

Table 1.

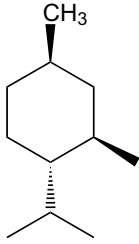
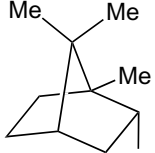
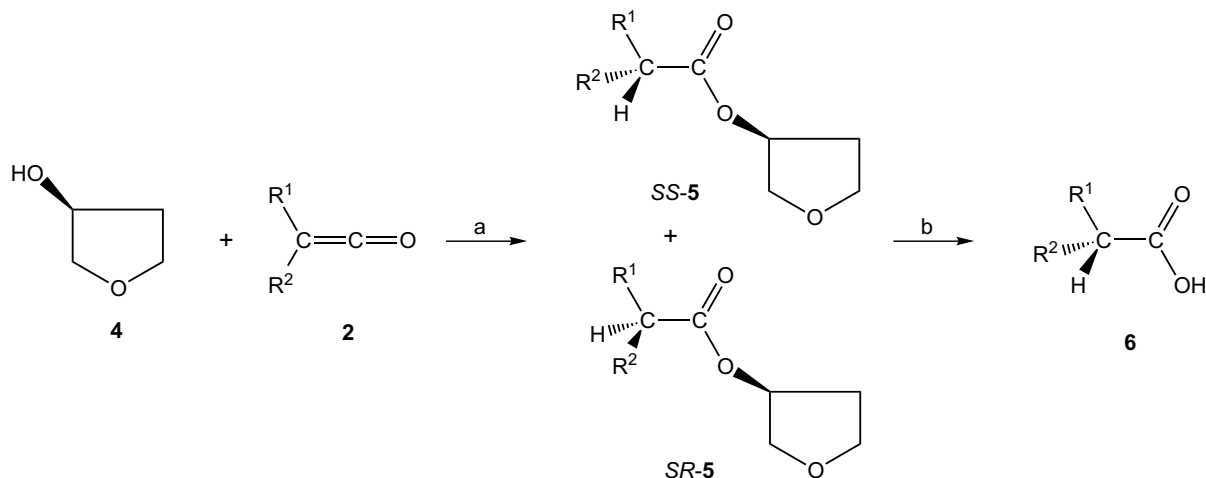
| Entry | Reaction conditions | R* | R ¹ | R ² | Ester 3 | | |
|-------|--------------------------------------|---|----------------|----------------|-----------|---|------------------------------------|
| | | | | | Yield (%) | [α] _D ²² (acetone <i>c</i> =1.5) | d.e. (%) (<i>SS</i> > <i>SR</i>) |
| 1 | <i>n</i> -BuLi Et ₂ Zn |  | Me | Ph | 82 | −32.5 | 62 |
| | | | Et | Ph | 78 | −28.4 | 60 |
| | | | Me | Cl | 83 | −22.5 | 48 |
| | | | Ph | Br | 73 | −28.3 | 45 |
| | | | | | | | |
| 2 | <i>n</i> -BuLi Et ₂ Zn |  | Me | Ph | 62 | +15.6 | 58 |
| | | | Et | Ph | 59 | +12.3 | 49 |
| | | | Me | Cl | 71 | +18.5 | 52 |
| | | | Ph | Br | 63 | +13.4 | 48 |

Table 2.

| Entry | Reaction conditions | R*OH | R ¹ | R ² | Ester 6 | | Acid 7 | | |
|-------|-----------------------------------|------|----------------|----------------|-----------|---------------------------|---|----------|---|
| | | | | | Yield (%) | (<i>SS</i> : <i>SR</i>) | [α] _D ²² | e.e. (%) | [α] _D ²² |
| 1 | <i>n</i> -BuLi–Et ₂ Zn | 4 | Me | Ph | 78 | 98:2 | +22.58 | 96 | +69.2 |
| 2 | <i>n</i> -BuLi–Et ₂ Zn | 4 | Et | Ph | 72 | 94:6 | +16.33 | 84 | +77.6 |
| 3 | <i>n</i> -BuLi–Et ₂ Zn | 4 | Br | Me | 80 | 90:10 | −9.35 | 80 | −20.0 |



Scheme 2. Reagents and conditions: (a) *n*-BuLi/Et₂Zn; (b) HCl/THF, (R¹=Me, R²=Ph; (ii) R¹=Et, R²=Ph; (iii) R¹=Me, R²=Br.

