

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

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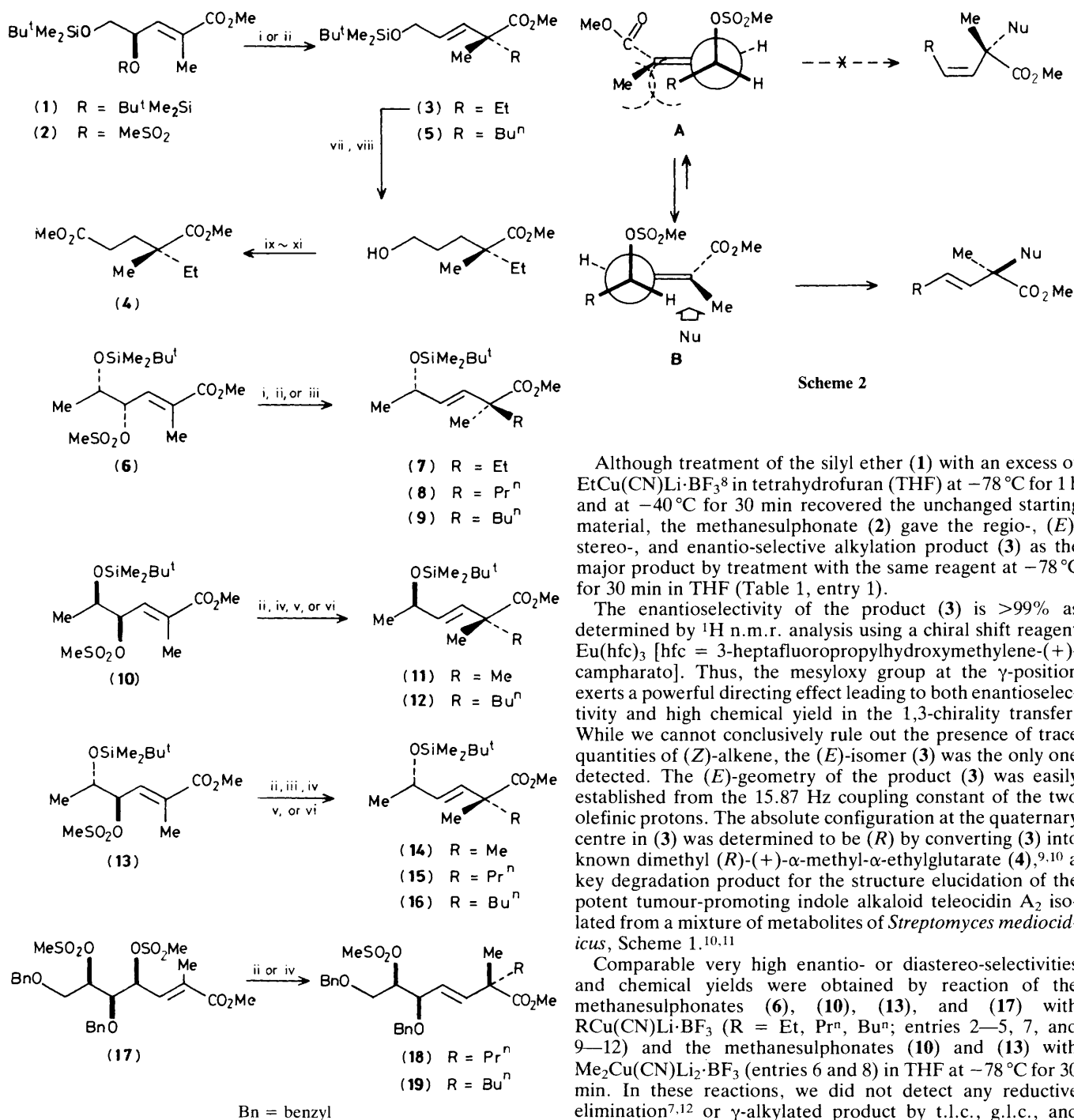
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An efficient synthesis of chiral quaternary carbon centres via $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2\text{BF}_3$ or $\text{RCu}(\text{CN})\text{Li}\text{BF}_3$ ($\text{R} \neq \text{Me}$) mediated 1,3-chirality transfer of α -alkyl- γ -mesyloxy- α,β -enoates is reported.

