by the addition of a solution of 1.14 g (5.96 mmol) of phenylselenenyl chloride[11] in 5 mL of THF over 2 min. The light yellow solution was stirred at −70 °C for 30 min and at 0 °C for 30 min. The solution was then quenched with 20 mL of 10% aqueous HCl. The mixture was washed with ether (2 × 25 mL), and the aqueous layer was basified with aqueous NaOH and extracted with ether (2 × 25 mL). The ethereal layer was dried ($MgSO_4$) and evaporated to a viscous, yellow oil. Bulb-to-bulb distillation [oven temperature 170–190 °C (0.15 torr)] afforded 0.954 g (51%) of **8**, a very viscous oil: $[\alpha]^{20}_D$ +63° (*c* 1.289, methanol); ^1H NMR ($CDCl_3$) δ 8.48–8.68 (m, 1), 8.18–8.43 (m, 1), 6.88–7.83 (m, 7), 4.48 (t, *J* = 8 Hz, 1), 3.85–4.18 (m, 1), 1.73–3.25 (m, 2), 2.55 and 2.63 (diastereomeric methyl s's, 3); EI mass spectrum, *m/z* 330, 332 (M^+ consisting of the two major selenium isotopes).

(2′*S*,4′*RS*)-4′-Phenylselenonicotine (9). To a solution of 6.51 g (0.0197 mol) of **8** in 150 mL of THF under nitrogen at room temperature was added 111 mL of 1.06 M borane in THF. The mixture was refluxed for 17 h. After cooling in an ice bath, the mixture was very carefully and slowly quenched with 145 mL of 6 N aqueous HCl. The solution was refluxed for 3 h, cooled, and washed with ether (2 × 100 mL). The aqueous layer was basified with aqueous NaOH and extracted with ether (3 × 50 mL). The combined ethereal layer was dried ($MgSO_4$) and evaporated to a yellow oil. Bulb-to-bulb distillation [oven temperature 140–150 °C (0.15 torr)] provided 3.68 g (59%) of **9**, an oil: $[\alpha]^{20}_D$ −113° (*c* 0.402, methanol); ^1H NMR ($CDCl_3$) δ 8.43–8.60 (m, 2), 7.13–7.88 (m, 7), 1.58–4.03 (m, 6), 2.18 (s, 3); EI mass spectrum, *m/z* 316, 318 (M^+ consisting of the two major selenium isotopes).

(*S*)-(−)-2,5-Dihydro-1-methyl-2-(3-pyridyl)pyrrole (6). To a solution of 1.0 g (3.15 mmol) of **9** in 20 mL of THF at 0 °C was gradually added 484 μL (4.73 mmol) of 30% H_2O_2. The solution was stirred at 0 °C for 30 min and room temperature for 1.5 h. To the solution was added 5 mL of 10% aqueous sodium sulfite followed by 10 mL of 10% aqueous Na_2CO_3. The mixture was extracted wtih ether (3 × 15 mL), and the combined ethereal layer was dried ($MgSO_4$) and evaporated to a reddish oil. Bulb-to-bulb distillation [oven temperature 60–70 °C (0.15 torr)] afforded 0.227 g (45%) of **6**, a colorless, mobile oil: dipicrate mp 182–186 °C; $[\alpha]^{20}_D$ −364° (*c* 0.313, methylene chloride); ^1H NMR ($CDCl_3$) δ 8.51 (m, 2), 7.69 (dt, *J* = 8, 2 Hz, 1), 7.25 (dd, *J* = 8, 5 Hz, 1), 5.85–6.03 (m, 1), 5.58–5.75 (m, 1), 4.20–4.43 (m, 1), 3.68 (AB q with extensive fine coupling, 2; each multiplet located at 3.98–4.10, 3.80–3.94, 3.38–3.53, and 3.21–3.36), 2.41 (s, 3); EI mass spectrum, *m/z* 160 (M^+), 82 (*N*-methylpyrrolinyl).

