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ASYMMETRIC 1,4-ADDITIONS OF COORDINATED MeCu.BF_3 TO CHIRAL ENOATES: ENANTIOSELECTIVE SYNTHESES OF (S)-(-)-CITRONELLIC ACID[1]

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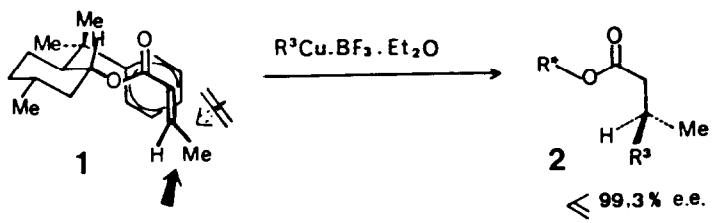
Abstract: $n$$Bu_3P$- or cyanide-stabilized RCu.BF_3 (R=Me, 4-Me-3-pentenyl) undergo efficient 1,4-additions to neopentylether-shielded *trans*-enoates. Thus chiral β-substituted carboxylic acids e.g. (S)-citronellic acid were obtained in high e.e. (Schemes 2 and 4).

Recently greater than 99% enantioselective C-C bond closure β to a carboxyl group has been accomplished[2] by BF_3-promoted 1,4-additions of organocopper reagents[3] to the crotonate derived from (-)-8-phenylmenthol[4] (Scheme 1). We ascribed the π-face selectivity of the reactions 1 → 2

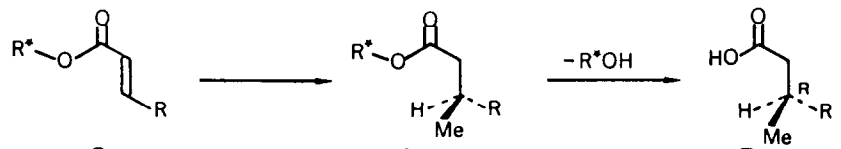
Scheme 1



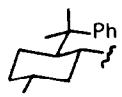
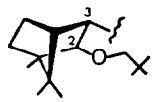
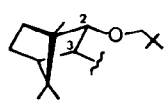
to an antiplanar C=C/C=O-disposition in the enoate and thus to a phenyl shielding of its C_β-*si*-face. Accordingly, by reversing the order of group introduction, either enantiomer of a β-substituted carboxylic acid should be accessible using the same chiral control element.

Prompted by the ubiquitous occurrence of methyl-substituted chiral centers in natural products, we concentrated our efforts on the conjugate addition of methylcopper derivatives to chiral enoates. Our results are depicted in the Scheme 2[5,6]. Initial attempts to add even a large excess of MeCu.BF_3 to the enoate 3a were impaired by the unfavorable stability/reactivity-ratio of the reagent (entry a)[2]. By contrast, upon stabilization of the methyl-copper species by $n$$Bu_3P$[1,6] its addition to 3a furnished the adduct 4a in 96% yield. Subsequent saponification of 4a gave the (R)-carboxylic acid 5, R=nBu in 86.5% enantiomeric excess (entry b). Realizing the increased flexibility offered by the antipodal auxiliaries 6 and 7 (Scheme 3)[1,7] the enoate 3c was treated with various methylcopper reagents. Whereas Me_2CuLi did not add at 0° within 2 hr (entry c), Bu_3P-coordinated MeCu.BF_3 gave the corresponding adduct 4c in 82% yield and with improved π-face differentiation (94%, entry d). A new, conveniently stable reagent obtained by mixing MeLi with CuCN (1 eq.) and $BF_3.Et_2O$ (1 eq.)[1,8] gave on addition to 3c followed by simple work-up the ester 4c in 80% yield with a somewhat lower induction (82% d.e. (entry e)). Comparison of entries f, d and h shows an increasing chiral induction (92% → 98% e.e.) parallel to the size of the resident

Scheme 2

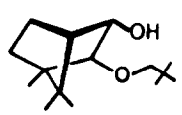


3 4 5

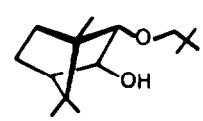
entry	R*	R	"MeCu·BF_3" Ligand	chem. yield % 4[6]	e.e.% 5[10]
a		nBu	none	28	78
b	- " -	nBu	nBu_3P: A[6]	96	86.5
c		nBu	Me_2CuLi	0	—
d	- " -	nBu	nBu_3P: B[6]	82	94
e	- " -	nBu	CN^-: C[6]	80	82
f	- " -	Et	nBu_3P: B[6]	85	92
g	- " -	Et	CN^-: C[6]	76	80
h		nC_8H_{17}	nBu_3P: B[6]	90	98 (S)

substituent R. The last entry h merits further attention since the enoate 3h derived from 7 afforded the (S)-carboxylic acid 5h with 98% overall enantioselection. Thus, alternating either the order of group introduction or the antipodal control elements, provides a high degree of flexi-