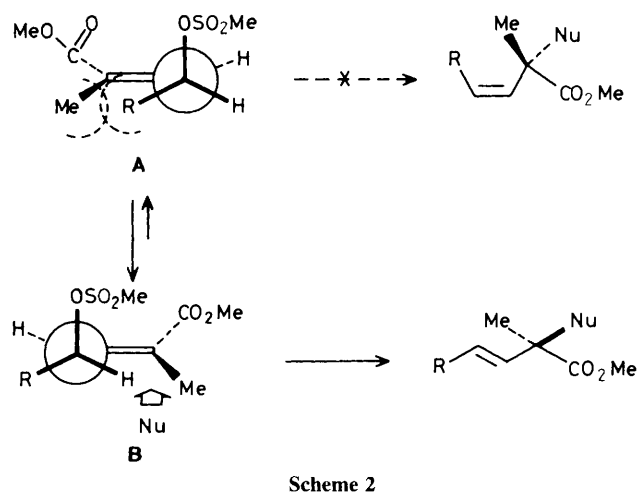
Novel synthetic methods which create chiral quaternary carbon centres with a high level of selectivity represent a challenge to organic chemists.¹ During recent years, enantioselective alkylations of chiral bicyclic lactams,² and use of acyclic α -alkyl- α -cyanoacetamides with pyrrolidines as chiral auxiliaries,³ and chiral β -hydroxy esters⁴ 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 silyloxy, acetonide, tetrahydropyranyl, ester, *etc.*, are not expected to survive the reaction



Scheme 1. Reagents: i, EtCu(CN)Li·BF₃; ii, BuⁿCu(CN)Li·BF₃; iii, PrⁿCu(CN)Li·BF₃; iv, Me₂Cu(CN)Li₂·BF₃; v, MeCu(CN)Li·BF₃; vi, Bu₂ⁿCu(CN)Li₂·BF₃; vii, H₂/5% Rh–Al₂O₃ in MeOH; viii, MeCN–H₂O–HF (98:1:1); ix, COCl₂–dimethyl sulphoxide–Et₃N; x, KMnO₄–Bu^tOH–NaH₂PO₄; xi, CH₂N₂.

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 reaction⁷ of α -alkyl- γ -mesyloxy- α,β -enoates.



Although treatment of the silyl ether (1) with an excess of EtCu(CN)Li·BF₃⁸ 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 A₂ 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·BF₃ (R = Et, Prⁿ, Buⁿ; entries 2–5, 7, and 9–12) and the methanesulphonates (10) and (13) with Me₂Cu(CN)Li₂·BF₃ (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 ourselves⁷ in studies on the alkylation of allylic compounds.

The chemical yield of the present 1,3-chirality transfer varies considerably depending upon the alkylocyanocopper–BF₃ reagent used. Thus, it is found that the use of RCu(CN)Li·BF₃ (R ≠ Me) rather than R₂Cu(CN)Li₂·BF₃ (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 alkylcycano-copper- BF_3 .^a

Entry	Substrate	Reagent	Product chemical yield/%	Enantio- or diastereo- selectivity ^b (absolute configuration at C-2)
1	(2)	$\text{EtCu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(3) 92 ^c	>99:1 (R)
2	(2)	$\text{Bu}^n\text{Cu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(5) 97	>98:2 (R)
3	(6)	$\text{EtCu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(7) 89	>99:1 (S)
4	(6)	$\text{Pr}^n\text{Cu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(8) 95	>99:1 (S)
5	(6)	$\text{Bu}^n\text{Cu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(9) 96	>99:1 (S)
6	(10)	$\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2\cdot\text{BF}_3$	(11) 96	
7	(10)	$\text{Bu}^n\text{Cu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(12) 98	>98:2 (R)
8	(13)	$\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2\cdot\text{BF}_3$	(14) 99	
9	(13)	$\text{Pr}^n\text{Cu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(15) 98	>99:1 (R)
10	(13)	$\text{Bu}^n\text{Cu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(16) 94	>99:1 (R)
11	(17)	$\text{Pr}^n\text{Cu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(18) 91	>99:1 (S)
12	(17)	$\text{Bu}^n\text{Cu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(19) 99	>99:1 (S)
13	(10)	$\text{MeCu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(11) 56 ^d	
14	(10)	$\text{Bu}^n_2\text{Cu}(\text{CN})\text{Li}_2\cdot\text{BF}_3$	(12) 74	>98:2 (R)
15	(13)	$\text{MeCu}(\text{CN})\text{Li}\cdot\text{BF}_3$	(14) 52 ^c	
16	(13)	$\text{Bu}^n_2\text{Cu}(\text{CN})\text{Li}_2\cdot\text{BF}_3$	(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 $\text{Pr}^n\text{Cu}(\text{CN})\text{Li}$ (0.68 mmol) in dry THF (5 ml) under Ar at -78°C $\text{BF}_3\cdot\text{Et}_2\text{O}$ (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 $\text{Eu}(\text{hfc})_3$. ^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 $\text{MeCu}(\text{CN})\text{Li}\cdot\text{BF}_3$, $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2\cdot\text{BF}_3$ 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 $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2\cdot\text{BF}_3$ or $\text{RCu}(\text{CN})\text{Li}\cdot\text{BF}_3$ ($\text{R} \neq \text{Me}$) 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.

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