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Highly Diastereoselective and Enantioselective Formal [4 + 1] Ylide Annulation for the Synthesis of Optically Active Dihydrofurans

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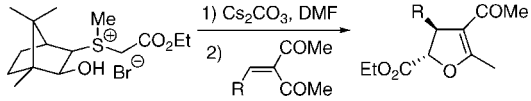

R = aryl, heteroaryl, cinnamyl, and alkyl
up to 95% ee and 15/1 trans/cis

On the basis of the reactions of camphor-derived sulfur ylide with α-ylidene-β-diketones, highly efficient and selective synthesis of optically active dihydrofurans has been achieved.

The formal [2 + 1] ylide cycloaddition[1] of α,β-unsaturated compounds has been widely applied in the enantioselective construction of small ring compounds such as epoxides,[1,2] cyclopropanes,[1,3] and aziridines[1,4] (types A and B in Scheme 1). However, as a potential tool for the creation of 5-membered heterocyclic compounds, the formal [4 + 1] ylide annulation (type C in Scheme 1) has less been explored.[5] Of the investigations, few have explored the possibility of the asymmetric reactions probably due to the difficulty associated with the regioselectivity, chemoselectivity, diastereoselectivity (cis/trans), and enantioselectivity.[6] As our ongoing research project on ylide reaction and its applications in organic synthesis,[7] we recently developed a highly diastereoselective and enantioselective formal [4 + 1] annulation reaction[8] of α-ylidene-β-diketones with sulfur ylide. This annulation leads to optically active dihydrofurans,[9] molecular skeletons frequently occurring in biologically active compounds[10] and extremely useful synthetic intermediates[11] since they can be readily converted to highly functionalized tetrahydrofuran. In this paper, we wish to report the results.

SCHEME 1. Regio- and Chemoselectivities of Ylide Cycloaddition

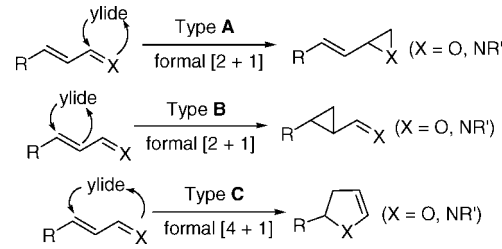

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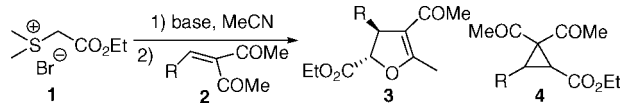
TABLE 1. Regio- and Chemoselective Synthesis of Dihydrofuran with Sulfur Ylide[a]



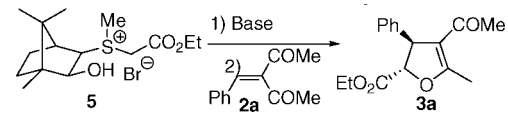
entry	2/R	base	3/4[b]	trans/cis[b]	yield (%)
1	**2a**/C_6H_5	Cs_2CO_3	>99/1	>50/1	95
2	**2a**/C_6H_5	DBU	>99/1	>50/1	96
3	**2b**/4-ClC_6H_4	Cs_2CO_3	>99/1	>50/1	94
4	**2c**/4-BrC_6H_4	Cs_2CO_3	>99/1	>50/1	94
5	**2d**/4-$NO_2C_6H_4$	DBU	>99/1	>50/1	94
6	**2e**/2,4-$Cl_2C_6H_3$	DBU	>99/1	>50/1	88
7	**2f**/4-MeC_6H_4	DBU	>99/1	>50/1	85
8	**2g**/2-furyl	Cs_2CO_3	>99/1	>50/1	90
9	**2h**/*E*-cinnamyl	Cs_2CO_3	5/1	>10/1	83
10	**2i**/Et	Cs_2CO_3	2/1	>50/1	58

[a] All reactions were carried out at 0 °C, base/**1**/**2** = 1.3/1.3/1.0 (molar ratio). [b] Determined by ^{1}H NMR and trans/cis was for **3**.

