An Efficient Synthesis of Chiral Quaternary Carbon Centres with High Optical Purity *Via* 1,3-Chirality Transfer

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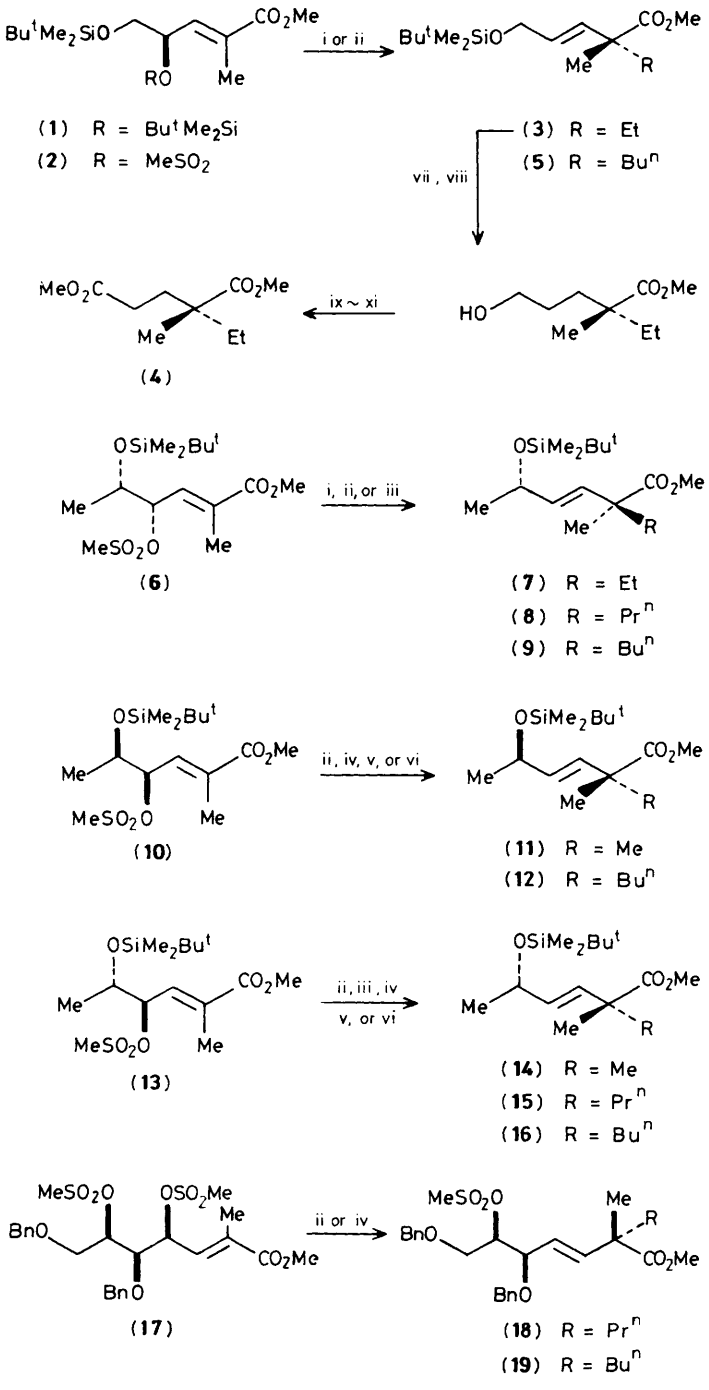
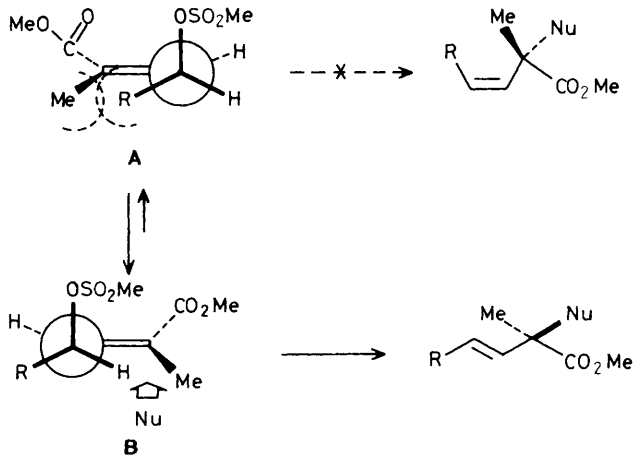
An efficient synthesis of chiral quaternary carbon centres *via* $Me_2Cu(CN)Li_2 \cdot BF_3$ or $RCu(CN)Li \cdot BF_3$ ($R \neq Me$) mediated 1,3-chirality transfer of α-alkyl-γ-mesyloxy-α,β-enoates is reported.

