25. Camphorsulfonamide-Shielded, Asymmetric 1,4-Additions and Enolate Alkylations; Synthesis of a Southern Corn Rootworm Pheromone

Preliminary Communication[1])

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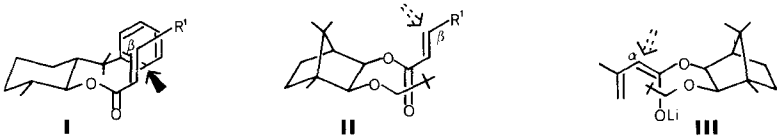
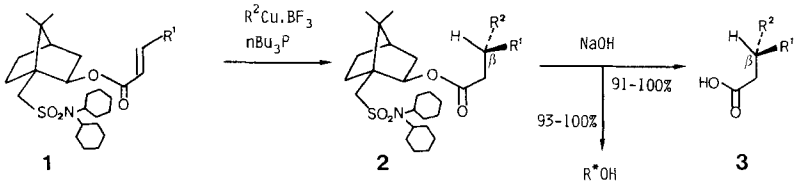
Using readily accessible 10-sulfonamido-isoborneols as regenerable, chiral auxiliaries, highly face-selective C–C-bond formations at C_α and C_β of carboxylates could be conveniently achieved. Thus, conjugated additions of RCu to enoates (**1**→**2**) furnished, after saponification, β-substituted carboxylic acids **3** in 94–98% e.e. Similarly, propionates **12** yielded after deprotonation, enolate alkylation, and reductive ester cleavage the (*R*)-alcohols **15** in 78–98% e.e. The acid (+)-**3e** was converted to the pheromone (–)-**11**.

Recently, we have reported up to 99% π-face-selective, $BF_3 \cdot OEt_2$-mediated conjugate additions[2]) of organocopper reagents to chiral enoates **I** [2] and **II** [3].



The enolate-face shielding on C_α-functionalization of the neopentyl ether **III** was comparatively less efficient (50% d.e.) [4]. Prompted by the practical utility of **1** (R^1=H) as a dienophile in asymmetric *Diels-Alder* reactions[3]) [6], we studied the applicability of the camphorsulfonamide group as a chiral 1,4-acceptor- and enolate-auxiliary.

Scheme 1



[1]) Presented in part at the Autumn Meeting of the Swiss Chemical Society, Berne, October 19, 1984.

[2]) For alternative asymmetric additions of organocopper reagents see [1].

[3]) Review: [5].

Table 1. *Preparation of Chiral β-Substituted Carboxylic Acids* **3** via *Conjugate Addition* **1→2**

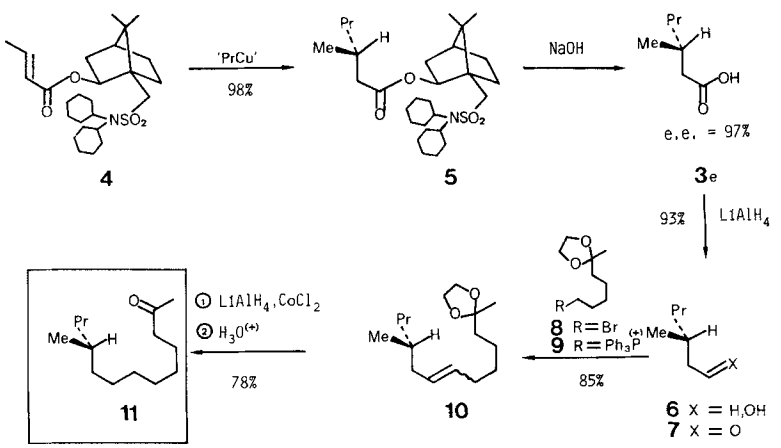
Entry	R^1	R^2	Mol-equiv. R^2-Cu[a])	Yield [%] of **2**	e.e.% of **3**
a	Me	Pr	2	98	95 (97)
b	Me	Bu	2	89	97
c	Me	Vinyl	10	80	98
d	Me	2-Propenyl	10	84	94
e	Pr	Me	10	89	94
f	Bu	Me	10	93	97

