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An Efficient Asymmetric Domino Reaction of Amino Aldehyde to β,γ-Unsaturated α-Keto Esters Using *trans*-Perhydroindolic Acid as a Chiral Organocatalyst

Shen, Jiefeng[a](申杰峰) An, Qianjin[b](安前进) Liu, Delong[b](刘德龙)
Liu, Yangang[b](刘燕刚) Zhang, Wanbin*[,a,b](张万斌)

[a] *School of Chemistry and Chemical Engineering*, *Shanghai Jiaotong University*, *Shanghai 200240*, *China*
[b] *School of Pharmacy*, *Shanghai Jiaotong University*, *Shanghai 200240*, *China*

An efficient asymmetric domino reaction of amino aldehyde to β,γ-unsaturated α-keto esters was achieved by using *trans*-perhydroindolic acid **1d** as a chiral organocatalyst with excellent asymmetric behavior. Under the optimal reaction conditions, products with more than 99% *de* and up to 93% *ee* were obtained in high chemical yield (up to 98%) for a series of β,γ-unsaturated α-keto esters. The methodology provided an efficient route to dihydropyran derivatives containing many substituent groups (including amino groups).

Keywords asymmetric domino reaction, β,γ-unsaturated α-keto esters, *trans*-perhydroindolic acid, organocatalyst

Introduction

Dihydropyran derivatives exhibit interesting biological activities and are structural subunits in numerous natural products and bioactive molecules;[1] they also serve as versatile and important building blocks in organic synthesis.[2] Several syntheses have been reported towards the preparation of this important structural motif,[3] however, the majority of reported procedures involve the synthesis of products with few substituents, and only one procedure involves the consturction of dihydropyrans containing amino groups, which is very important functional group and could be further functionalized.[3c] A convenient and enantioselective approach to highly substituted dihydropyran derivatives (containing amino groups) is therefore desirable.

Our group have been developing novel and easily accessible organocatalysts for use in asymmetric transformations.[4] Recently our attention turned to the use of *trans*-perhydroindolic acid (**1a**) (a key intermediate used in the synthesis of the ACE inhibitor trandolapril)[5] and its isomers **1b**—**1d** (Figure 1). These molecules are unique in that they possess a rigid bicyclic structure, with the two H atoms attached to the bridgehead C atoms being *trans* to each other. So, they can be used as efficient organocatalysts for asymmetric Michael additions of aldehydes to nitroolefins.[4f] They were also used in asymmetric domino reactions of aldehyde esters with β,γ-unsaturated α-keto esters possessing excellent asymmetric catalytic behavior (up to 99% *ee*, *de* and yield).[4g] Encouraged by the excellent catalytic ability of these proline-like molecules, we therefore utilised them in asymmetric domino Michael addition/cyclisation reactions of amino aldehyde to β,γ-unsaturated α-keto esters.

Experimental

General

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Varian MERCURY plus-400 spectrometer with TMS as an internal stan-

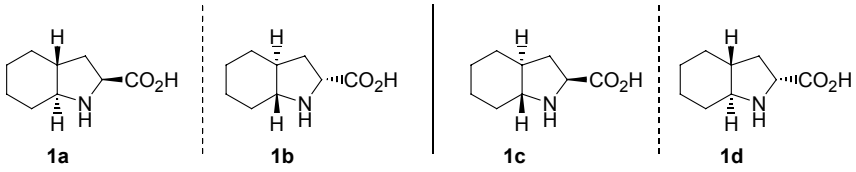

Figure 1 Trandolapril intermediate **1a** and its byproducts **1b**—**1d**.

* E-mail: wanbin@sjtu.edu.cn; Tel.: 0086-021-54743265; Fax: 0086-021-54743265
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dard. HRMS was performed at the Analysis Center of Shanghai Jiao Tong University. Enantioselectivity was measured by high performance liquid chromatography (HPLC) using Daicel Chiralcel AD-H, OD-H, AS-H, OJ-H and OZ-H column with hexane/*i*-propyl alcohol as eluent. Column chromatography was performed using 100—200 mesh silica gel. All commercially available substrates were used as received. β,γ-Unsaturated α-keto esters (**2**)[6] and 4-methyl-*N*-(3-oxopropyl)benzenesulfonamide (**3**)[7] were prepared according to literature procedures.

General procedure for the Michael addition

The catalyst **1d** (1.69 mg, 0.01 mmol), DABCO (2.24 mg, 0.02 mmol), enone **3** (0.1 mmol) and aldehyde **4** (0.2 mmol) were added to a screw-capped vial containing *n*-butanol (1 mL) at room temperature. The reaction mixture was stirred at the same temperature until complete consumption of enone **3** (monitored by TLC). The solvent was then evaporated and the residue was purified by flash column silica-gel chromatography (PE/EA, $V:V=4:1$) to provide the corresponding Michael adducts. Diastereoselectivity (*de*) and the enantiomeric excess (*ee*) were determined by HPLC analysis of the pure product.