Since Payne documented the first example for the construction of dihydrofuran using sulfur ylide,[5a] there have been several reports[5,6a] involved in the formation of dihydrofuran via ylide cyclization. However, few general asymmetric versions have been developed via a chiral ylide due to the difficult control of regio- and/or chemoselectivities (type A and/or type B vs type C in Scheme 1). Gratifyingly, we found that sulfonium salt **1**, after deprotonation by DBU or Cs_2CO_3, could react with **2a** to afford dihydrofuran with specific regioselectivity (**3a**/**4a** >99/1), chemoselectivity (no epoxide was observed), and excellent stereoselectivity (trans/cis > 50/1) (entries 1 and 2, Table 1). Further studies revealed that a variety of α-ylidene-*β*-diketones were suitable substrates for this reaction. As shown in Table 1, the annulation reaction proceeded well with R being aryl or 2-furyl group, and only a single regio- and stereoisomer was isolated regardless of the electronic properties of aryl groups (entries 1−8). However, the regioselectivity decreased greatly when R was *E*-cinnamyl or ethyl (entries 9 and 10).

In view of the successful application of camphor-derived sulfide[4a,b,7a,12] in enantioselective ylide epoxidation, cyclopropanation, and aziridination, we envisaged that sulfonium salt **5** could be a potential reagent for the asymmetric formal [4 + 1] annulation for the synthesis of dihydrofuran derivatives. With **2a** as a model substrate, a systematic survey on reaction conditions revealed that solvent, base, temperature, and the diastereomeric purity of sulfonium salt **5**[13] strongly influenced the regioselectivity, chemoselectivity, and diastereoselectivity, as well as enantioselectivity (entries 1−18, Table 2). For example, when the reaction was run in CH_3CN in the presence of Na_2CO_3, only a trace amount of product was observed while 95% yield, 51% ee, and 6/1 trans/cis ratio could be obtained in the case of Cs_2CO_3 used as a base (entries 4 and 5). Of the solvents screened, DMF was found to be the optimal one. Lowering temperature benefited both the enantioselectivity and the trans/cis ratio of the reaction. For example, decreasing the reaction temperature from 0 to −40 °C increased the ee value from 73% ee to 87% ee with a slight loss of yields (entries 14−16). The enantioselectivity of the reaction is also dependent upon the diastereoisomeric purity of salt **5**. For example, salt **5** with a dr ratio of 8.3/1 reacted with 3-benzylidenepentane-2,4-dione (**2a**) in the presence of Cs_2CO_3 afforded the desired **3a** in 92% yield with 87% ee while a nearly diasteromeric pure salt **5** (dr >50/1) favored to give dihydrofurans product **3a** with high diastereoselectivities in 99% yield and up to 91% ee could be achieved (entries 16−18, Table 2) at −40 °C in DMF.

TABLE 2. Effects of Reaction Conditions on the Cyclization



entry[a]	temp (°C)	base	solvent	trans/cis[b]	ee (%)[c]	yield (%)[d]
1	0	*t*-BuOK	MeCN	6.2/1	52	90
2	0	KOH	MeCN	7/1	56	90
3	0	K_2CO_3	MeCN	6/1	51	82
4	0	Na_2CO_3	MeCN			trace
5	0	Cs_2CO_3	MeCN	6/1	51	95
6	0	Cs_2CO_3	PhMe	>99/1	6	15
7	0	Cs_2CO_3	$PhCF_3$	>99/1	0	8
8	0	Cs_2CO_3	DCM	7.8/1	19	80
9	0	Cs_2CO_3	DCE	7.5/1	20	88
10	0	Cs_2CO_3	Et_2O	12/1	20	25
11	0	Cs_2CO_3	THF	5/1	56	95
12	0	Cs_2CO_3	DME	6/1	60	97
13	0	Cs_2CO_3	PhMe	>99/1	6	15
14	0	Cs_2CO_3	DMF	5/1	73	97
15	−20	Cs_2CO_3	DMF	6.5/1	80	96
16	−40	Cs_2CO_3	DMF	11/1	87	92
17[e]	−40	Cs_2CO_3	DMF	10/1	87	94
18[f]	−40	Cs_2CO_3	DMF	10/1	91	99