Anal. Calcd for $C_{22}H_{18}N_8O_{14}$ (dipicrate): C, 42.72; H, 2.91; N, 18.12. Found: C, 42.91; H, 3.09; N, 18.10.

Acknowledgment. We thank Henry V. Secor and Dr. Jeffrey I. Seeman for helpful discussions and Anne Donathan for secretarial assistance.

Registry No. **1**, 54-11-5; **2**, 487-19-4; **6**, 85026-74-0; **6** dipicrate, 85026-75-1; **7**, 486-56-6; **8** (isomer 1), 84960-83-8; **8** (isomer 2), 84960-84-9; **9** (isomer 1), 84960-85-0; **9** (isomer 2), 84960-86-1; **10**, 3000-74-6; phenylselenenyl chloride, 5707-04-0.

Alkylation of Allylic Derivatives. 6. Regiochemistry of Alkylation of Allylic Acetates with Dialkylcuprates

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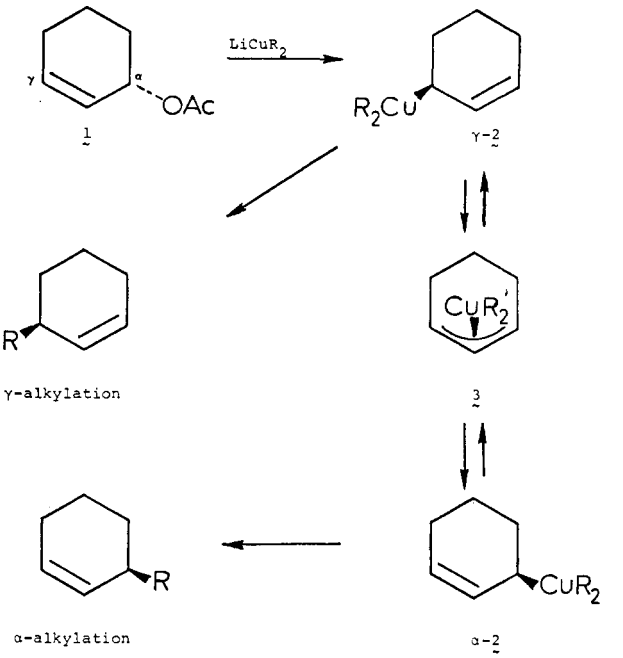
Recently we concluded that the mechanistic pathway for alkylation of allylic carboxylates with cuprates involves oxidative addition with allylic rearrangement to give a σ-allylcopper(III) complex (γ-**2**) as illustrated for the cyclohexenyl system (**1**) in Scheme I.[1a] The stereochemistry

Scheme I. Mechanistic Pathway for Alkylation of 2-Cyclohexenyl Acetate with Dialkyl Cuprates



of alkylation shows that the **1** → γ-**2** transformation is stereospecific as well as regiospecific and in unhindered systems gives the anti-σ-allyl complex (γ-**2**) as shown in the scheme.[1,2] Evidence for oxidative addition with allylic rearrangement is that excess γ-alkylation is involved in all cases where regiospecificity[3] has been observed. The reason for the S_N2' regiochemistry is thought to result from prior complexation of the cuprate with the double bond to give a cuprate–olefin π complex that is converted to γ-**2**.[1]

The initially formed copper(III) complex (γ-**2**) can (1) undergo stereospecific[4] reductive elimination to give anti-γ-alkylation or (2) isomerize to the π-allyl complex (**3**) in which case stereochemistry is preserved but regiochemistry is lost. The regiochemistry of alkylation depends on the relative rates of these two processes, and this seems to depend on the nature of the ligands on copper.[1b] With lithium dialkylcuprates little if any regiospecificity is observed in either cyclic[2,5] or acyclic[6,7] systems. This indicates that the **2** → **3** isomerization is fast relative to reductive elimination when there are two alkyl ligands on copper.