Methyl 2-hydroxy-3-(4-methylphenylsulfonamido)-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4a**): White solid. m.p. 147—148 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, $J=8.2$ Hz, 2H), 7.37—7.02 (m, 6H), 6.13 (d, $J=2.4$ Hz, 1H), 5.68 (d, $J=2.4$ Hz, 1H), 3.77 (s, 3H), 3.63—3.48 (m, 1H), 3.13—2.96 (m, 1H), 2.83—2.80 (m, 1H), 2.40 (s, 3H), 2.17—2.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 143.6, 140.9, 139.7, 136.5, 129.9, 129.1, 128.6, 127.6, 127.3, 116.0, 93.1, 53.2, 42.5, 42.1, 37.2, 21.8; HRMS (ESI) calcd for $C_{21}H_{23}NNaO_6S$ [M+Na$^+$]: 440.1138, found 440.1148. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, $V:V=82:18$, UV 254 nm, 0.65 mL/min, $t_{R1}=21.97$ min (major) and $t_{R2}=27.20$ min (minor); *ee*=93%; *de*>99%.

Ethyl 2-hydroxy-3-(4-methylphenylsulfonamido)-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4b**): White solid. m.p. 95—96 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59—7.56 (m, 2H), 7.44—7.04 (m, 6H), 6.13 (d, $J=2.4$ Hz, 1H), 5.67 (d, $J=2.0$ Hz, 1H), 4.26—4.21 (m, 2H), 3.62—3.57 (m, 1H), 3.14—2.92 (m, 1H), 2.89—2.72 (m, 1H), 2.40 (d, 3H), 2.11 (m, 1H), 1.27 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7, 143.3, 141.0, 139.8, 136.5, 129.9, 129.0, 128.6, 127.6, 127.3, 115.7, 93.1, 61.9, 42.5, 42.1, 37.2, 21.7, 14.3; HRMS (ESI) calcd for $C_{22}H_{25}NNaO_6S$ [M+Na$^+$] 454.1295, found 454.1269. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, $V:V=88:12$, UV 254 nm, 0.5 mL/min, $t_{R1}=47.56$ min (major) and $t_{R2}=51.20$ min (minor); *ee*=91%; *de*>99%.

Isopropyl 2-hydroxy-3-(4-methylphenylsulfonamido)-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4c**): White solid. m.p. 140—141 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, $J=8.2$ Hz, 2H), 7.36—7.01 (m, 6H), 6.10 (d, $J=2.4$ Hz, 1H), 5.70 (s, 1H), 5.11—5.08 (m, 1H), 3.61—3.57 (m, 1H), 3.03—2.98 (m, 1H), 2.83—2.78 (m, 1H), 2.39 (s, 3H), 2.14—2.10 (m, 1H), 1.27—1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 143.5, 141.2, 140.0, 136.6, 129.9, 129.1, 128.7, 127.7, 127.4, 115.5, 93.1, 69.8, 42.5, 42.3, 37.2, 29.9, 21.9; HRMS (ESI) calcd for $C_{23}H_{27}NNaO_6S$ [M+Na$^+$] 468.1514, found 468.1460. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, $V:V=88:12$, UV 254 nm, 0.8 mL/min, $t_{R1}=24.21$ min (major) and $t_{R2}=26.56$ min (minor); *ee*=92%; *de*>99%.

Methyl 4-(4-fluorophenyl)-2-hydroxy-3-(4-methylphenylsulfonamido)methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4e**): White solid. m.p. 66—67 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66—7.53 (m, 2H), 7.31—7.18 (m, 2H), 7.11—7.08 (m, 2H), 7.02—6.98 (m, 2H), 6.09 (d, $J=2.4$ Hz, 1H), 5.65 (s, 1H), 3.79 (s, 3H), 3.62—3.58 (m, 1H), 3.06—2.92 (m, 2H), 2.81—2.76 (m, 1H), 2.47—2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 143.8, 139.8, 136.5, 130.6, 128.8, 127.3, 116.0, 115.8, 93.2, 52.8, 42.6, 41.9, 36.2, 30.0, 21.8; HRMS (ESI) calcd for $C_{21}H_{22}FNNaO_6S$ [M+Na$^+$] 458.1044, found 458.1050. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, $V:V=87:13$, UV 254 nm, 1.0 mL/min, $t_{R1}=24.84$ min (major) and $t_{R2}=29.13$ min (minor); *ee*=92%; *de*>99%.

Methyl 4-(2-chlorophenyl)-2-hydroxy-3-(4-methylphenylsulfonamido)methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4f**): White solid. m.p. 70—71 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, $J=8.2$ Hz, 2H), 7.26—7.19 (m, 6H), 6.02 (d, $J=2.8$ Hz, 1H), 5.70 (s, 1H), 3.77 (s, 3H), 3.12—3.09 (m, 1H), 2.96—2.77 (m, 2H), 2.39 (s, 3H), 2.34—2.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 143.6, 140.4, 138.5, 136.6, 134.4, 130.1, 129.9, 128.7, 127.7, 127.2, 114.6, 92.6 52.7, 42.2, 34.7, 31.1, 21.7; HRMS (ESI) calcd for $C_{21}H_{22}ClNNaO_6S$ [M+Na$^+$] 474.0749, found 474.0760. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, $V:V=87:13$, UV 254 nm, 1.0 mL/min, $t_{R1}=24.76$ min (major) and $t_{R2}=31.77$ min (minor); *ee*=83%; *de*>99%.