[a] Molar ratio: **5**/base/**2a** = 1.3/1.3/1.0, dr (at sulfur atom) of **5** is 8.3/1. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC for the trans-isomer. [d] Yield of **3a**. [e] Dr (at sulfur atom) of **5** is 17.6/1. [f] Dr (at sulfur atom) of **5** is >50/1.

Having established the optimal conditions for the synthesis of optically active dihydrofurans, we investigated the scope and limitation of the substrates by employing various alkylidene and 3-arylidene-2,4-pentanediones. As summarized in Table 3, various α-ylidene-*β*-diketones prove to be good substrates for this annulation reaction. Both aliphatic and aromatic diketones were favored to give dihydrofurans over the competing cyclopropanes. For example, various *β*-aryl- and heteroaryl-substituted diketones **2a**−**g** all worked well to afford the desired products with excellent selectivities (**3**/**4** >99/1, trans/cis up to

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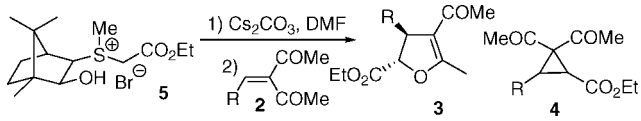
(13) For details, please see the Supporting Information.

TABLE 3. Stereoselective Synthesis of Dihydrofurans via Camphor-Derived Sulfur Ylide[a]



entry	2/R	3/4[b]	trans/cis[b]	yield (%)[c]	ee[d]
1	**2a**/C_6H_5	>99/1	10/1	99	91
2	**2b**/4-ClC_6H_4	>99/1	9/1	97	90
3[e]	**2b**/4-ClC_6H_4	>99/1	15/1	88	93
4	**2c**/4-BrC_6H_4	>99/1	9/1	93	89
5[e]	**2c**/4-BrC_6H_4	>99/1	14/1	90	94
6	**2d**/4-$NO_2C_6H_4$	>99/1	9/1	96	89
7[e]	**2d**/4-$NO_2C_6H_4$	>99/1	12/1	95	92
8	**2e**/2,4-$Cl_2C_6H_3$	>99/1	9/1	99	81
9	**2f** (4-MeC_6H_4)	>99/1	10/1	80[f]	88
10	**2g** (2-furyl)	>99/1	6.5/1	94	89
11	**2h** (*E*-cinnamyl)	10/1	14/1	89	94
12	**2i** (Et)	7/1	12/1	86	95

[a] −40 °C, dr (at sulfur atom) of **5** is >50/1, molar ratio: Cs_2CO_3/**5**/**2** = 1.3/1.3/1.0. [b] Determined by ^{1}H NMR. [c] Yield of **3**. [d] Determined by chiral HPLC for the trans-isomer of compound **3**. [e] Reaction was carried out at −60 °C. [f] −45 °C, 17% of **2f** was recovered.

15/1 and ee up to 94%) in good yields (entries 1−10). Although cyclopropanes were observed in the cases of substrates **2h** and **2i**, the dihydrofurans were isolated in 89% and 86% yields, respectively (entries 11 and 12, Table 3). Thus, the current formal [4 + 1] ylide annulation reaction provides an easy access to the optically active functionalized dihydrofurans.

Products **3a**−**i** were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectra. The absolute configuration of **3c** was determined by X-ray analysis and was assigned as 2*S*,3*S*.[13]

In summary, we have developed an efficient protocol for the preparation of optically active dihydrofurans in high to excellent yields with high selectivities via the reaction between chiral sulfur ylide and α-ylidene-β-diketones. The protocol further expanded the synthetic potential of ylide chemistry. The chiral sulfide is readily available from cheap D-camphor in two-steps in 10-g scale and is recoverable.[14] The high chemoselectivity, good diastereoselectivity, high enantioselectivity, and the easily accessible starting material make this reaction potentially useful in organic synthesis.

