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Chiral dihydropyranones via hetero Diels–Alder reaction of Danishefsky's diene and α-ketoesters: a high-throughput screening approach

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Abstract—The chiral Lewis acid-catalyzed hetero Diels–Alder reaction between Danishefsky's diene and sterically hindered α-ketoesters has been optimized using a validated high-throughput screening method. The yields and enantioselectivities of three chiral dihydropyranones obtained by this multi-substrate one-pot screening approach are in excellent agreement with individual screening results. Employing ethyl benzoylformate, ethyl 3-methyl-2-oxobutyrate, and dihydro-4,4-dimethyl-2,3-furandione in one reaction mixture allowed a fast evaluation of chiral Lewis acid composition, solvent, temperature, catalyst loading, and dienophile concentration. The crude product mixtures were analyzed by HPLC using two chiral stationary phases coupled in series to avoid time-consuming work-up procedures.

1. Introduction

Many biologically active compounds, such as pharmaceuticals, agrochemicals, flavors, and nutrients are chiral with more than 50% of today's top-selling drugs being single enantiomers. The increasing demand for enantiopure chemicals has been accompanied by significant progress in asymmetric synthesis[1] and catalysis,[2] and by the development of analytical techniques for the determination of the enantiomeric purity of chiral compounds.[3] The constant search for new asymmetric synthetic methods has been substantially facilitated by the development of high-throughput screening (HTS) procedures that allow fast identification of effective catalysts and optimization of reaction conditions.[4] Recently, a HTS method utilizing chiral chromatography has been developed by us and others.[5] Employing three representative prochiral aldehydes in the β-amino alcohol-promoted enantioselective alkylation of aldehydes with diethyl zinc, we were able to demonstrate that multi-substrate one-pot screening followed by chiral gas chromatography provides yields, stereoselectivity, catalytic activity, chiral induction, and substrate tolerance of a catalyst in a single experiment.

The asymmetric Diels–Alder reaction promoted by chiral Lewis acids (CLA's) is one of the most versatile and powerful methods for the total synthesis of natural products.[6] The concept of Lewis acid catalysis using chiral ligands such as BINOL, BINAP, TADDOL, and bisoxazolines has also been applied to a variety of hetero Diels–Alder (HDA) reactions.[7] Aldehydes and imines have frequently been employed as dienophiles in asymmetric $[2\pi + 4\pi]$-cycloadditions providing a convenient access to partly unsaturated six-membered heterocycles.[8] By contrast, only a few examples of enantioselective cycloadditions with ketones have been reported in the literature because of their inherently low reactivity.[9] The cycloaddition of dienes and ketones provides instant access to chiral dihydropyranones exhibiting a stereogenic quaternary carbon atom.[10] Dihydropyranones have been utilized as important building blocks in the natural product synthesis of carbohydrates, pheromones, insect toxins, antitumor agents, antibiotics, and antiinflammatory sesterterpenoids.[11] To date, high yields and enantioselectivities have been observed for HDA reactions using alkyl pyruvates, 2,3-butanedione, 3-phenyl-2,3-propanedione, or ethyl ketomalonate as the dienophile (Scheme 1). The variety of ligands

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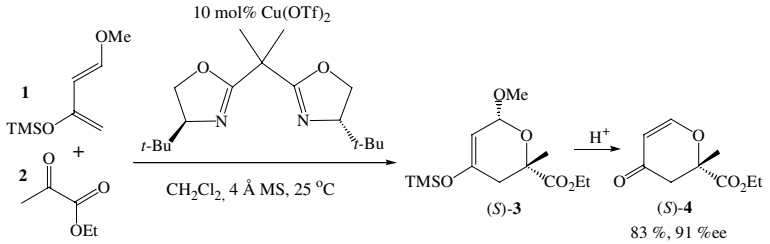


Scheme 1. CLA-catalyzed cycloaddition between Danishefsky's diene, **1**, and ethyl pyruvate, **2**.