Methyl 4-(4-chlorophenyl)-2-hydroxy-3-(4-methylphenylsulfonamido)methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4g**): White solid. m.p. 148—149 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, $J=8.2$ Hz, 2H), 7.27—7.21 (m, 4H), 7.09—7.05 (m, 2H), 6.07 (d, $J=2.4$ Hz, 1H), 5.66 (s, 1H), 3.79 (s, 3H), 3.63—3.58 (m, 1H), 3.24—3.18 (m, 1H), 3.02—2.98 (m, 1H), 2.82—2.70 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ: 163.8, 143.8, 143.7, 139.7, 139.5, 136.3, 133.4, 129.9, 129.2, 128.7, 127.3, 115.2, 93.1 52.8, 42.5, 36.4, 31.1, 21.8; HRMS (ESI) calcd for $C_{21}H_{22}ClNNaO_6S$ [M+Na^+] 474.0749, found 474.0754. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, V∶V=85∶15, UV 254 nm, 0.7 mL/min, t_{R1}=26.45 min (major) and t_{R2}=29.49 min (minor); *ee*=92%; *de* >99%.

Methyl 4-(2-bromophenyl)-2-hydroxy-3-((4-methylphenylsulfonamido)methyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (**4h**): White solid. m.p. 82—83 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59—7.55 (m, 2H), 7.35—6.92 (m, 6H), 6.02 (d, J=2.8 Hz, 1H), 5.70 (s, 1H), 3.78 (s, 3H), 3.15—3.08 (m, 2H), 2.99—2.76 (m, 1H), 2.40 (s, 3H), 2.37—2.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 143.6, 140.3, 136.5, 133.4, 129.9, 129.3, 129.1, 128.2, 127.61, 127.4, 125.2, 114.6, 92.6, 52.7, 42.2, 37.4, 21.7; HRMS (ESI) calcd for $C_{21}H_{22}BrNNaO_6S$ [M+Na^+] 518.0243, found 518.0259. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, V∶V=87∶13, UV 254 nm, 1.0 mL/min, t_{R1}=25.93 min (major) and t_{R2}=34.75 min (minor); *ee*=91%; *de*>99%.

Methyl 4-(3-bromophenyl)-2-hydroxy-3-(4-methylphenylsulfonamido)methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4i**): White solid. m.p. 88—89 ℃; ^{1}H NMR (400 MHz, CD_3OD) δ: 7.68—6.99 (m, 8H), 5.91 (d, J=2.6 Hz, 1H), 5.60 (d, J=2.0 Hz, 1H), 3.74 (s, 3H), 3.33—3.26 (m, 1H), 2.98—2.92 (m, 1H), 2.55—2.49 (m, 1H), 2.37 (s, 3H), 2.13—1.94 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ: 163.8, 144.5, 143.6, 140.6, 136.5, 131.2, 130.4, 130.1, 129.6, 127.3, 126.9, 113.6, 91.9, 51.6, 43.2, 41.5, 37.8, 20.48; HRMS (ESI) calcd for $C_{21}H_{22}BrNNaO_6S$ [M+Na^+] 518.0243, found 518.0251. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, V∶V=87∶13, UV 254 nm, 0.85 mL/min, t_{R1}=23.87 min (major) and t_{R2}=29.81 min (minor); *ee*=85%; *de*>99%.

Methyl 4-(4-bromophenyl)-2-hydroxy-3-(4-methylphenylsulfonamido)methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4j**): White solid. m.p. 77—79 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J=8.2 Hz, 2H), 7.41 (d, J=8.2 Hz, 2H), 7.27—7.23 (m, 2H), 7.04—6.99 (m, 2H), 6.09 (d, J=2.6 Hz, 1H), 5.64 (s, 1H), 5.20—5.16 (m, 1H), 3.80 (s, 3H), 3.63—3.58 (m, 1H), 3.15—2.88 (m, 1H), 2.79—2.75 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 143.8, 140.1, 136.4, 132.2, 130.4, 129.9, 127.3, 121.4 (s), 115.1, 93.0, 52.8, 42.4, 36.5, 29.9, 21.8; HRMS (ESI) calcd for $C_{21}H_{22}BrNNaO_6S$ [M+Na^+] 518.0243, found 518.0405. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, V∶V=87∶13, UV 254 nm, 0.85 mL/min, t_{R1}=27.58 min (major) and t_{R2}=30.24 min (minor); *ee*=92%; *de*>99%.