Experimental Section

Synthesis of Sulfonium Salt 5. Camphor-derived sulfide **6**[15] (3.44 g, 17.2 mmol) was mixed with ethyl α-bromoacetate (2.87 g, 17.2 mmol) in ether and the resulting mixture was stirred at −20 °C for 96 h. The product **5** was obtained as a white solid by washing with *n*-hexane. Yield: 5.74 g (91%, dr 17.6/1). It can be recrystallized from CH_2Cl_2/MeOH to give the **5** with a dr ratio >50/1. Mp 168−170 °C; IR (film) ν/cm^{-1} 3153 (br), 2964 (m), 1737 (s), 1455 (w), 1210 (m), 1080 (m); ^{1}H NMR (300 MHz, DMSO-d_6/DMSO) δ 6.49 (d, J = 6.0 Hz, 1H), 4.75 (d, J_{AB} = 15.9 Hz, 1H), 4.64 (d, J_{AB} = 15.9 Hz, 1H), 4.34 (d, J = 7.5 Hz, 1H), 4.27 (q, J = 6.9 Hz, 2H), 3.92 (dd, J = 6.9, 6.3 Hz, 1H), 3.16 (s, 3H), 2.35 (d, J = 4.5 Hz, 1H), 1.91−1.82 (m, 1H), 1.56−1.47 (m, 1H), 1.28 (t, J = 7.3 Hz, 3H), 1.24−1.05 (m, 5H), 0.90 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6/ DMSO) δ 165.1, 77.7, 65.0, 63.7, 50.9, 48.1, 47.3, 46.0, 32.4, 28.3, 23.2, 21.9, 21.1, 14.8, 12.2; MS (ESI) *m*/*z* 287.2 (M + Br$^-$). Anal. Calcd for $C_{15}H_{27}BrO_3S$: C, 49.04; H, 7.41. Found: C, 49.00; H, 7.37. $[\alpha]^{20}_D$ +88.0 (*c* 0.6, MeOH).

General Procedure for the Enantioselective Synthesis of Dihydrofurans (3b as an example). To a solution of sulfur salt **5** (100 mg, 0.27 mmol) and Cs_2CO_3 (86 mg, 0.26 mmol) in DMF (1.5 mL), which had been stirred for 45 min at −60 °C, was added a solution of compound **2b** (44 mg, 0.2 mmol) in DMF (1.5 mL). The reaction mixture was stirred until the starting material disappeared (determined by TLC), and then passed through a short silica gel column (eluted with ethyl acetate). After removal of the solvent under reduced pressure, the crude mixture was directly purified by flash chromatography on silica gel to give the pure product. Yield 54 mg (88%). For trans-isomer: IR (film) ν/cm^{-1} 3062 (w), 2925 (w), 2853 (w), 1757 (s), 1676 (m), 1629 (m), 1602 (s), 1491 (m); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.32 (dd, J = 6.3, 1.8 Hz, 2H), 7.18 (dd, J = 6.3, 2.1 Hz, 2H), 4.72 (d, J = 5.1 Hz, 1H), 4.47 (dd, J = 4.8, 1.5 Hz, 1H), 4.34−4.25 (m, 2H), 2.43 (d, J = 1.5 Hz, 3H), 1.99 (s, 3H), 1.33 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 169.5, 168.7, 140.6, 133.3, 129.1, 128.4, 115.1, 85.5, 61.9, 52.5, 29.5, 14.9, 14.0; MS (EI) *m*/*z* (% rel intensity) 308 (2.1) M$^+$, 43 (100); HRMS (MALDI/DHB) calcd for $C_{16}H_{18}O_4Cl$ + 1 (M$^+$ + H) 309.0885, found 308.0888. HPLC analysis (Chiralcel AD-H, 2/100 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm; t_r(minor) = 32.10 min, t_r(major) = 22.32 min) gave the isomeric composition of the product: 93% ee. $[\alpha]^{20}_D$ +176.6 (*c* 1.00, $CHCl_3$).