[a]) *i*) Addition of R^2Li (4 mmol; see *Footnote 6*) to CuI · $P(Bu)_3$ complex in Et_2O at −78°, stirring for 30 min → −30°. *ii*) Addition of $BF_3 \cdot OEt_2$ (4 mmol) at −78°; *iii*) Addition of enoate **1** (0.4–2 mmol) in Et_2O/THF 4:1 at −78°, warming up to −40° over 5 to 20 h. *iv*) Addition of sat. aq. NH_4Cl/Et_2O, stirring of the Et_2O phase with MCPBA (4 mmol) for 10 min and workup.

As indicated in *Scheme 1* and *Table 1*, treatment of crotonates **1a–d**[4])[5]) with $RCu \cdot PBu_3 \cdot BF_3$[6]) at −78°C→−40°C in Et_2O/THF ~15:1 furnished the 1,4-adducts **2a–d**[4]) in good-to-excellent yields. Saponification of **2** (1N NaOH, in aq. EtOH, reflux) gave the β-substituted carboxylic acids **3a–d** in 94–98% e.e.[7]) with virtually complete recovery of the crystalline auxiliary. The sense of induction at C_β of **3** was readily reversed either by interchanging R^1 and R^2 (see *Table 1*, examples a/e, b/f) or by using the antipodal inductor group [6].

The acid **3e**[4]), obtained in 97% e.e. *via* the sequence **4**[4])→**5**[4])→**3e** (or in 94% e.e. from **1e**) served as a key intermediate for the synthesis of the southern corn rootworm phe-

Scheme 2



[4]) All new compounds were characterized by IR, ^{1}H-NMR and MS.

[5]) The chiral esters **1**, **4** and **12** were prepared [7] by heating a mixture of the chiral alcohol (1 mol-equiv.), AgCN (1.4 mol-equiv.) and the corresponding acid chloride (2.0 mol-equiv.) in benzene at reflux for 4 h under Ar.

[6]) The starting reagents MeLi, PrLi, CH_2=CHLi and CH_2=CH(CH_3)Li were prepared by metalation of MeI, PrBr, vinyl chloride and 2-propenyl bromide with a lithium dispersion (3 mol-equiv.) in Et_2O (THF for vinyl chloride) using a *Vibromix*.

[7]) The enantiomeric purities of carboxylic acids **3** were determined by HPLC analyses of their (*S*)-α-naphthylethylamides [8] and their absolute configurations established by chiroptic comparison.

romone **11** [9][8]) *(Scheme 2)*. Reduction of **3e** with $LiAlH_4$ (2 mol-equiv. Et_2O, 0° →+20°, 2 h) followed by oxidation [11] of the alcohol **6**[4]) ($(COCl)_2$, DMSO, −50 to −60°, 1 h) gave aldehyde **7**[4]) (80%) which on *Wittig* reaction (add BuLi (1 mmol) to phosphonium bromide **9**[9]) (1.2 mmol) in THF at −78° →+20→−78°, add **7** (0.5 mmol) at −78° →+20°) yielded the olefin **10**[4]). Hydrogenation of **10** under non-epimerizing conditions[10]) (add $LiAlH_4$ (0.7 mmol) to a solution of dry $CoCl_2$ (0.7 mmol) and ketal **10** (0.3 mmol) in THF at −78°, stir at +20°, 24 h) [14] and subsequent acetal cleavage ($HOAc/H_2O$, 4:1, 50°, 30 min) afforded the pheromone **11**[4]) in high enantiomeric purity ($[\alpha]_D^{24°} = -1.61°$ ($c = 4.1$, $CHCl_3$); [10a]: $[\alpha]_D^{24°} = -1.71°$ ($c = 8.6$, $CHCl_3$)) identified by comparison (IR, ^{1}H-NMR and MS) with the published spectral data of **11** [10].