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(3) In this series the terms regiospecific and regioselective are used in the same sense as stereospecific and stereoselective as defined by Zimmerman et al. Zimmerman, H. E.; Singer, L.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1959**, *81*, 108 in footnote 16. Thus, if two isomeric allylic carboxylates related to the same allylic intermediate (e.g., anion, cation, radical, or π-allyl complex) give the same alkylation product, or mixtures with the same composition, there is no regiospecificity. If in this case one of two possible alkylation products predominates the reaction is regioselective but not regiospecific. Put another way, if there is excess α- or γ-alkylation in a system related to a symmetrical allylic intermediate (such as the cyclohexenyl system), the reaction is regiospecific. Regiospecificity can be partial (mixtures with different compositions derived from isomeric allylic carboxylates or excess γ-alkylation is an unbiased symmetrical system) as well as complete (e.g., exclusive γ-alkylation for both allylic isomers or in a symmetrical system).
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0022-3263/83/1948-1531$01.50/0

Table I. Optical Activity of *trans*-3,5-Dimethylcyclohexene (5) Obtained by Alkylation of (−)-*cis*-5-Methyl-2-cyclohexenyl Acetate (*cis*-4-OAc) with $LiCuMe_2$

optical purity of (−)-*cis*-4-OAc,[a] %	rotation of 5,[b] deg	optical purity of (−)-5, %	excess γ-alkylation, %
50	−0.7[c]	0.3	0.6
52	−1.2[d]	0.5	1.0

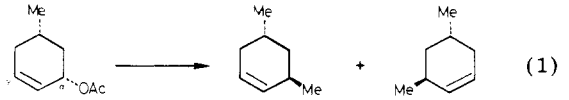
[a] Optical purities determined directly with a chiral NMR shift reagent, Eu(hfbc)$_3$. [b] Rotations are $[\alpha]^{25}_D$ (*c* 3.5–9, $CHCl_3$). [c] Measured rotation 10 times larger than experimental error. [d] Measured rotation 50 times larger than experimental error.

On the other hand, substantial regiospecificity is observed with several mixed cuprates such as LiCu(R)CN,[6,8,10] LiCu(R)(CH_3NPh),[1b] and LiCu(R)(N(Ph)CO_2CHMe_2).[9] In these cases excess γ-alkylation is observed. For example, alkylation of α- or γ-deuterated *cis*-5-methyl-2-cyclohexenyl acetate (*cis*-4-OAc) with LiCu(CH_3)CN give 96% γ-alkylation and 4% α-alkylation.[10] Thus, when one of the two alkyl ligands in **2** is replaced by a cyano group, reductive elimination is fast relative to formation of the π-allyl complex (**3**) in unbiased systems.

The mechanism in Scheme I requires that γ-alkylation predominate to some extent—the operational significance of the isomeric σ-allyl complexes (α-**2** and γ-**2**) vanishes if there is no evidence for excess γ-alkylation. In an earlier paper[2] we reported that alkylation of *cis*-4-OAc and *trans*-4-OAc with lithium dimethylcuprate is stereospecific—*cis*-4-OAc gives *trans*-3,5-dimethylcyclohexene (*trans*-**5**) and *trans*-4-OAc gives *cis*-5. The regiochemistry was investigated with α- and γ-deuterated *cis*-4-OAc, and it was found that the C-1, C-3 deuterium distribution in the alkylation product (*trans*-**5**-d_1) was the same, within experimental error, for samples derived from *cis*-4-OAc-α-d_1 and *cis*-4-OAc-γ-d_1. However, the only analytical method available at the time, ^{1}H NMR analysis, is not very precise and not suitable for detecting small levels of regiospecificity.[3]

4-OAc 5

We now reinvestigated the regiochemistry of alkylation of 4-OAc with lithium dimethylcuprate using a far more sensitive analytical method for detecting a slight excess of α- or γ-alkylation in this unbiased system. In this work we have investigated the alkylation of optically active *cis*-4-OAc. As shown by eq 1, enantiomers result from α- and γ-alkylation. The absolute configurations shown in the equation were determined previously.[11] Because of the large absolute rotation of *trans*-**5**, $[\alpha]^{25}_D$ 211° (neat),[11] 235° ($CHCl_3$), retention of a fraction of a percent of optical activity can be detected.