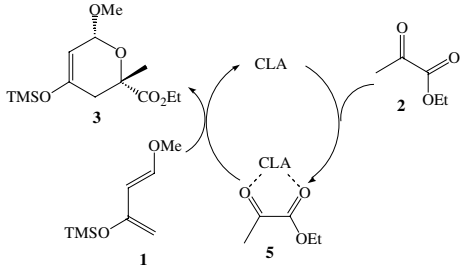
available for chiral Lewis acid catalysis and the need for fast optimization of reaction conditions require a high-throughput screening approach that facilitates a rapid development of synthetic methods toward chiral dihydropyranones.

We herein report a multi-substrate one-pot screening method based on enantioselective chromatography that allows a fast and comprehensive optimization of the chiral Lewis acid-catalyzed HDA reaction between 1-methoxy-3-trimethylsiloxy-1,3-butadiene, **1**, and α-activated ketones. Through simultaneous screening of three representative dienophiles and consecutive HPLC analysis we have been able to study the use of different chiral Lewis acids under various reaction conditions for the preparation of dihydropyranones.

2. Results and discussion

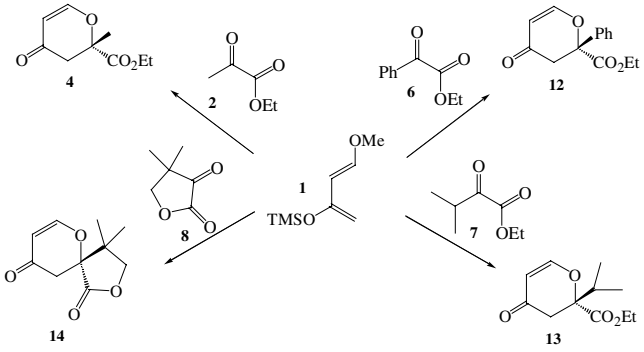
Initially, we followed Jorgensen's protocol to prepare 2-ethoxycarbonyl-5,6-dihydro-2-methylpyran-4-one, **4**, from ethyl pyruvate, **2**, using 10 mol% of 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]-Cu(OTf)$_2$ as the chiral Lewis acid in dichloromethane.[12] We obtained HDA product (*S*)-**4** after acidic treatment of intermediate cycloadduct **3** in 83% yield and 91% enantiomeric excess (Scheme 1).[13]

It is generally assumed that bidentate bisoxazoline ligands and dienophile **2** form the activated Cu(II) complex **5**. Coordination of ketoester **2** to the chiral Lewis acid reduces the energy of the LUMO of the dienophile and therefore increases its reactivity for cycloaddition with an electron-rich diene. Cycloaddition of activated **2** with Danishefsky's diene **1** yields monodentate cycloadduct **3**, which is released from the catalyst and the unloaded CLA can enter another catalytic cycle, Scheme 2.



Scheme 2. Catalytic cycle of the HDA reaction.

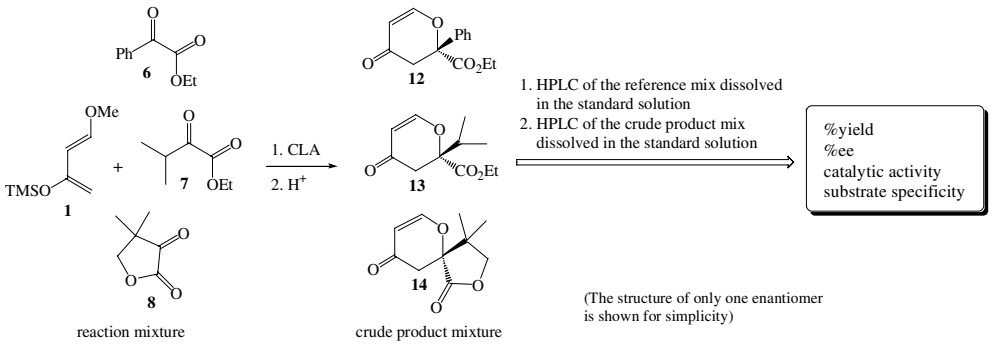
In addition to ethyl pyruvate **2**, ethyl benzoylformate **6**, ethyl 3-methyl-2-oxobutyrate **7**, and 2,3-butanedione **9**, have been used in cycloadditions with diene **1**. The enantioselective cycloaddition of ethyl ketomalonate **10** and 1-methoxybuta-1,3-diene **11** or unactivated 1,3-conjugated dienes has also been reported.[14] Notably, dihydro-4,4-dimethyl-2,3-furandione **8** has not been utilized for the synthesis of dihydropyranones to date. Introducing α-ketolactone **8** to the cycloaddition with **1** would provide access to a new highly versatile spirane **14** exhibiting a stereogenic quaternary carbon atom as the spiro center, Scheme 3.



