# 287. High Asymmetric Induction in Conjugate Additions of RCu · BF₃ to Chiral Enoates

Preliminary Communication[1])

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## Summary

1,4-Additions of PhCu · BF₃, $n$-Bu · BF₃ and MeCu · BF₃ to the *trans*-8-phenyl-menthyl enoates **1** proceeded with high chiral induction. Saponification of the resulting esters **2** gave the corresponding enantiomerically pure $\beta$-substituted alkanoic acids **3** and the recovered (–)-8-phenylmenthol in good overall yields. Analogous additions to the *cis*-crotonate **1** led preferentially to the acids **3** enantiomeric to those obtained from the *trans*-crotonate **1**, although with lower selectivity. A stereochemical model is proposed consistent with the observed results *(Scheme 2, Table)*.

The highly enantioselective formation of C,C-bonds is of fundamental importance in organic synthesis[2]). Elegant efforts to achieve asymmetric induction in *Michael* reactions involve the use of chiral basic catalysts [2], cosolvents [3] and nucleophiles [4]. However, enantioselective C,C-bond closure $\beta$ to a carbonyl group has been accomplished more efficiently by 1,4-addition of organometallic reagents to $a,\beta$-unsaturated oxazolines [5], $t$-leucine-, $t$-butylester-aldimines [6], oxazepines [7], carboxylic amides derived from $l$-ephedrine [8] and $a$-carbonyl-$a,\beta$-ethylenic sulfoxides [9][3]). All these methods rely on a rigid substrate conformation owing to a chelation with the metal. We report here an entirely different concept which in terms of flexibility and efficiency offers an advantageous alternative.

Recently, the BF₃-mediated 1,4-addition of organocopper reagents to $a,\beta$-unsaturated carbonyl compounds has been reported by *Yamamoto et al.* [12] *(Scheme 1)*. The particularly smooth reaction may be attributed to a transition state **A** [12] or **B** implying either a synplanar or antiplanar C=C/C=O-arrangement. In context with asymmetric ene [13] and cycloaddition reactions [14–16] we assume that enoates of secondary alcohols prefer a conformation where the C=O is anti-

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[1])   Presented by one of us *(W.O.)* at the 11th Northeast Regional Meeting of the American Chemical Society, Rochester, Oct. 19, 1981.

[2])   Reviews [1].

[3])   For further methods to generate a chiral center in a $\beta$-position to a carbonyl group see [10] [11].

*Scheme 1*



A

C = C/C = O
synplanar

B

C = C/C = O
antiplanar
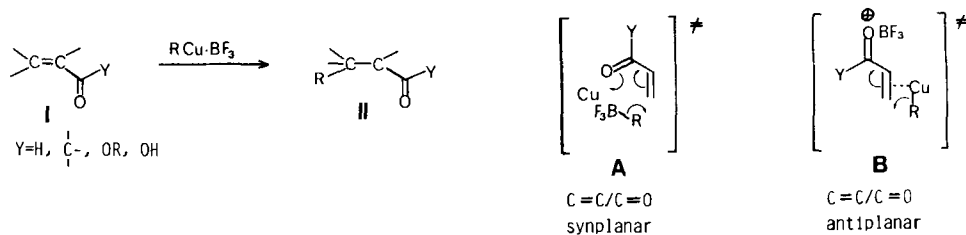
planar with the olefinic C,C-, and synplanar with the alkoxy-C,H-bonds; further-more, in enoates derived from (−)-8-phenylmenthol [14] **1** of from other secondary alcohols [16] the appropriately positioned aryl group may shield selectively one enantiotopic face of the enoate. The conformational rigidity of such enoates as well as the $\pi,\pi$-orbital overlap should be enhanced by the coordination of the C=O group with a *Lewis* acid.

Accordingly we anticipated that a reagent $R^3Cu \cdot BF_3$ could add to the 8-phenyl-menthyl enoates **1** preferentially at the olefinic face opposite to the phenyl ring *via* a transition state **B** *(Scheme 2)*. The experimental results in support of this hypothesis are summarized in *Scheme 2* and the *Table*.

Esterification[4]) of *trans*-crotonic acid and *trans*-2-heptenoic acid [18] furnished the *trans*-enoates **1** ($R^1 = H$, $R^2 = Me$) and **1** ($R^1 = H$, $R^2 = n$-Bu), respectively whilst the *cis*-crotonate **1** ($R^1 = Me$, $R^2 = H$) was prepared by esterification[4]) of tetrolic

*Scheme 2*
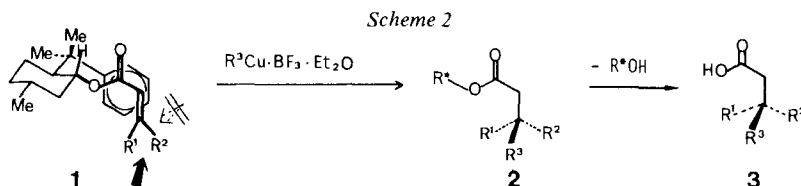


Table. *1,4-Additions of $R^3Cu \cdot BF_3$ to chiral enoates **1**→**2** and enantiomeric purity of the thus obtained $\beta$-substituted alkanoic acids **3***

| Entry | $R^1$ | $R^2$ | $R^3$ | Yield of **2** % | e.e. of **3** % |
|---|---|---|---|---|---|
| a | H | Me | $C_6H_5$ | 76 | > 99[a]) 99.3[b]) |
| b | H | Me | $n$-$C_4H_9$ | 75.4 | > 99[c]) 99.5[b]) |
| c | Me | H | $C_6H_5$ | 36 (72)[d]) | 24[a]) |
| d | Me | H | $n$-$C_4H_9$ | 76 | 70[c]) |
| e | H | $n$-$C_4H_9$ | Me | 28 (48)[d]) | 78[c]) |

[a]) ¹H-NMR. (360 MHz) and HPLC. (SiO₂, hexane/EtOAc/MeOH 3:7:0,24) of amide derived from **3** and L-phenylalaninol.
[b]) **3a**: $[\alpha]_D^{25} = -56.8°$ ($c = 9$, $C_6H_6$); **3b**: $[\alpha]_D^{25} = -4.18$ (neat).
[c]) HPLC. (SiO₂ hexane/EtOAc/MeOH 3:7:0.24) of amide derived from **3** and D-phenylglycinol.
[d]) Yield in parenthesis based on recovered **1**.