(R¹=CH₃, R²=Ph) on hydrolysis with conc. HCl in THF for 48 h at room temperature gave (*S*)-(+)-2-phenylpropanoic acid in 82% yield, e.e. 96% [[α]_D²²=+69.2 (*c*=1.4, CHCl₃)]. The absolute configuration was assigned to the 2-phenylpropanoic acid by comparison with the specific rotation of (*S*)-(+)-enantiomer.¹⁴

The proton transfer at C2 in ketene **2** from **4** is the key and crucial step for induction of stereoselectivity. Reactions carried out in the presence of catalytic Et₂Zn lead

to a high degree of diastereoselectivity, possibly due to chelation control with Zn.

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References

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9. Ketenes were generated in situ from the corresponding acid chlorides and Et₃N. The pale yellow colored ketenes were used immediately for the addition reactions.
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11. A solution of (*S*)-(+)-3-hydroxy tetrahydrofuran **4** (176 mg, 2 mmol) in anhydrous toluene was prepared at -90°C (5 mol) in dry toluene under a N₂ atmosphere. Ketene **2** (R¹=C₂H₅ and R²=Ph) prepared from 2-phenylbutyryl chloride (364 mg, 2 equiv.) was added and stirred for 12 h at 0°C. Saturated brine solution (50 ml) was added and the reaction mixture extracted with ether (3×50 ml), dried (MgSO₄), concentrated (in vacuo) to yield **5** (d.e. 45%). The reaction was carried out in the presence of different bases: pyridine, KO^tBu, Dabco and DBU. The d.e. ranges are from 8–46% with the maximum d.e. obtained with Dabco and the minimum with pyridine 8%.
12. **Reaction conditions:** A solution of **4** (88 mg, 1 mmol) in dry toluene (10 ml) at -78°C was treated with 1 ml of *n*-BuLi (2.48 M hexane solution, 1 equiv.) under a N₂ atmosphere. The solution was stirred for 15 min then methyl phenyl ketene **2** (i) (from 168 mg of *n*-propanonyl chloride, 1 equiv.) and 5.80 ml of Et₂Zn (1 M toluene solution, 2.2 equiv.) were added. The reaction was stirred at this temperature for 1 h and then for 12 h at 0°C. Saturated brine solution (25 ml) added and extracted with ether (3×25 ml), the ether extract dried (MgSO₄) and concentrated in vacuo to yield **5** as an oil which was purified by flash chromatography over Al₂O₃ (benzene).
13. The structures of all the compounds were confirmed by IR, ¹H and ¹³C NMR. For **5** (Table 2, entry 2) NMR data are as follows:
¹H (CDCl₃, 200 MHz, δ ppm): 0.89, 0.91 (3H, 2t, *J*=7.5 Hz, CH₃ (4)), 1.90 (4H, m, CH₂, (3,4')), 3.39, 3.41 (1H, 2t, *J*=7.5 Hz, CH (2)), 3.80 (4H, m, CH₂ (2', 5')), 5.25 (1H, m, CH (3')), 7.12, 7.15 (5H, 2s, Ph).
Assignment of resonances. ¹³C, ¹H correlations for **5** (*SS+RS*): ¹³C (CDCl₃, 100 MHz, δ ppm): C₂=52.907, 52.969; C₃=26.166, 26.263, C₄=11.662, C₂'=72.567, 72.429, C₃'=74.528, 74.547, C₄'=32.179, 32.441, C₅'=66.404, 66.434. The ratio of peaks at 3.39 and 3.41 for CH-2 in the ¹H NMR and at 52.907 and 52.969 for C₂ in ¹³C NMR was used to estimate the diastereomeric excess in **5**.
14. An optically pure sample of (*S*)-(+)-2-phenylpropanoic acid from Aldrich, Milwaukee, WI, USA, had [α]²⁰=+72 (*c*=1.6, CHCl₃); (*S*)-(+)-2-phenyl butyric acid had [α]¹⁹=+92 (*c*=0.9, toluene) and (*S*)-(-)-2-bromopropionic acid had [α]²⁰=-25 (neat).