Scheme 3. Scope of the HDA reaction using α-activated ketones **6**–**8** and Danishefsky's diene.

We employed 10 mol% 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]-Cu(OTf)$_2$ in the HDA reaction between diene **1** and dienophiles **6**–**8** using dichloromethane as the solvent to afford 2-ethoxycarbonyl-5,6-dihydro-2-phenylpyran-4-one **12**, 2-ethoxycarbonyl-5,6-dihydro-2-*iso*-propylpyran-4-one **13**, and 4,4-dimethyl-2,6-dioxa-spiro[4.5]dec-7-ene-1,9-dione **14**. In contrast to the excellent results observed for the CLA-catalyzed synthesis of **4** under the same conditions, we obtained dihydropyranones **12**–**14** in only 59% (20% ee), 42% (18% ee), and 12% (12% ee) yield, respectively. We therefore decided to develop an HTS protocol for optimizing the HDA reaction conditions including the composition of the CLA, solvent, catalyst amount, and substrate concentration (Scheme 4).

To tailor the HTS methodology previously used for the evaluation of the β-amino alcohol-catalyzed enantio-



Scheme 4. HTS of the HDA reaction using α-ketoesters **6**–**8**.

selective alkylation of prochiral aldehydes to the HDA reaction,[5d,e] we used Danishefsky's diene and dienophiles **6**–**8** to synthesize racemic dihydropyranones **12**–**14** in 43–63% yield following a literature procedure that was not further optimized.[15] With these references in hand, we then developed a three substrate one-pot HTS method based on chiral HPLC to avoid a time-consuming work-up of the crude HDA product mixture. We were able to separate cycloadducts **12**–**14** into enantiomers by HPLC using Chiralpak AS and Chiralcel OJ, respectively. However, HTS using α-ketoesters **6**–**8** in one reaction mixture required an efficient HPLC method that separated the starting materials as well as the enantiomers of all three cycloadducts in a single run. We found that this could be achieved by coupling two HPLC columns (Phenylglycine and Chiralpak AS) in series (Fig. 1).

Based on a literature survey of chiral Lewis acids employed in HDA reactions and initial screening in our laboratories, Cu(II), Sc(III), Yb(III), In(III) triflates, and bisoxazolines **L1**–**L4** were selected as promising CLA candidates (Fig. 2). We thus employed chiral Lewis acids derived from metal triflates **a**–**d** and ligands **L1**–**L4** and an equimolar mixture of α-ketoesters **6**–**8** in simultaneous screening experiments. Utilizing racemic references of **12**–**14** to determine individual response factors, we were able to obtain yields and enantiomeric purities for each cycloadduct after fast filtration of the crude product mixture and subsequent HPLC analysis.

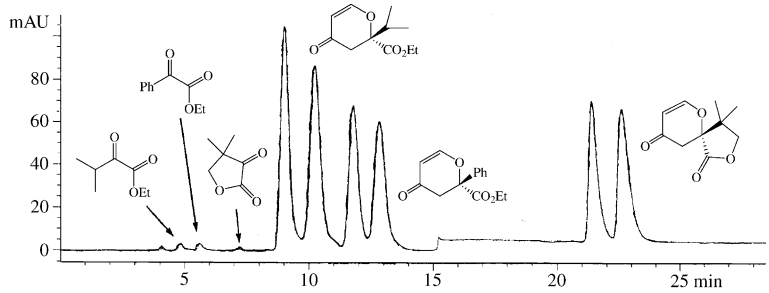


Figure 1. Separation of ketoesters **6**–**8** and the enantiomers of HDA adducts **12**–**14** in a single HPLC run. Chiral HPLC was performed on phenylglycine (4.6 × 250 mm) and Chiralpak AS (4.6 × 50 mm) coupled in series.