(2*S*,3*S*)-Ethyl Acetyl-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxylate (3a). Yield 99%. Trans-isomer: mp 57−59 °C; IR (film) ν/cm^{-1} 3029 (w), 2982 (w), 2926 (w), 1756 (s), 1675 (m), 1629 (m), 1603 (s); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.39−7.21 (m, 5H), 4.78 (d, J = 5.1 Hz, 1H), 4.48 (dd, J = 4.8, 1.5 Hz, 1H), 4.35−4.24 (m, 2H), 2.43 (d, J = 1.5 Hz, 3H), 1.99 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 169.6, 168.4, 142.0, 128.9, 127.4, 127.0, 114.9, 85.8, 61.7, 53.0, 29.5, 14.7, 14.0; MS (EI) *m*/*z* (% rel intensity) 275 (10.4) M$^+$ + H, 274 (2.6) M$^+$. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.05; H, 6.63. HPLC analysis (Chiralcel OJ, ^{i}PrOH/hexanes, 10/100, 0.8 mL/min, 238 nm; t_r(minor) = 13.18 min, t_r(major) = 16.04 min) gave the isomeric composition of the product: 91% ee. $[\alpha]^{20}_D$ +142.1 (*c* 1.40, $CHCl_3$).

4-Acetyl-3-(4-bromophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylate (3c). Yield 90%. Trans-isomer: IR (film) ν/cm^{-1} 3062 (w), 2981 (w), 2925 (w), 1757 (s), 1676 (m), 1629 (m), 1602 (s); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.47 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 4.72 (d, J = 4.8 Hz, 1H), 4.46 (dd, J = 4.5, 0.9 Hz, 1H), 4.33−4.25 (m, 2H), 2.43 (d, J = 0.9 Hz, 3H), 2.00 (s, 3H), 1.33 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 169.5, 168.6, 141.1, 132.1, 128.8, 121.4, 115.1, 85.5, 61.9, 52.6, 29.5, 14.9, 14.1; MS (EI) *m*/z (% rel intensity) 352 (1.3) M$^+$, 43 (100); HRMS (MALDI/DHB) calcd for $C_{16}H_{18}O_4Br$ + 1 (M$^+$ + H) 353.0385, found 353.0383. HPLC analysis (Chiralcel AD-H, 2/100 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm; t_r(minor) = 44.80 min, t_r(major) = 30.46 min) gave the isomeric composition of the product: 94% ee. $[\alpha]^{20}_D$ +177.1 (*c* 1.00, $CHCl_3$).

(2*S*,3*S*)-Ethyl 4-Acetyl-5-methyl-3-(4-nitrophenyl)-2,3-dihydrofuran-2-carboxylate (3d). Yield 95%. Trans-isomer: liquid, IR (film) ν/cm^{-1} 3062 (w), 2983 (w), 2925 (w), 2854 (w), 1757 (s), 1676 (m), 1628 (m), 1599 (m), 1521 (s); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 8.23 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2H), 4.76 (d, J = 5.1 Hz, 1H), 4.61 (d, J = 4.5 Hz, 1H), 4.35−4.26 (m, 2H), 2.46 (s, 3H), 2.09 (s, 3H), 1.34 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 169.1, 168.8, 149.4, 147.2, 128.1, 124.1, 115.7, 84.8, 62.1, 52.8, 29.4, 15.1, 14.0; MS (EI) *m*/*z* (% rel intensity) 319 (1.5) M$^+$, 43 (100); HRMS (MALDI/DHB) calcd for $C_{16}H_{18}O_6N$ + 1 (M$^+$ + H) 320.1137, found 320.1129. HPLC analysis (Chiralcel AD-H, 20/100 ^{i}PrOH/hexanes, 0.5 mL/min, 254 nm; t_r(minor) = 24.82 min, t_r(major) = 36.17 min) gave the isomeric composition of the product: 92% ee. $[\alpha]_D$ +286.7 (*c* 1.00, $CHCl_3$).

