μL, 0.25 mmol) was added. The mixture was cooled to 0 °C, and diene **1** (69.7 mg, 0.375 mmol) was added. The contents were stirred at 0 °C for 48 h, and then TFA (0.1 mL) was added to this solution. The mixture was stirred overnight [monitored by TLC (petroleum ether/ethyl acetate, 5:1)]. Saturated $NaHCO_3$ (5 mL) was added, and the solution was stirred for an additional 5 min. It was diluted with 5 mL CH_2Cl_2 and filtered through a plug of Celite. The resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and then the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude final product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to afford a colorless viscous liquid (33 mg, 70% yield, 99% ee). The ee was determined by HPLC analysis using a chiral OD column (hexane/2-propanol 90:10, 1.0 mL/min, t_r (minor) = 10.0 min, t_r (major) = 12.1 min). $[\alpha]^{25}_D$ = −81.4 (*c* 0.36, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.39 (m, 5H), 5.45 (s, 1H), 5.40 (dd, J = 14.1, 3.6 Hz, 1H), 2.83 (dd, J = 16.8, 14.1 Hz, 1H) 2.60 (dd, J = 16.8, 3.6 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 192.4, 174.4, 138.2, 128.8, 126.2(2C), 105.2, 80.9, 42.4, 21.2. HRMS: calcd for $C_{12}H_{12}O_2$ (Na+) 211.0730, found 211.0737.

1-Hydroxy-5-methoxy-1-phenylhex-4-en-3-one (4a). Intermediate **4a** [white solid (41.3 mg, 75% yield, mp = 65−66 °C)] could be isolated by flash chromatography (petroleum ether/ethyl acetate, 5:1) at the end of the reaction of benzaldehyde with diene **1** before treatment with TFA. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24−7.11 (m, 5H), 5.26 (s, 1H), 5.03 (m, 1H), 3.89 (d, J = 2.2 Hz, 1H), 3.49 (s, 3H), 2.68 (d, J = 6.1 Hz, 2H), 2.19 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.1, 174.3, 143.2, 128.4, 127.4, 125.7, 99.1, 70.6, 55.6, 52.3, 20.1, HRMS calcd for $C_{13}H_{16}O_3$ (Na+) 243.0992, found 243.0997.

Acknowledgment. The authors thank the National Natural Science Foundation of China (nos. 20225206, 20472056, and 20390055), and the Ministry of Education of China (nos. 104209, 20030610021, and others) for financial support. The authors are also grateful to Prof. Guolin Zhang of Chengdu Institute of Biology, Chinese Academy of Sciences, China, for fruitful discussions.

Supporting Information Available: Experimental procedure for the asymmetric HDA reactions and the characterization of **3a**−**3z**, **4a**, and **4o**, including ^{1}H and ^{13}C NMR, HRMS data, HPLC conditions, data in CIF format, etc. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051458S