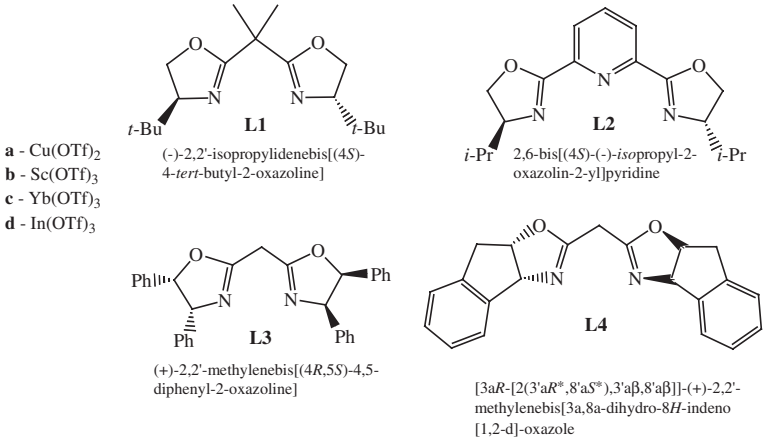


Figure 2. Lewis acids and bisoxazoline ligands used.

Table 1. HTS results for **12** in THF

Ligand	Lewis acid			
	$Cu(OTf)_2$ % yield (ee)	$Sc(OTf)_3$ % yield (ee)	$Yb(OTf)_3$ % yield (ee)	$In(OTf)_3$ % yield (ee)
L1	89 (42)	26 (6)	70 (4)	26 (9)
L2	34 (58)	30 (10)	51 (32)	83 (18)
L3	57 (74)	45 (12)	51 (14)	55 (19)
L4	91 (59)	31 (16)	82 (0)	28 (12)

Conditions: 10 mol% catalyst, 1 equiv of **1**, concentration of **6** was 0.1 M, 25 °C, 20 h.

Table 2. HTS results for **13** in THF

Ligand	Lewis acid			
	$Cu(OTf)_2$ % yield (ee)	$Sc(OTf)_3$ % yield (ee)	$Yb(OTf)_3$ % yield (ee)	$In(OTf)_3$ % yield (ee)
L1	87 (17)	16 (16)	20 (18)	51 (16)
L2	54 (10)	22 (17)	33 (24)	60 (23)
L3	69 (12)	19 (17)	32 (23)	52 (17)
L4	80 (56)	18 (0)	28 (16)	41 (16)

Conditions: 10 mol% catalyst, 1 equiv of **1**, concentration of **7** was 0.1 M, 25 °C, 20 h.

Table 3. HTS results for **14** in THF

Ligand	Lewis acid			
	$Cu(OTf)_2$ % yield (ee)	$Sc(OTf)_3$ % yield (ee)	$Yb(OTf)_3$ % yield (ee)	$In(OTf)_3$ % yield (ee)
L1	28 (48)	16 (26)	12 (10)	7 (28)
L2	12 (25)	18 (22)	18 (26)	15 (3)
L3	12 (12)	20 (12)	14 (18)	12 (6)
L4	24 (25)	14 (5)	7 (12)	8 (12)

Conditions: 10 mol% catalyst, 1 equiv of **1**, concentration of **8** was 0.1 M, 25 °C, 20 h.

The HTS results for cycloadducts **12**–**14** using 10 mol% of all 16 CLA combinations in THF are shown in Tables 1–3.