Scheme 3



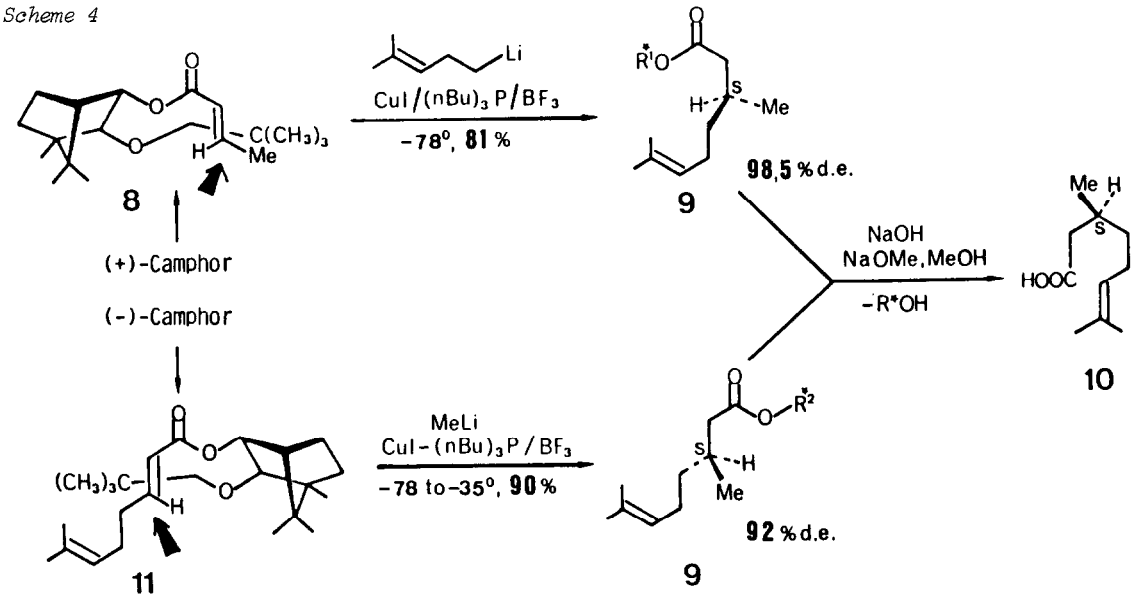
6



7

bility in synthesis. This is further illustrated by the preparation of (S)-citronellic acid (Scheme 4) which is difficult to obtain in optically pure form[19] and which is an interesting synthetic precursor[20]. Addition of 4-methyl-3-pentenylcopper/BF_3/nBu_3P-complex to crotonate 8[21] followed

Scheme 4



by saponification of the resulting product 9 afforded acid 10 efficiently with 98.5% overall enantioselectivity. Reduction of ester 9 with $LiAlH_4$ gave (S)-citronellol (88%) together with the regenerated auxiliary 6 (81%). Permutation of both the resident group and the chirality of the control moiety is exemplified by the transformation 11 → 9 yielding also (S)-citronellic acid of 92% optical purity.[10]

In summary we believe that asymmetric carbon-carbon bond construction by Lewis-acid promoted 1,4-additions, Diels-Alder-[17] and ene-reactions[22] of chiral enoates are of practical value in organic synthesis. These findings are currently exploited for the syntheses of natural products. Moreover we are exploring the utility of cyanide stabilized organocopper-Lewis-acid-reagents, particularly in additions to epoxides and Michael acceptors.

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

[6] The enoates were prepared by successive treatment of the corresponding acid with $(COCl)_2$ and R*OH/AgCN[7]. Carboxylic acids 3c, 3h, R*=H were obtained by Horner reaction[8]. For the conversions 3 → 4 freshly prepared 1.2N solutions of MeLi in ether (MeI + Li) have been employed under argon with vigorous stirring as follows: A: CuI(10eq) add MeLi(10eq). -10°, 20 min. → -78°, add nBu$_3$P (10eq), 10 min, add $BF_3.Et_2O$(10eq), 1h, add 3 (1eq), then -10°, 6h/aq.NH_4Cl, 2 chromatographies (SiO_2); B: nBu$_3$P-CuI[9] (10eq), -78°, add MeLi(10eq) over 30 min → -20° → -78°, add $BF_3.Et_2O$(10eq) over 30 min, 1h, add 3 (1eq) over 40 min, -78°, 2h then -35°, 16h/aq. NH_4Cl, 2 chromatographies; C: anhydr. CuCN (5eq), -78°, add MeLi (5eq) → -10° → -78° add $BF_3.Et_2O$ (5eq), 1h, add 3 (1eq) over 45 min → -20°, 16 h/aq. sat. NH_4OH/NH_4Cl (1:22), flash chromatography. Saponification 4 → 5: 2N NaOMe in MeOH (33 eq), H_2O (5eq), 75°, 15 h (87-99%).

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[21] 8 was converted to 9 using the following conditions: CuI(2eq), ether, 0°, add nBu$_3$P (2eq) → +20° → -65° add freshly prepared (RBr/Li) 4-methyl-3-pentenyllithium over 30 min. → -10°, 20 min, → -78° add $BF_3.Et_2O$ (2eq), 1.5h, add 8 (1eq) over 1h/aq. NH_4Cl, chromatography.

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