(14) 60−70% sulfide **6** was recovered.

(15) For the synthesis of sulfide **6** see: Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Huang, Y.-Z.; Li, F.-W. *J. Org. Chem.* **1996**, *61*, 489.

(2*S*,3*R*)-Ethyl 4-Acetyl-3-(2,4-dichlorophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylate (3e). Yield 99%. Trans-isomer: liquid, IR (film) ν/cm^{-1} 3023 (w), 2981 (m), 2926 (m), 1755 (s), 1678 (m), 1631 (m), 1603 (m); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.44 (d, J = 1.8 Hz, 1H), 7.27−7.23 (m, 1H), 7.09 (d, J = 8.7 Hz, 1H), 5.01 (dd, J = 4.8, 1.5 Hz, 1H), 4.69 (d, J = 4.8 Hz, 1H), 4.35−4.23 (m, 2H), 2.44 (d, J = 0.9 Hz, 3H), 1.98 (s, 3H), 1.33 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 169.3, 169.0, 137.7, 134.0, 133.8, 129.6, 129.3, 127.9, 114.5, 85.0, 61.9, 48.7, 29.3, 14.9, 14.0; MS (EI) *m/z* (% rel intensity) 342 (5.7) M^+, 43 (100); HRMS (MALDI/DHB) calcd for $C_{16}H_{17}O_4Cl_2$ + 1 (M^+ + H) 343.0482, found 343.0477. HPLC analysis (Chiralcel AD-H, 2/100 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm; t_r(minor) = 24.72 min, t_r(major) = 21.32 min) gave the isomeric composition of the product: 81% ee. $[\alpha]^{20}_D$ +127.5 (*c* 0.95, $CHCl_3$).

(2*S*,3*S*)-Ethyl 4-Acetyl-5-methyl-3-*p*-tolyl-2,3-dihydrofuran-2-carboxylate (3f). Yield 80%. Trans-isomer: liquid; IR (film) ν/cm^{-1} 3023 (w), 2981 (m), 2924 (m), 2854 (w), 1756 (s), 1767 (m), 1629 (m), 1603 (s); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.18−7.11 (m, 4H), 4.76 (d, J = 4.8 Hz, 1H), 4.45 (dd, J = 4.8, 0.9 Hz, 1H), 4.33−4.24 (m, 2H), 2.43 (d, J = 1.2 Hz, 3H), 2.34 (s, 3H), 1.95 (s, 3H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 169.8, 168.4, 139.1, 137.2, 129.6, 126.9, 115.0, 86.0, 61.7, 52.8, 29.6, 21.0, 14.8, 14.0; MS (EI) *m/z* (% rel intensity) 288 (3.9) M^+, 43 (100); HRMS (MALDI/DHB) calcd for $C_{17}H_{21}O_4$ + 1 (M^+ + H) 289.1427, found 289.1434. HPLC analysis (Chiralcel OJ, 10/100 ^{i}PrOH/hexanes, 0.8 mL/min, 254 nm; t_r(minor) = 10.32 min, t_r(major) = 14.51 min) gave the isomeric composition of the product: 88% ee. $[\alpha]^{20}_D$ +146.6 (*c* 0.85, $CHCl_3$).