We found that CLA's derived from copper triflate and bisoxazolines **L1** and **L4** afforded superior results over the corresponding Sc(III), Yb(III), and In(III) complexes. Although $Cu(OTf)_2$ was found to be the most effective Lewis acid, the choice of the chiral ligand proved to have a strong influence on the yields and enantioselectivities obtained for cycloadducts **12**–**14**. Bisoxazoline **L4** gave superior results in the Cu(II)-catalyzed formation of **12** and **13** whereas **a**–**L1** was found to catalyze the formation of **14** with the highest yields and ees. Employing **a**–**L4** in the HDA reaction afforded **12** in 91% yield and 59% ee and **13** in 80% and 56% ee, respectively. The high steric constraints that were to be expected during the cycloaddition between **1** and **8** resulted in significantly lower yields and stereoselectivity. Accordingly, dihydropyranone **14** was obtained in only 28% yield and 48% ee using **a**–**L1** as the CLA.

We decided to evaluate the accuracy of our HTS method by comparison with results obtained by individual HDA reactions of dienophiles **6**–**8**, Table 4. We were pleased

Table 4. Comparison of simultaneous and individual screening results

Ligand	Screening method	**12** % yield (ee)	**13** % yield (ee)	**14** % yield (ee)
L1	Individual (THF)	95 (40)	88 (18)	24 (51)
	HTS (THF)	89 (42)	87 (17)	28 (48)
	HTS (CH_2Cl_2)	62 (21)	51 (10)	10 (29)
L2	Individual (THF)	34 (57)	59 (12)	14 (22)
	HTS (THF)	34 (58)	54 (10)	12 (25)
	HTS (CH_2Cl_2)	39 (18)	48 (28)	11 (13)
L3	Individual (THF)	63 (68)	73 (6)	13 (12)
	HTS (THF)	57 (74)	69 (12)	12 (12)
	HTS (CH_2Cl_2)	22 (61)	18 (17)	10 (0)
L4	Individual (THF)	95 (64)	80 (54)	25 (26)
	HTS (THF)	91 (59)	80 (56)	24 (25)
	HTS (CH_2Cl_2)	28 (59)	32 (31)	8 (5)

$Cu(OTf)_2$ (10 mol%), 1 equiv of **1**, concentration of **6** was 0.1 M, 25 °C, 20 h.

to find that the yields and ee's determined by our multi-substrate one-pot screening protocol were in very good agreement with individual screening experiments.[16] For example, employing $Cu(OTf)_2$ and bisoxazoline **L1** in our HTS method gave cycloadducts **12**–**14** in 89%, 87%, and 28%, whereas individual screening provided **12**–**14** in 95%, 88%, and 24%, respectively. The enantiomeric excess obtained by HTS was determined as 42%, 17%, and 48%, whereas the control experiments gave 40%, 18%, and 51%, respectively. Notably, yields obtained for **12**–**14** by HTS were usually slightly lower than individual screening results, whereas ee's observed by both methods proved to be very close with no systematic deviations being observed.

Comparison of THF and dichloromethane showed that THF affords superior yields and enantioselectivities (Table 4).[17] For example, high-throughput screening of the CLA-catalyzed cycloaddition between diene **1** and dienophiles **6**–**8** using $Cu(OTf)_2$ and bisoxazoline **L1** in THF gave **12** in 89% yield and 42% ee. Replacement of THF by dichloromethane decreased the results to 62% yield and 21% ee. Employing the same CLA in the synthesis of **13** and **14** also gave better results when THF was used as the solvent. A similar trend was observed when ligands **L3** and **L4** were used in combination with $Cu(OTf)_2$. For instance, **12** was prepared in 57% (74% ee) using **a**–**L3** as the CLA in THF, whereas only 22% (61% ee) was obtained in dichloromethane. Screening results with **a**–**L2** showed that THF affords better results for the synthesis of **12** and **14**, whereas dichloromethane is a superior solvent for the preparation of **13**. Further variation of the reaction conditions revealed that the highest yields are obtained at 0.1 M concentration of dienophile **6** using 10 mol% of **a**–**L4** while the enantioselectivity of the HDA reaction proved to be indepen-