Methyl 4-(2,6-dichlorophenyl)-2-hydroxy-3-(4-methylphenylsulfonamido)methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4k**): White solid. m.p. 174—175℃; ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.52—7.25 (m, 6H), 6.61—6.48 (m, 1H), 5.96 (d, J=2.4 Hz, 1H), 5.78 (s, 1H), 4.4—4.45 (m, 1H), 3.71 (s, 3H), 3.16—3.09 (m, 1H), 2.89—2.78 (m, 1H), 2.60—2.49 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ: 162.9, 143.2, 140.8, 137.3, 136.7, 135.6, 130.8, 129.7, 128.8, 127.1, 112.9, 91.7, 51.4, 42.4, 38.8, 34.6, 20.7; HRMS (ESI) calcd for $C_{21}H_{21}Cl_2NNaO_6S$ [M+Na^+] 508.0359, found 508.0374. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), Hexane/*i*-PrOH, V∶V=87∶13, UV 254 nm, 1.0 mL/min, t_{R1}=37.28 min (major) and t_{R2}=49.13 min (minor); *ee*=92%; *de*>99%

Methyl 2-hydroxy-3-((4-methylphenylsulfonamido)-methyl)-4-*p*-tolyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4l**): White solid. m.p. 155—156 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J=8.2 Hz, 2H), 7.27—7.16 (m, 2H), 7.10 (d, J=7.6 Hz, 2H), 7.01 (d, J=7.8 Hz, 2H), 6.11 (d, J=2.4 Hz, 1H), 5.64 (s, 1H), 3.77 (s, 3H), 3.58—3.51 (m, 1H), 3.50—3.39 (m, 1H), 3.10—2.95 (m, 1H), 2.84—2.79 (m, 1H), 2.40 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0, 143.6, 139.6, 137.9, 137.3, 136.6, 129.8, 128.4, 127.3, 116.3, 93.2, 52.7, 42.8, 36.8, 29.9, 21.8, 21.3; HRMS (ESI) calcd for $C_{22}H_{25}NNaO_6S$ [M+Na^+] 454.1295, found 454.1294; HPLC conditions: The enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, V∶V=87∶13, UV 254 nm, 0.8 mL/min, t_{R1}=25.30 min (major) and t_{R2}=28.39 min (minor); *ee*=92%; *de*>99%.

Methyl 2-hydroxy-4-(3-methoxyphenyl)-3-(4-methylphenylsulfonamido)methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4m**): White solid. m.p. 89—90 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58—7.52 (m, 2H), 7.24—7.16 (m, 3H), 6.80 (m, 1H), 6.74—6.65 (m, 2H), 6.10 (d, J=2.4 Hz, 1H), 5.68 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.60—3.41 (m, 1H), 3.16—2.98 (m, 1H), 2.85—2.61 (m, 1H), 2.38 (s, 3H), 2.15—2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 160.1, 143.6, 142.7, 139.6, 136.5, 129.9, 127.2, 120.9, 115.9, 114.1, 113.1, 93.0, 55.5, 52.7, 42.3, 41.5, 37.3, 21.7; HRMS (ESI) calcd for $C_{22}H_{25}NNaO_7S$ [M+Na^+] 470.1244, found 470.1254. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, V∶V=88∶12, UV 254 nm, 0.8 mL/min, t_{R1}=35.24 min (major) and t_{R2}=48.87 min (minor); *ee*=82%; *de*>99%.

Methyl 2-hydroxy-4-(4-methoxyphenyl)-3-(4-methylphenylsulfonamido)methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4n**): White solid. m.p. 63—64 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, J=8.2 Hz, 2H), 7.29—7.17 (m, 2H), 7.04 (d, J=8.8 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 6.13—6.05 (m, 1H), 5.64 (d, J=2.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.60—3.44 (m, 1H), 3.05—2.98 (m, 1H), 2.84—2.79 (m, 1H), 2.40 (s, 3H),

2.13—2.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 143.4, 140.1, 136.6, 133.6, 129.3, 129.2, 126.9, 115.1, 114.0, 91.9, 54.6, 51.5, 43.5, 41.6, 37.2, 20.3; HRMS (ESI) calcd for $C_{22}H_{25}NNaO_7S$ [M + Na$^+$] 470.1244, found 470.1235. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, *V* : *V* = 85 : 15, UV 254 nm, 0.80 mL/min, t_{R1} = 29.07 min (major) and t_{R2} = 32.19 min (minor); *ee* = 85%; *de* > 99%.

Methyl 2-hydroxy-3-(4-methylphenylsulfonamido)-methyl-4-(naphthalen-2-yl)-3,4-dihydro-2*H*-pyran-6-carboxylate (**4o**): White solid. m.p. 89—91 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92—7.76 (m, 2H), 7.57 (s, 1H), 7.54—7.50 (m, 1H), 7.28—7.23 (m, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.05 (d, *J* = 2.6 Hz, 1H), 5.65 (d, *J* = 2.2 Hz, 1H), 3.77 (s, 3H), 3.49—3.44 (m, 1H), 2.95—2.89 (m, 1H), 2.53—2.49 (m, 1H), 2.29—2.25 (m, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.6, 140.0, 138.4, 129.8, 128.9, 128.0, 127.9, 127.9, 127.9, 127.9, 115.7, 93.1, 52.7, 42.3, 37.4, 30.0, 21.7; HRMS (ESI calcd for $C_{25}H_{25}NNaO_6S$ [M + Na$^+$] 490.1295, found 490.1308. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, *V* : *V* = 87 : 13, UV 254 nm, 1.0 mL/min, t_{R1} = 26.22 min (major) and t_{R2} = 32.22 min (minor); *ee* = 88%; *de* > 99%.