(2*S*,3*S*)-Ethyl 4-Acetyl-3-(2-furyl)-5-methyl-2,3-dihydrofuran-2-carboxylate (3g). Yield 94%. Trans-isomer: liquid; IR (film) ν/cm^{-1} 2960 (w), 2924 (s), 2854 (w), 1756 (s), 1676 (m), 1603 (s); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.37 (t, J = 0.9 Hz, 1H), 6.33 (q, J = 1.2 Hz, 1H), 6.17 (d, J = 3.3 Hz, 1H), 4.94 (d, J = 4.8 Hz, 1H), 4.62 (d, J = 4.2 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 2.39 (d, J = 1.2 Hz, 3H), 2.08 (s, 3H), 1.33 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 169.4, 168.8, 153.6, 142.2, 112.6, 110.5, 106.8, 82.8, 61.9, 46.4, 29.2, 14.9, 14.0; MS (EI) *m/z* (% rel intensity) 264 (3.1) M^+, 43 (100); HRMS (MALDI/DHB) calcd for $C_{14}H_{17}O_5$ + 1 (M^+ + H) 265.1075, found 265.1071. HPLC analysis (Chiralcel AD-H, 2/100 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm; t_r(minor) = 26.48 min, t_r(major) = 28.37 min) gave the isomeric composition of the product: 89% ee. $[\alpha]^{20}_D$ +197.5 (*c* 0.93, $CHCl_3$).

(2*S*,3*S*,*E*)-Ethyl 4-Acetyl-5-methyl-3-styryl-2,3-dihydrofuran-2-carboxylate (3h). Yield 89%. Trans-isomer: liquid; IR (film) ν/cm^{-1} 3025 (w), 2980 (m), 2932 (w), 1754 (s), 1674 (m), 1625 (m), 1600 (s); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.40−7.24 (m, 5H), 6.55 (d, J = 15.6 Hz, 1H), 6.24 (dd, J = 15.6, 7.8 Hz, 1H), 4.78 (d, J = 4.8 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 4.14−4.09 (m, 1H), 2.36 (d, J = 0.9 Hz, 3H), 2.19 (s, 3H), 1.33 (t, J = 7.2 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 194.1, 169.7, 168.3, 136.2, 132.1, 129.0, 128.5, 127.8, 126.3, 114.1, 83.4, 61.7, 50.6, 29.5, 14.9, 14.0; MS (EI) *m/z* (% rel intensity) 300 (0.9) M^+, 43 (100); HRMS (MALDI/DHB) calcd for $C_{18}H_{21}O_4$ + 1 (M^+ + H) 301.1422, found 301.1434. HPLC analysis (Chiralcel OD-H, 5/95 ^{i}PrOH/hexanes, 0.8 mL/min, 254 nm; t_r(minor) = 25.65 min, t_r(major) = 18.63 min) gave the isomeric composition of the product: 94% ee. $[\alpha]^{20}_D$ +242.1 (*c* 0.85, $CHCl_3$).

(2*S*,3*S*)-Ethyl 4-Acetyl-3-ethyl-5-methyl-2,3-dihydrofuran-2-carboxylate (3i). Yield 86%. Trans-isomer: liquid; IR (film) ν/cm^{-1} 2966 (m), 2931 (m), 1755 (s), 1673 (m), 1627 (s), 1601 (m); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 4.64 (d, J = 4.2 Hz, 1H), 4.24 (q, J = 6.9 Hz, 2H), 3.31−3.24 (m, 1H), 2.31 (d, J = 0.9 Hz, 3H), 2.26 (s, 3H), 1.85−1.76 (m, 1H), 1.57−1.47 (m, 1H), 1.29 (t, J = 6.9 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 170.6, 167.2, 116.2, 82.0, 61.5, 49.2, 29.3, 26.4, 15.2, 14.0, 10.1; MS (EI) *m/z* (% rel intensity) 226 (2.7) M^+, 43 (100); HRMS (EI) calcd for $C_{12}H_{18}O_4$ (M^+) 226.1205, found 226.1211. HPLC analysis (Chiralcel OD-H, 2/100 ^{i}PrOH/hexanes, 0.8 mL/min, 254 nm; t_r(minor) = 13.75 min, t_r(major) = 16.01 min) gave the isomeric composition of the product: 95% ee. $[\alpha]^{20}_D$ +52.7 (*c* 0.85, $CHCl_3$).

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Supporting Information Available: Full experimental details, CIF file for **3c**, and chiral HPLC spectra of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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