[4]) The corresponding acid was treated with (−)-8-phenylmenthol [14] (0.5 mol-equiv.), dicyclohexyl-carbodiimide (1 mol-equiv.) and $p$-$N$, $N$-dimethylaminopyridine [17] in CH₂Cl₂ at room temperature for 16 h to give the esters **1** in 83–95% yield.

acid [19] and subsequent partial hydrogenation in presence of *Lindlar*-catalyst. In analogy to the described procedure [12], PhLi (2 mol-equiv.) was added to purified CuI (2 mol-equiv.) in ether at $-40°\rightarrow -20°$. Successive slow addition of $BF_3 \cdot Et_2O$ (2mol-equiv.) and of the enoate **1a** (1 mol-equiv.) to the dark solution at $-70°$, stirring of the mixture for 10 min at $-70°$, raising the temperature slowly to $+25°$, quenching with sat. aq. $NH_4Cl$-solution and work-up yielded the 1,4-adduct **2a**[5]) in 76% yield. Saponification[6]) of **2a** allowed the recovery of the auxiliary $(-)$-8-phenylmenthol (98% yield) and afforded $(R)$-$(-)$-3-phenyl-butyric acid (**3a**) in over 99% enantiomeric purity. This dramatically high induction was assigned by chiroptic measurements [20] and further confirmed by conversion of **3a** into the amide of L-phenylalaninol[7]) and subsequent analysis of the latter [21] by HPLC. and $^1$H-NMR. in comparison with the amide obtained[7]) from racemic 3-phenylbutyric acid and L-phenylalaninol. Under analogous reaction conditions as described for the conversion **1a**$\rightarrow$**2a** $n$-BuCu $\cdot$ $BF_3$ was added to the *trans*-crotonate **1** giving the expected ester **2b** in 75.4% yield. Saponification[6]) of **2b** gave optically pure $(-)$-$(S)$-3-methylheptanoic acid (**3b**). The absolute configuration of **3b** was determined by its optical rotation [22] which indicated an enantiomeric purity of 99.5% in agreement with the HPLC. analysis [21] of the corresponding D-phenylglycinol amide[7]). Similar 1,4-addition of PhCu $\cdot$ $BF_3$ and of $n$-BuCu $\cdot$ $BF_3$ to the *cis*-crotonate **1** gave after saponification[6]) $(+)$-$(S)$-3-phenyl-butyric acid (**3c**, 24% e.e.) and $(+)$-$(R)$-3-methylheptanoic acid (**3d**, 70% e.e.), respectively, which were analyzed as described above. Although the sign of asymmetric induction in the reaction *cis*-**1**$\rightarrow$**2c** and *cis*-**1**$\rightarrow$**2d** agrees with our stereochemical model its is definitely lower. *Cis/trans*-isomerization of the *cis*-crotonate **1** prior to 1,4-addition seems unlikely since *cis*-**1** was recovered unchanged after partial conversion to **2c**. Nevertheless, by reversing the order of group introduction, either enantiomer of a $\beta$-substituted carboxylic acid **3** should be accessible in high enantiomeric excess *via* the *trans*-esters **1**. Thus, addition of MeCu $\cdot$ $BF_3$[8]) to the *trans*-2-heptenoate **1** and saponification[6]) of the adduct **2e** yielded $(+)$-$(R)$-3-methylheptanoic acid (**3d**≡**3e**) in over 72% chiral purity.

Further options include the use of new, either '*si*-face' or '*re*-face' directing auxiliary alcohols, which are presently being developed in this laboratory[9]). Combination of these possibilities with a plethora of known stereocontrolled routes to $\alpha,\beta$-conjugated esters [23] offers considerable promise. We are exploring systematically the scope and limitations of this asymmetric 1,4-addition reaction as well as its applicability to the synthesis of natural products.

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[5]) All new compounds were characterized by IR., $^1$H-NMR. (360 MHz) and mass spectroscopy.

[6]) Compound **2** (0.66 mmol) was heated in a mixture of 11.6N NaOMe in MeOH (7.5 ml) and water (4 mol-equiv.) at 75° for 24 h. Subsequent work-up and separation of neutral and acidic products furnished $(-)$-8-phenylmenthol and the corresponding acid **3**.

[7]) The corresponding acid **3** was heated in an excess of oxalyl chloride at 40° for 2 h. After evaporation a solution of the residue in dioxane was added slowly to a mixture of the chiral amine (1.1 mol-equiv.), NEt$_3$ (2 mol-equiv.) in dioxane at $+5°$. Stirring of the mixture at RT. for 2 h. work-up and rapid chromatography (SiO$_2$, hexane/EtOAc, 2:3) gave the corresponding amide in over 70% yield.

[8]) 10 Mol-equiv., $-65°$ for 10 h$\rightarrow$ $+20°$.

[9]) See for example the preceding communication [16].

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