287. High Asymmetric Induction in Conjugate Additions of $RCu \cdot BF_3$ to Chiral Enoates

Preliminary Communication[1])

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(11.XI.81)

Summary

1,4-Additions of $PhCu \cdot BF_3$, *n*-$Bu \cdot BF_3$ and $MeCu \cdot BF_3$ to the *trans*-8-phenylmenthyl enoates **1** proceeded with high chiral induction. Saponification of the resulting esters **2** gave the corresponding enantiomerically pure β-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 β to a carbonyl group has been accomplished more efficiently by 1,4-addition of organometallic reagents to α,β-unsaturated oxazolines [5], *t*-leucine-, *t*-butylester-aldimines [6], oxazepines [7], carboxylic amides derived from *l*-ephedrine [8] and α-carbonyl-α,β-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 BF_3-mediated 1,4-addition of organocopper reagents to α,β-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-

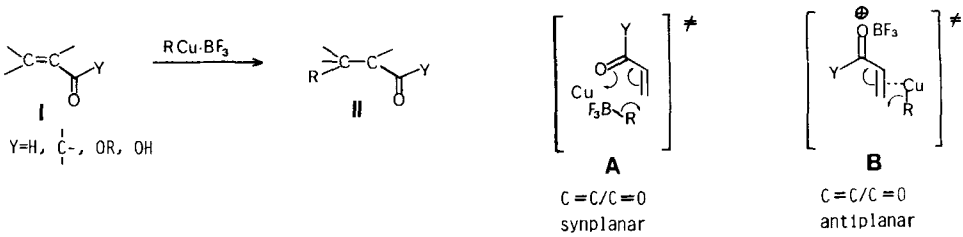
[1]) Presented by one of us *(W. O.)* at the 11th Northeast Regional Meeting of the American Chemical Society, Rochester, Oct. 19, 1981.

[2]) Reviews [1].

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

0018-019X/81/8/2808-04$01.00/0

Scheme 1



planar with the olefinic C,C-, and synplanar with the alkoxy-C,H-bonds; furthermore, 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 π,π-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-phenylmenthyl 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

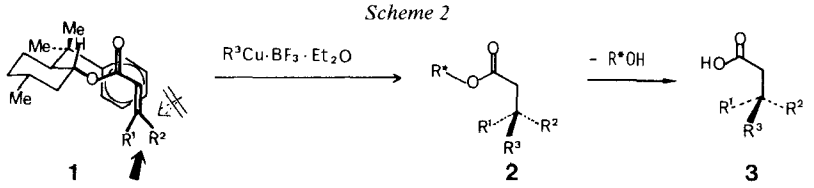


Table. *1,4-Additions of $R^3Cu \cdot BF_3$ to chiral enoates* **1**→**2** *and enantiomeric purity of the thus obtained β-substituted alkanoic acids* **3**

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]) ^{1}H-NMR. (360 MHz) and HPLC. (SiO_2, 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. (SiO_2 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.), dicyclohexylcarbodiimide (1 mol-equiv.) and *p-N,N*-dimethylaminopyridine [17] in CH_2Cl_2 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-phenylbutyric 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**→**2a** *n*-BuCu · 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 · BF_3 and of *n*-BuCu · BF_3 to the *cis*-crotonate **1** gave after saponification[6]) (+)-(*S*)-3-phenylbutyric 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**→**2c** and *cis*-**1**→**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 β-substituted carboxylic acid **3** should be accessible in high enantiomeric excess *via* the *trans*-esters **1**. Thus, addition of MeCu · 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 α,β-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 → +20°.

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

Financial support of this work by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung, Sandoz SA*, Basel, and *Givaudan SA*, Vernier, is gratefully acknowledged. We also thank Mr. *J.P. Saulnier*, Mr. *A. Pinto* and Mrs. *D. Clément* for NMR. and MS. measurements.

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