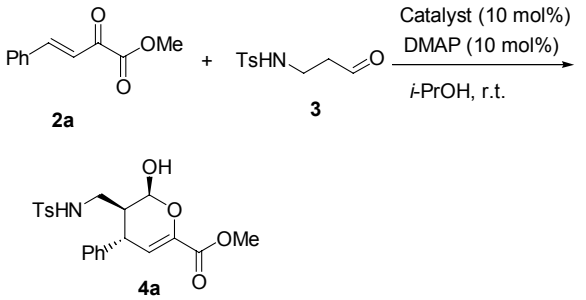
Methyl 4-(furan-2-yl)-2-hydroxy-3-(4-methylphenylsulfonamido)methyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**4p**): White solid. m.p. 101—102 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 8.2 Hz, 2H), 7.33—7.29 (m, 1H), 7.28—7.22 (m, 2H), 6.36—6.23 (m, 1H), 6.10 (d, *J* = 2.8 Hz, 2H), 5.64 (s, 1H), 3.77 (s, 3H), 3.19—2.88 (m, 4H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 153.4, 143.7, 142.3, 140.1, 136.8, 129.9, 127.3, 112.7, 110.7, 107.4, 92.8, 52.7, 42.3, 31.5, 29.9, 21.7; HRMS (ESI) calcd for $C_{19}H_{21}NNaO_7S$ [M + Na$^+$] 430.0931, found 430.0928. HPLC conditions: the enantiomeric excess and diastereoselective excess were determined by HPLC (Chiralcel AD-H), hexane/*i*-PrOH, *V* : *V* = 87 : 13, UV 254 nm, 0.8 mL/min, t_{R1} = 32.89 min (major) and t_{R2} = 40.31 min (minor); *ee* = 92%; *de* > 99%.

Results and Discussion

1a—**1d** were first used in asymmetric domino Michael addition/cyclisation reactions of amino aldehyde with β,γ-unsaturated α-keto esters to determine the effect the configuration of the catalysts had on the reactions. Thus, the reaction of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**2a**) with 4-methyl-*N*-(3-oxopropyl)-benzenesulfonamide (**3**) was carried out in the presence of 10 mol% of catalyst **1a**—**1d** and DMAP in *i*-PrOH at room temperature.

As shown in Table 1, catalyst **1a** and its enantiomer **1b** gave good yields of product but only moderate enantioselectivity (Entries 1, 2). Their diastereomers **1c** and **1d** both provided good enantioselectivities and yields (Entries 3, 4). It was interesting that only one pair of peaks of product was found during the HPLC experimentals. *trans*-Perhydroindolic acids are comparably more efficient than *L*-proline (Entry 5), thus the catalyst **1d** was used in subsequent reactions.

Table 1 Asymmetric domino reaction with different catalysts[a]



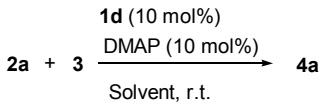
Entry	Catalyst	Time/h	Yield[b]/%	*ee*[c]/%
1	**1a**	24	83	−51
2	**1b**	24	82	52
3	**1c**	24	90	−78
4	**1d**	24	92	79
5	*L*-proline	24	81	27

[a] Reactions were conducted with (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (0.1 mmol) and 4-methyl-*N*-(3-oxopropyl)benzenesulfonamide (0.2 mmol) by using10 mol% catalyst and DMAP in *i*-PrOH at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC with more than 99% *de*.

The influence of solvent on the reaction was then investigated in the presence of 10 mol% **1d** at room temperature in *i*-PrOH (Table 2). In low polarity solvents such as toluene and Et_2O, low yields and enantioselectivities were obtained (Entries 1, 2). When using moderately polar solvents such as CH_2Cl_2 and $CHCl_3$, no obvious improvement in reactivity was observed (Entries 3, 4). If DMF was used as the solvent, the reaction activity and enantioselectivity were improved significantly (Entry 5). Therefore we envisaged alcohol solvents would be most suitable for the asymmetric domino reaction. The reaction was performed in MeOH, EtOH and *n*-PrOH with excellent asymmetric catalytic results being obtained (Entries 6—8). A range of other alcohol solvents *i*-PrOH, *n*-BuOH, *iso*-pentanol and *tert*-pentanol were also examined, and *n*-BuOH provided the most promising result (Entry 10). *n*-BuOH was therefore used as the solvent of choice in the following reactions.

Several bases were examined as additives in the reaction. As shown in Table 3, a majority of the basic additives (Entries 1 vs. 2—8) dramatically shortened the length of the reaction time, providing excellent diastereoselectivity, good enantioselectivity, and good yields. Acidic additives did not improve the reaction.