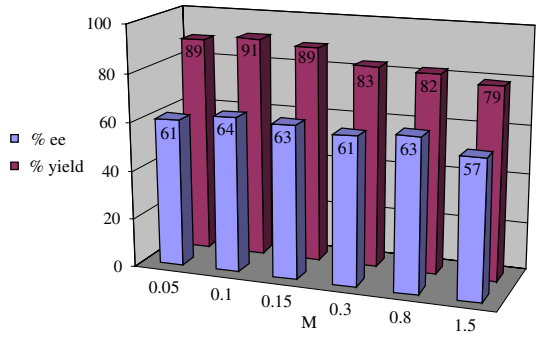


Figure 3. Study of the effect of the concentration of dienophile **6** in THF on the **a**–**L4**-catalyzed HDA reaction at 25 °C.

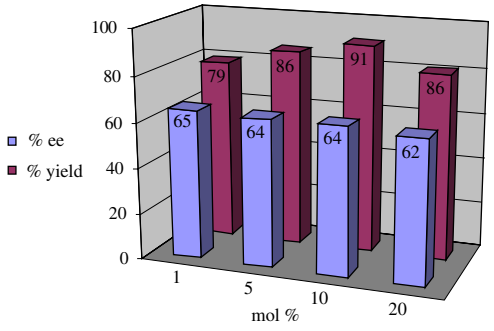


Figure 4. Effect of catalyst loading on the **a**–**L4**-catalyzed HDA reaction between Danishefsky's diene and α-ketoester **6** at 25 °C.

dent of the substrate concentration and catalyst loading, Figures 3 and 4.

As a result of our screening and optimization studies we were able to prepare dihydropyranone (+)-**12** in 95% yield and 64% ee by employing $Cu(OTf)_2$ and bisoxazoline **L4** in the HDA reaction between Danishefsky's diene and α-ketoester **6**. Reducing the reaction temperature did not improve the enantioselectivity of the HDA reaction. We obtained (+)-**12** in 95% yield and 65% ee at 0, −15, and −78 °C. The **a**–**L4**-catalyzed formation of cycloadduct (−)-**13** was found to proceed with 80% yield and 54% ee at 25 and 0 °C. However, yields and enantioselectivity of the formation of **13** increased to 97% yield and 68% ee at −15 °C and to 88% yield and 74% ee at −78 °C. In contrast, (+)-**14** was obtained in 24% yield and 51% ee using **a**–**L1** as the CLA at 25 °C and a decrease in the reaction temperature did not improve results. The broad range of yields and stereoselectivities obtained by the CLA-catalyzed synthesis of **12**–**14** reflects the different steric demands of the dienophiles used. In particular, the rigid structure of α-ketolactone **8** can be expected to impede the formation of a CLA complex and reaction with diene **1** to give sterically crowded spiro compound **14**. The increasing yields of **13** obtained at lower temperatures may be attributed to reduced polymerization of diene **1**. It should also be noted that the structure of the chiral Lewis acid or the possible coexistence of catalytically active species that may afford different enantioselectivity and turnover is not known but can be expected to have a profound effect on the temperature dependence of the yield and stereoselectivity of the cycloaddition. Lewis acids have also been reported to catalyze the a Mukaiyama aldol addition of trimethylsilyl enolethers to ketones.[18] The formation of dihydropyranones **12**–**14** from diene **1** and ketones **6**–**8** may proceed via Mukaiyama aldol reaction and cycloaddition. Both mechanisms have been observed in CLA-catalyzed reactions between silyloxybutadienes and carbonyl compounds.[19] Competition between these reaction pathways might not be detrimental to the overall yield but it could diminish the enantioselectivity and account for the unexpected temperature effects on the stereoselectivity.