The versatility of camphorsulfonamides as practical π-face-shielding elements is further exemplified by the asymmetric enolate alkylations[11]) presented in *Scheme 3* and *Table 2*.

Scheme 3

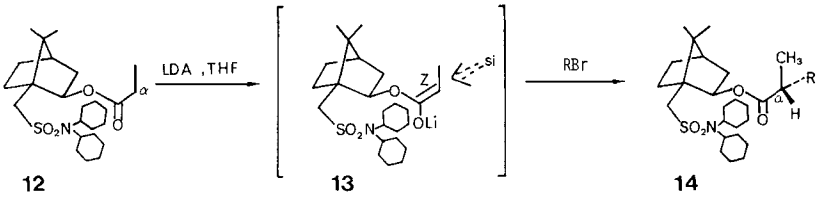
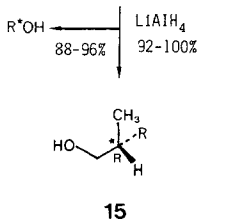


Table 2. *Asymmetric Alkylation/Reduction* **12**→**14**→**15**

Entry	R	Purification of **14** (m.p. °C)	Yield% of **14**	e.e.% of **15**
a	$PhCH_2$	crude	84	89
		1 cryst. (179–81)	61	98
b	CH_2=CH–CH_2	crude	94	88
c	Pr[a])	crude	92	78

[a]) Add a solution of PrBr in THF/HMPA (3 mol-equiv.) to enolate **13**.



Kinetically controlled deprotonation [16] of the propionate **12**[4]) (LDA (1.1. mol-equiv.), THF, −78°) followed by addition of a primary bromide to the enolate **13** gave the chiral α-substituted esters **14**[4]) in 84–94% yields and with 78 to 89% diastereoface differentiation. The diastereomeric purity of **14a** was raised to 98% d.e. by simple crystallization. Notably, even the non-activated PrBr led to the alkylation product **14c** in 92% yield (78% d.e.). Reductive cleavage ($LiAlH_4$ (2 mol-equiv.), Et_2O, 0–20°, 30 min) of

[8]) For other syntheses of the pheromone **11** see [10].

[9]) Bromide **8**[4]) was prepared by treatment of 1-bromo-6-heptene with $Hg(OAc)_2$ + TsOH in ethylene glycol/THF (30 min, +20°), followed by addition of $PdCl_2$, LiCl, $LiCO_3$, $CuCl_2$ (heating at reflux for 2 h) [12]. A mixture of bromide **8** and PPh_3 was slowly warmed up to 160° and kept at this temperature for 6 h to give the salt **9** (90%).

[10]) Under these conditions, (*R*)-citronellic acid was hydrogenated without epimerization, whereas considerable racemization occurred on hydrogenation with Pd/C, EtOH, H_2 (1 atm, 20°) [13]. An analogous epimerization may account for the relatively low optical rotation reported for synthetic **11** [10b].

[11]) For other asymmetric enolate alkylations see [15].

the alkylated esters **14** gave the unchanged auxiliary and the (*R*)-alcohols **15** in 78–98% e.e.[12]).

The asymmetric α- and β-functionalizations of esters, described above, are currently the subject of further investigation in this laboratory.

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[12]) As expected, deprotonation of **12** with LDA in THF/HMPA 4:1 followed by addition of benzyl bromide and subsequent crystallization and reduction furnished the enantiomer of alcohol **15a** in 80% e.e. The enantiomeric purity of the alcohols **15** was determined by HPLC analysis [8] either of their carbamates derived from (*R*)-α-naphthylethylisocyanate (entry a, *Table 2*) or of the (*S*)-α-naphthylethylamides obtained from **15** by successive *Jones'* oxidation and amidation (entries b, c).