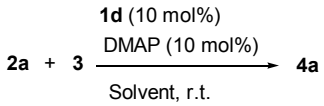
Table 2 The influence of solvent on the asymmetric domino reaction[a]



Entry	Solvent	Time/h	Yield[b]/%	*ee*[c]/%
1	Toluene	14 d	35	60
2	Et_2O	14 d	41	60
3	CH_2Cl_2	14 d	37	57
4	$CHCl_3$	14 d	43	68
5	DMF	96	92	70
6	MeOH	96	98	82
7	EtOH	72	79	85
8	*n*-PrOH	36	80	85
9	*i*-PrOH	24	92	79
10	*n*-BuOH	36	93	88
11	*iso*-Pentanol	36	87	87
12	*tert*-Pentanol	72	83	78

[a] Reactions were conducted with 0.1 mmol of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate and 0.2 mmol of 4-methyl-*N*-(3-oxopropyl)-benzenesulfonamide in the presence of 10 mol% **1d** and DMAP in a solvent at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC with more than 99% *de*.

Table 3 The influence of additive on the asymmetric domino reaction[a]



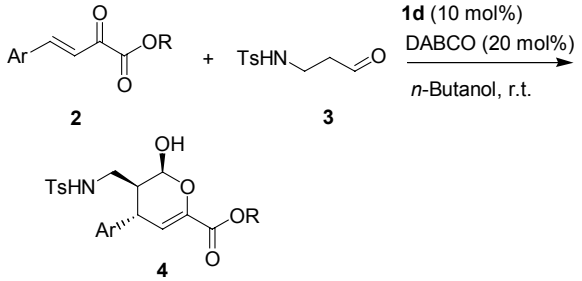
Entry	Additive	Time/h	Yield[b]/%	*ee*[c]/%
1	None	8 d	82	84
2	Et_3N	48	93	90
3	DABCO	24	93	90
4	TMEDA	36	89	87
5	DIPEA	48	97	87
6	DMAP	36	93	87
7	Cinchona alkali	36	87	89
8	NaOAc	36	80	81
9	2-$ClC_6H_4CO_2H$	8 d	62	87
11[d]	DABCO	24	94	93
12[e]	DABCO	8	81	90

[a] Reactions were conducted with 0.1 mmol (*E*)-methyl 2-oxo-4-phenylbut-3-enoate and 0.2 mmol 4-methyl-*N*-(3-oxopropyl)-benzenesulfonamideby using 10 mol% **1d** in the presence of additive in *n*-BuOH at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC with more than 99% *de*. [d] 20 mol% DABCO was used. [e] 50 mol% DABCO was used.

DABCO proved to be the best additive according to a combination of enantioselectivity, reaction time and yield. Increasing the quantity of additive from 10 to 20 mol% increased the enantioselectivity. Increasing the quantity of additive to 50 mol% decreased enantioselectivity and yield, however a reduction in reaction time was observed.

With the above optimal reaction conditions in hand, the asymmetric domino reaction was applied to a series of aromatic β,γ-unsaturated α-keto esters (Table 4). At first, the influence of the ester group on the reaction outcome was examined (Entries 1—4). The methyl ester (with little steric hindrance) gave the best result (Entry 1). The effects of substituents on the aromatic ring were then investigated. β,γ-Unsaturated α-keto esters with electron-withdrawing (Entries 5—11) and electon-donating (Entries 12—14) substituents on the aromatic group provided products in excellent yield and good enantioselectivity. Excellent diasteroeslectivities and enantioselectivies were also obtained when the phenyl group was replaced with a naphthalene or furan ring (Entries 15 and 16). The present catalytic system is

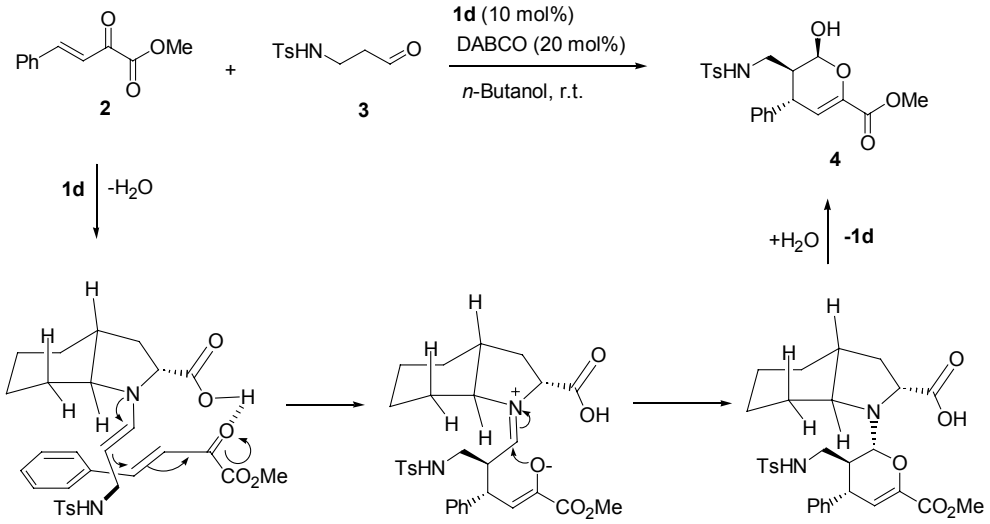
Table 4 Asymmetric domino reaction for a seriesof the aromatic β,γ-unsaturatedα-keto esters with **1d** as a catalyst[a]