3. Conclusion

We have used a validated multi substrate high-throughput screening approach for a fast and comprehensive optimization of the chiral Lewis acid-catalyzed hetero Diels–Alder reaction between Danishefsky's diene **1** and α-ketoesters **6**–**8**. Employing two chiral stationary phases coupled in series in the HPLC analysis of the crude product mixture obtained by simultaneous screening experiments of three different dienophiles avoids time-consuming work-up procedures and provides yields and enantioselectivities of chiral Lewis acid catalysts in a single screening experiment followed by two HPLC runs. Optimization of the chiral Lewis acid composition, solvent, catalyst loading, and dienophile concentration resulted in the quantitative formation of dihydropyranones **12** and **13** in 65% and 68% ee, respectively, at room temperature. Due to the high steric hindrance expected during the cycloaddition of **1** and α-ketolactone **8**, adduct **14** was formed in only 28% yield and 51% ee.

4. Experimental section

4.1. Methods

Chemicals were of reagent grade and used without further purification. All reactions were carried out under a nitrogen atmosphere and anhydrous conditions. Flash chromatography was performed on SiO_2 (particle size 0.032–0.063 mm). GC–MS was performed on a 15 m DB-1 GC column using a Fison Instruments MD800 capillary GC–Mass spectrometer equipped for EI. NMR spectra were obtained at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) on a Varian FT-NMR spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm relative to TMS. All HPLC chromatograms were obtained using an HP 1050 HPLC at a flow rate of 1 mL/min and UV detection at 254 nm. Samples were dissolved in hexanes/EtOH = 1:1 at a concentration of 1 mg/mL and separated on a phenylglycine (4.6 × 250 mm) and a Chiralpak AS (4.6 × 50 mm) column coupled in series. The mobile phase initially consisted of hexanes/EtOH = 9:1 and was changed to 25% EtOH within 1 min after 10 min.

4.2. General screening procedure

A mixture of 10 mol% of the Lewis acid and the chiral ligand in a ratio of 1:1.1 in 1 mL of anhydrous THF was stirred in the presence of 4 Å molecular sieves for 1 h under a nitrogen atmosphere. A solution containing 0.2 mmol of each ketoester in 1 mL of THF was added dropwise and stirred for another 30 min. Then, 1.1 equiv of Danishefsky's diene was added using a syringe and the reaction mixture stirred for 20 h. Addition of a solution of 10 mL of dichloromethane and 1.5 mL of 2 M HCl in diethyl ether was followed by stirring for another 2 h. The solvents were removed by evaporation and the crude product mixture dissolved in 2 mL of dichloromethane and filtered through silica gel using hexanes/ethyl acetate (2:1) as the eluent. The organic solvents of the filtrate were removed in vacuo and the residue used for chiral HPLC analysis without further purification.

4.3. HPLC analysis

Remaining ketoesters and enantiomers of dihydropyranones **12**–**14** of the crude product mixture were separated by HPLC on a phenylglycine (4.6×250 mm) and a Chiralpak AS (4.6×50 mm) column coupled in series using gradient elution. The mobile phase containing hexanes/EtOH = 9:1 was changed after 10 min to 25% EtOH within 1 min. Analytes were detected by UV at 254 nm. The chromatographic enantioselectivity, α, was calculated as 1.2 (**12**), 1.2 (**13**), and 1.1 (**14**). The dihydropyranones can also be separated individually on Chiralpak AS (4.6×50 mm) using hexanes/EtOH = 4:1 as the mobile phase with enantioselectivities of 1.5 (**12**), 2.1 (**13**), and 1.9 (**14**). In all cases, the levorotatory enantiomer was eluated first. Individual response factors were determined for all three HDA products using standard solutions of known concentrations for quantification and calculation of yields. Dilution experiments revealed excellent linearity of dihydropyranone responses over the concentration range observed in standard solutions and product mixtures.