Novel synthetic methods which create chiral quaternary carbon centres with a high level of selectivity represent a challenge to organic chemists.[1] During recent years, enantioselective alkylations of chiral bicyclic lactams,[2] and use of acyclic α-alkyl-α-cyanoacetamides with pyrrolidines as chiral auxiliaries,[3] and chiral β-hydroxy esters[4] greatly contributed to progress in the synthesis of chiral quaternary centres.[5] Although these are useful methods, there still remains the basic problem of the removal of the chiral auxiliaries using strong mineral acids.[2a,3] In these conditions, labile protective and functional groups such as siloxy, acetonide, tetrahydropyranyl, ester, *etc.*, are not expected to survive the reaction



Scheme 1. *Reagents:* i, $EtCu(CN)Li{\cdot}BF_3$; ii, $Bu^nCu(CN)Li{\cdot}BF_3$; iii, $Pr^nCu(CN)Li{\cdot}BF_3$; iv, $Me_2Cu(CN)Li_2{\cdot}BF_3$; v, $MeCu(CN)Li{\cdot}BF_3$; vi, $Bu^n_2Cu(CN)Li_2{\cdot}BF_3$; vii, H_2/5% Rh–Al_2O_3 in MeOH; viii, MeCN–H_2O–HF (98 : 1 : 1); ix, $COCl_2$–dimethyl sulphoxide–Et_3N; x, $KMnO_4$–Bu^tOH–NaH_2PO_4; xi, CH_2N_2.



Scheme 2

conditions. Attempts to construct the quaternary centres from chiral monoalkylated amides have also been unsatisfactory.[3,6] We describe here a highly enantioselective synthesis of chiral quaternary centres with selectivity approaching 100% *via* a 1,3-chirality transfer reaction[7] of α-alkyl-γ-mesyloxy-α,β-enoates.

Although treatment of the silyl ether (**1**) with an excess of $EtCu(CN)Li{\cdot}BF_3$[8] in tetrahydrofuran (THF) at −78 °C for 1 h and at −40 °C for 30 min recovered the unchanged starting material, the methanesulphonate (**2**) gave the regio-, (*E*)-stereo-, and enantio-selective alkylation product (**3**) as the major product by treatment with the same reagent at −78 °C for 30 min in THF (Table 1, entry 1).

The enantioselectivity of the product (**3**) is >99% as determined by ^1H n.m.r. analysis using a chiral shift reagent $Eu(hfc)_3$ [hfc = 3-heptafluoropropylhydroxymethylene-(+)-campharato]. Thus, the mesyloxy group at the γ-position exerts a powerful directing effect leading to both enantioselectivity and high chemical yield in the 1,3-chirality transfer. While we cannot conclusively rule out the presence of trace quantities of (*Z*)-alkene, the (*E*)-isomer (**3**) was the only one detected. The (*E*)-geometry of the product (**3**) was easily established from the 15.87 Hz coupling constant of the two olefinic protons. The absolute configuration at the quaternary centre in (**3**) was determined to be (*R*) by converting (**3**) into known dimethyl (*R*)-(+)-α-methyl-α-ethylglutarate (**4**),[9,10] a key degradation product for the structure elucidation of the potent tumour-promoting indole alkaloid teleocidin A_2 isolated from a mixture of metabolites of *Streptomyces mediocidicus*, Scheme 1.[10,11]

Comparable very high enantio- or diastereo-selectivities and chemical yields were obtained by reaction of the methanesulphonates (**6**), (**10**), (**13**), and (**17**) with $RCu(CN)Li{\cdot}BF_3$ (R = Et, Pr^n, Bu^n; entries 2—5, 7, and 9—12) and the methanesulphonates (**10**) and (**13**) with $Me_2Cu(CN)Li_2{\cdot}BF_3$ (entries 6 and 8) in THF at −78 °C for 30 min. In these reactions, we did not detect any reductive elimination[7,12] or γ-alkylated product by t.l.c., g.l.c., and ^1H n.m.r. analyses. It is evident from these data that the absolute configuration and the optical purity of the chiral quaternary centres reflect almost completely the stereochemistry of the mesyloxy group at the γ-position of the substrates (*anti* S_N2' reaction). This finding is in accord with the results reported by Fleming,[13] Goering,[14] and ourselves[7] in studies on the alkylation of allylic compounds.