Entry	4	Ar	R	Tim/h	Yield[b]/%	*ee*[c]/%
1	**4a**	C_6H_5	Me	24	94	93
2	**4b**	C_6H_5	Et	12	88	91
3	**4c**	C_6H_5	*i*-Pr	12	90	92
4	**4d**	C_6H_5	Bn	12	87	-d
5	**4e**	*p*-FC_6H_4	Me	12	92	92
6	**4f**	*o*-ClC_6H_4	Me	12	88	83
7	**4g**	*p*-ClC_6H_4	Me	12	93	92
8	**4h**	*o*-BrC_6H_4	Me	12	89	84
9	**4i**	*m*-BrC_6H_4	Me	24	89	85
10	**4j**	*p*-BrC_6H_4	Me	12	94	92
11	**4k**	2,6-$Cl_2C_6H_4$	Me	12	90	92
12	**4l**	*p*-$CH_3C_6H_4$	Me	12	90	92
13	**4m**	*m*-$MeOC_6H_4$	Me	12	90	82
14	**4n**	*p*-$MeOC_6H_4$	Me	36	96	85
15	**4o**	2-Nap.	Me	12	91	88
16	**4p**	2-Furanyl	Me	12	90	92

[a] Reactions were conducted with 0.1 mmol of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate and 0.2 mmol of 4-methyl-*N*-(3-oxopropyl)-benzenesulfonamide by using 10 mol% **1d** and 20 mol% DABCO in *n*-BuOH at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC with more than 99% *de*. [d] The sample could not be separated by chiral HPLC.

Scheme 1 Proposed mechanism for the stereochemical outcome



therefore suitable for domino reactions with a range of substituted β,γ-unsaturated α-keto esters. The aforementioned methodology provides an efficient synthetic pathway to the synthesis of highly substituted dihydropyran derivatives containing unusual amino group.

To determine the absolute configuration of the domino reaction product, X-ray crystallography studies were performed. Unfortunately a single crystal of the corresponding chiral product could not be obtained. Referring to our previous work in this area, the hemiacetal hydroxyl group and the adjacent ester group should lie on the opposite side of the phenyl ring.[4g]

Thus, a transition state model was proposed to account for the stereochemical outcome when using **1d** as the catalyst (Scheme 1). The aldehyde amine **3** reacts with **1d** to give a nucleophilic enamine intermediate whilst the (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**2a**) is directed toward the carboxylic acid group by a hydrogen bond (with the molecule lying behind the enamine) enhancing the electrophilic character of **2a**. The resulting enamine attacks the double C—C bond of **2a** (from above the plane of the alkene) to give the imine-enol intermediate with the adjacent amino group lying on the opposite side of the phenyl ring. Following cyclization, front-side attack by H_2O gives the desired product **4** and catalyst **1d**.

Conclusions

To summarise, we have developed an efficient asymmetric domino Michael addition/cyclization reaction of amino aldehyde to β,γ-unsaturated α-keto esters. Using *trans*-perhydroindolic acid **1d** as the chiral organocatalyst, products were obtained with more than 99% *de* and 93% *ee* and in high yield (up to 98%). The methodology was applied to a wide range of β,γ-unsaturated α-keto esters. Highly substituted dihydropyran derivatives containing an amino group were readily prepared using mild reaction conditions.

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References

[1] (a) Andrew, G. H. W. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1363; (b) Gunatilaka, A. A. L. *J. Nat. Prod*. **2006**, *69*, 509; (c) George, B.; Celine, C.; Bernard, M. *Synlett* **2005**, 587; (d) Girgis, A. S.; Ismail, N. S.; Farag, H. F. *Eur. J. Med. Chem*. **2011**, *46*, 2397.

[2] For reviews, see: (a) Yeung, K.-S.; Paterson, I. *Chem. Rev*. **2005**, *105*, 4237; (b) Kang, E. J.; Lee, E. *Chem. Rev*. **2005**, *105*, 4348; (c) Inoue, M. *Chem. Rev*. **2005**, *105*, 4379; (d) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev*. **2005**, *105*, 4406; (e) Nakata, T. *Chem. Rev*. **2005**, *105*, 4314; (f) Goldring, W. P. D.; Pattenden, G. *Acc. Chem. Res*. **2006**, *39*, 354; (g) Yet, L. *Chem. Rev*. **2003**, *103*, 4283; For selelcted papers, see: (h) Evans, D. A.; Thomson, R. J.; Franco, F. *J. Am. Chem. Soc*. **2005**, *127*, 10816; (i) Fehr, M. J.; Consiglio, G.; Scalone, M.; Schmid, R. *J. Org. Chem*. **1999**, *64*, 5768.