4.4. 2-Ethoxycarbonyl-5,6-dihydro-2-methylpyran-4-one, 4[9b]

^{1}H NMR: δ 1.23 (t, $J = 9.4$ Hz, 3H), 1.63 (s, 3H), 2.65 (d, $J = 16.7$ Hz, 1H), 3.02 (d, $J = 16.7$ Hz, 1H), 4.24 (q, $J = 9.4$ Hz, 2H), 5.42 (1H, $J = 7.2$ Hz, 1H), 7.38 (d, $J = 7.2$ Hz, 1H). ^{13}C NMR: δ 14.7, 24.4, 26.6, 44.7, 83.1, 115.6, 162.6, 191.1, 197.8. EI-MS (70 eV): m/z (%): 184 (19, M^+), 111 (100, M^+-CO_2Et), 84 (12, M^+-CO_2Et, $-C_2H_3$). Ee = 91%, $[\alpha]_D^{22} = +138.3$ (c 1.2, CH_2Cl_2).

4.5. 2-Ethoxycarbonyl-5,6-dihydro-2-phenylpyran-4-one, 12[9b]

^{1}H NMR: δ 1.20 (t, $J = 9.2$ Hz, 3H), 3.04 (d, $J = 17.8$ Hz, 1H), 3.42 (d, $J = 17.8$ Hz, 1H), 4.20 (q, $J = 9.2$ Hz, 2H), 5.47 (1H, $J = 8.0$ Hz, 1H), 7.38–7.44 (m, 3H), 7.52–7.58 (m, 3H). ^{13}C NMR: δ 14.3, 44.7, 63.0, 86.0, 108.6, 125.2, 129.0, 129.3, 136.9, 161.6, 169.6, 189.8. EI-MS (70 eV): m/z (%): 246 (4, M^+), 173 (100, M^+-CO_2Et), 103 (88, M^+-CO_2Et, $-C_3H_2O_2$), 77 (58, Ph^+). Ee = 40%, $[\alpha]_D^{22} = +17.45$ (c 1.2, CH_2Cl_2).

4.6. 2-Ethoxycarbonyl-5,6-dihydro-2-*iso*-propylpyran-4-one, 13[12]

^{1}H NMR: δ 0.96 (d, $J = 8.3$ Hz, 3H), 1.02 (d, $J = 8.3$ Hz, 3H), 1.22 (t, $J = 9.2$ Hz, 3H), 2.21 (m, 1H), 2.77 (d, $J = 16.0$ Hz, 1H), 2.90 (d, $J = 16.0$ Hz, 1H), 4.20 (q, $J = 9.2$ Hz, 2H), 5.41 (1H, $J = 7.7$ Hz, 1H), 7.40 (d, $J = 7.7$ Hz, 1H). ^{13}C NMR: δ 14.5, 16.9, 17.1, 35.0, 40.8, 62.3, 88.7, 107.6, 162.5, 170.4, 190.7. EI-MS (70 eV): m/z (%): 212 (21, M^+), 169 (5, $M^+-C_3H_7$) 139 (100, M^+-CO_2Et), 97 (80, $M^+-C_3H_6$, $-CO_2Et$). Ee = 68%, $[\alpha]_D^{22} = -22.1$ (c 1.2, CH_2Cl_2).

4.7. 4,4-Dimethyl-2,6-dioxa-spiro[4.5]dec-7-ene-1,9-dione, 14

^{1}H NMR: δ 1.08 (s, 3H), 1.20 (s, 3H), 2.63 (d, $J = 18.8$ Hz, 1H), 2.73 (d, $J = 18.8$ Hz, 1H), 3.96 (d, $J = 9.0$ Hz, 1H), 4.22 (d, $J = 9.0$ Hz, 1H), 5.50 (d, $J = 7.5$ Hz, 1H), 7.22 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR: δ 18.7, 21.8, 36.3, 43.3, 77.7, 85.4, 107.6, 159.5, 188.6. EI-MS (70 eV): m/z (%): 196 (41, M^+), 181 (6, M^+-Me) 127 (89, $M^+ + H^+$, $-C_3H_2O_2$), 67 (100, $M^+-C_3H_2O_2$, $-CO_2$,$-Me$). Ee = 49%, $[\alpha]_D^{22} = -69.4$ (c 1.2, CH_2Cl_2). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16; O, 32.62. Found: C, 61.00; H, 6.34; O, 33.01.

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