The chemical yield of the present 1,3-chirality transfer varies considerably depending upon the alkylcyanocopper–BF_3 reagent used. Thus, it is found that the use of $RCu(CN)Li{\cdot}BF_3$ (R ≠ Me) rather than $R_2Cu(CN)Li_2{\cdot}BF_3$ (R ≠ Me) for the formation of quaternary centres is essential (compare entries 7 and 10 with 14 and 16, respectively). In sharp contrast, since a substantial amount of starting material was

Table 1. Chemical yields and enantio- or diastereo-selectivity in the reactions of α-alkyl-γ-mesyloxy-α,β-enoates with alkylcyanocopper– BF_3.[a]

Entry	Substrate	Reagent	Product chemical yield/%	Enantio- or diastereoselectivity[b] (absolute configuration at C-2)
1	(**2**)	$EtCu(CN)Li\cdot BF_3$	(**3**) 92[c]	>99 : 1 (*R*)
2	(**2**)	$Bu^nCu(CN)Li\cdot BF_3$	(**5**) 97	>98 : 2 (*R*)
3	(**6**)	$EtCu(CN)Li\cdot BF_3$	(**7**) 89	>99 : 1 (*S*)
4	(**6**)	$Pr^nCu(CN)Li\cdot BF_3$	(**8**) 95	>99 : 1 (*S*)
5	(**6**)	$Bu^nCu(CN)Li\cdot BF_3$	(**9**) 96	>99 : 1 (*S*)
6	(**10**)	$Me_2Cu(CN)Li_2\cdot BF_3$	(**11**) 96	
7	(**10**)	$Bu^nCu(CN)Li\cdot BF_3$	(**12**) 98	>98 : 2 (*R*)
8	(**13**)	$Me_2Cu(CN)Li_2\cdot BF_3$	(**14**) 99	
9	(**13**)	$Pr^nCu(CN)Li\cdot BF_3$	(**15**) 98	>99 : 1 (*R*)
10	(**13**)	$Bu^nCu(CN)Li\cdot BF_3$	(**16**) 94	>99 : 1 (*R*)
11	(**17**)	$Pr^nCu(CN)Li\cdot BF_3$	(**18**) 91	>99 : 1 (*S*)
12	(**17**)	$Bu^nCu(CN)Li\cdot BF_3$	(**19**) 99	>99 : 1 (*S*)
13	(**10**)	$MeCu(CN)Li\cdot BF_3$	(**11**) 56[d]	
14	(**10**)	$Bu^n{}_2Cu(CN)Li_2\cdot BF_3$	(**12**) 74	>98 : 2 (*R*)
15	(**13**)	$MeCu(CN)Li\cdot BF_3$	(**14**) 52[e]	
16	(**13**)	$Bu^n{}_2Cu(CN)Li_2\cdot BF_3$	(**16**) 70	>99 : 1 (*R*)

[a] All reactions were carried out at least in duplicate and the following procedure for the preparation of the quaternary centre is typical. To a stirred solution of $Pr^nCu(CN)Li$ (0.68 mmol) in dry THF (5 ml) under Ar at −78 °C $BF_3\cdot Et_2O$ (0.082 ml) was added dropwise and the mixture was stirred for 10 min. The methanesulphonate (**13**) (0.227 mmol) in dry THF (2 ml) at −78 °C was added to the mixture with stirring and the mixture was stirred for 30 min. After the usual work-up, the product was purified, if necessary, by SiO_2 flash chromatography with n-hexane–EtOAc (10 : 1) to yield pure product (**15**) (70 mg, 98% yield after Kugelrohr distillation). [b] Determined by 200 MHz ^1H n.m.r. spectroscopy with $Eu(hfc)_3$. [c] S_N2 Substitution product (*ca.* 3.5%) was also isolated. [d] Unchanged starting material (42%) was recovered. [e] Unchanged starting material (46%) was recovered.

recovered with the use of $MeCu(CN)Li\cdot BF_3$, $Me_2Cu(CN)Li_2\cdot BF_3$ is necessary for the clean chirality transfer (compare entries 6 and 8 with 13 and 15, respectively, Table 1).

There remains an important question why all substrates were exclusively transformed into the (*E*)-alkenes. It has been reported that the transition structures of types (A) and (B) are the most likely to be concerned in the nucleophilic reactions on the basis of molecular orbital considerations.[15] The energy difference between (A) and (B) could arise from the steric hindrance exerted by the methyl group on the double bond and the R group (alkyl side chain). For conformer (A), unfavourable interactions between the methyl group and the R group are present. Molecular models suggest that the attack of the reagent on the surface *anti* to the electron withdrawing mesyloxy group *via* conformer B is demanded sterically. Thus, the conformer B would explain the (*E*)-stereoselection as well as the *anti* S_N2' reaction.

In summary, the present 1,3-chirality transfer reaction of α-alkyl-γ-mesyloxy-α,β-enoates with $Me_2Cu(CN)Li_2\cdot BF_3$ or $RCu(CN)Li\cdot BF_3$ (R ≠ Me) provides a simple and efficient route to a range of stereoisomerically pure chiral α,α-dialkylated (*E*)-β,γ-enoates, not readily accessible by other means.†

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† All new compounds have been fully characterized spectrally and have elemental compositions determined by high-resolution mass spectroscopy and/or combustion analysis. Preparative methods of all optically active substrates will be presented in a full paper.