[3] (a) Eiden, F.; Winkler, W. *Arch. Pharm*. **1986**, *319*, 704; (b) Macdonald, S. J. F.; Huizinga, W. B.; Thomas, C. M. *J. Org. Chem*. **1988**, *53*, 3373; (c) Zhuang, W.; Jacob, T.; Jørgensen, K. A. *Chem. Commun*. **2000**, 459; (d) Robert, A. S.; Stuart, L. S. *Angew. Chem., Int. Ed*. **2001**, *40*, 3417; (e) Kobayashi, S.; Masashi, O.; Hirofumi, O.; Fujikawa, S. *Chem. Eur. J*. **2006**, *12*, 5962; (f) Wang, J.; Yu, F.; Zhang, X. J.; Ma, D. W. *Org. Lett*. **2008**, *10*, 2561; (g) Lao, J.-H.; Zhang, X.-J.; Wang, J.-J.; Li, X.-M.; Yan, M.; Luo, H.-B. *Tetrahedron*: *Asymmetry* **2009**, *20*, 2818; (h) Yao, W.; Wu, Y.; Wang, G.; Zhang, Y.; Ma, C. *Angew. Chem., Int. Ed*. **2009**, *48*, 9713; (i) Yao, W.; Pan, L.; Wu, Y.; Ma, C. *Org. Lett*. **2010**, *12*, 2422; (j) Xu, Z. H.; Liu, L.; Kraig, W.; Wang, H. *Angew. Chem., Int. Ed*. **2011**, *50*, 3484; (k) Wang, J. J.; Hu, Z. P.; Lou, C. L.; Liu, J. L.; Li, X. M.; Yan, M. *Tetrahedron* **2011**, *67*, 4578; (l) Hayat, I.; Satoshi,

S.; Yusuke, Y.; Yusuke, S.; Hayashi, Y. *Angew*. *Chem*., *Int*. *Ed*. **2011**, *50*, 3774.

[4] (a) Sun, L.; Zhang, Z.; Xie, F.; Zhang, W. *Chin*. *J*. *Org*. *Chem*. **2008**, *28*, 574 (in Chinese); (b) Ma, Y.; Zhang, Y. J.; Jin, S.; Li, Q.; Li, C.; Lee, J.; Zhang, W. *Tetrahedron Lett*. **2009**, *50*, 7388; (c) Jin, S.; Li, C.; Ma, Y.; Kan, Y.; Zhang, Y. J.; Zhang, W. *Org*. *Biomol*. *Chem*. **2010**, *8*, 4011; (d) Ma, Y.; Jin, S.; Kan, Y.; Zhang, Y. J.; Zhang, W. *Tetrahedron* **2010**, *66*, 3849; (e) Zhang, Z.; Xie, F.; Jia, J.; Zhang, W. *J*. *Am*. *Chem*. *Soc*. **2010**, *132*, 15939; (f) Zhao, L.; Shen, J.; Liu, D.; Liu, Y.; Zhang, W. *Org*. *Biomol*. *Chem*. **2012**, *10*, 2840; (g) Shen, J.; Liu, D.; An, Q.; Liu, Y.; Zhang, W. *Adv*. *Synth*. *Catal*. **2012**, doi: 10.1002/adsc.201200456.

[5] (a) Henning, R.; Urbach, H. *Tetrahedron Lett*. **1983**, *24*, 5343; (b) Brion, F.; Buendia, J.; Marie, C. *EP 267098*, **1986**; (c) Henning, R.; Urbach, H. *US 4691022*, **1987**; (d) Nuhrich, A.; Moulines, J. *Tetrahedron* **1991**, *47*, 3075; (e) Brion, F.; Marie, C.; Mackiewicz, P.; Roul, J. M.; Buendia, J. *Tetrahedron Lett*. **1992**, *33*, 4889; (f) Kalaus, E.; Frank, O. *US 6599318*, **1999**; (g) Muller, P.; Nury, P. *Org*. *Lett*. **1999**, *1*, 439; (h) Juhl, K.; Jørgensen, K. A. *Angew*. *Chem*., *Int*. *Ed*. **2003**, *42*, 1498; (i) Cid, P.; Polabo, S. L. *WO 05054194*, **2005**; (j) Li, J.-H.; Zhong, J.-F.; Shi, H.-L. *Chin*. *J*. *Pharm*. **2007**, *38*, 465.

[6] (a) Marie, R.; Marion, H. *J*. *Am*. *Chem*. *Soc*. **1928**, *50*, 2506; (b) Marie, R.; Elise, T.; Margaret, S. *J*. *Am*. *Chem*. *Soc*. **1935**, *57*, 211; (c) Stecher, E. D.; Ryder, H. F. *J*. *Am*. *Chem*. *Soc*. **1952**, *74*, 4392; (d) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Joergensen, K. A. *J*. *Org*. *Chem*. **2000**, *65*, 4487; (e) Varano, F.; Catarzi, D.; Colotta, V.; Filacchioni, G.; Galli, A.; Costagli, C.; Carlà, V. *J*. *Med*. *Chem*. **2002**, *45*, 1035.

[7] (a) Levchine, I.; Rajan, P.; Borloo, A.; Bollaert, W.; Haemers, A. *Synthesis* **1994**, 37; (b) Carballo, R. M.; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S.; Padron, J. I. *Org*. *Lett*. **2006**, 8, 3837.

(Zhao, C.)