(−)-*cis*-4-OAc (+)-*trans*-**5** α-alkylation (−)-*trans*-**5** γ-alkylation (1)

The results of the key experiments are presented in Table I. In these experiments (*S*)-(−)-*cis*-4-OAc was alkylated with 2 equiv of halide-free LiCu(CH_3)$_2$ in ether at 0 °C. The optical purities of the two samples of (−)-*cis*-4-OAc were determined directly with the chiral NMR shift reagent, tris(heptafluorobutyrylcamphorato)europium.[12] These values are in good agreement with the optical purities of (−)-*cis*-4-OH (determined by rotation)[13] from which the samples of (−)-*cis*-4-OAc were prepared.

As indicated in the table, alkylation results in almost complete loss of optical activity. However, slight activity is consistently observed, and this results from formation of (3*S*,5*R*)-(−)-*trans*-**5**, which is about 1% as active as the (*S*)-(−)-*cis*-4-OAc from which it is derived. Put another way, alkylation in this unbiased system involves about 1% excess γ-alkylation.

The present results are compatible with the view that the S_N2' σ-allyl complex (γ-**2**) is the initial product-forming intermediate as indicated in Scheme I. In work to be reported elsewhere, we have obtained similar results for alkylation of bicyclo[3.2.1]oct-3-en-2-yl acetate (**6**) with lithium dimethylcuprate.[10] A slight excess of γ-alkylation can also be detected in this unbiased system by using optically active *exo*-**6** and examining the sign and magnitude of the rotation of the alkylation product, 2-methylbicyclo[3.2.1]oct-3-ene (**7**).[14] Thus, with sensitive analytical methods, excess γ-alkylation can be detected for a reaction heretofore thought to be nonregiospecific[3] (i.e., alkylation of allylic carboxylates with dialkylcuprates).[2,6]

6 **7**

Experimental Section

Materials. ***cis*-5-Methyl-2-cyclohexenol** (*cis*-4-OH) was prepared and resolved as reported earlier.[15] NMR data have been reported elsewhere.[11]

(−)-*cis*-5-Methyl-2-cyclohexenyl Acetate (*cis*-4-OAc)[16] was prepared from (−)-*cis*-4-OH by the method reported earlier for the preparation of racemic *cis*-4-OAc.[17] The cis acetate (*cis*-4-OAc) has the following spectral data: ^{1}H NMR (CCl_4) δ 5.73 (ddd, 1 H, *J* = 10, 5, 3 Hz), 5.48 (brd, 1 H, *J* = 10 Hz), 5.23 (m, 1 H), 2.3–1.1 (m, 5 H), 1.99 (s, 3 H), 1.01 (d, 3 H, *J* = 6 Hz). Optical purities of samples of (−)-*cis*-4-OAc were determined with a chiral NMR shift reagent. With Eu(hfbc)$_3$[12] ΔΔδ = 0.22 for the acetyl methyl singlet with an *R*/*S* ratio of 0.3. A sample of (−)-*cis*-4-OAc, $[\alpha]^{25}_D$ −2.7° (*c* 3, $CHCl_3$), was found to be 50 ± 0.2% optically pure.[18] This corresponds to an absolute rotation of $[\alpha]^{25}_D$ 5.4° ($CHCl_3$) for *cis*-4-OAc.

Ethereal MeLi (Ventron) was standarized by a double titration method,[19] and CuI was purified as described elsewhere.[20] Diethyl ether was purified by distillation from sodium benzophenone ketyl under nitrogen.

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Lithium dimethylcuprate was prepared as follows. A solution of 1.02 g (2.1 mmol) of $(Bu_2S)_2CuI$[21] in 10 mL of ether was placed in a 15-mL centrifuge tube fitted with a septum cap. The tube was purged with dry nitrogen and cooled to −78 °C. Addition of 2.1 mmol of ethereal MeLi resulted in precipitation of yellow MeCu. The resulting suspension was centrifuged and the supernatant liquid forced out through a Teflon cannula with dry nitrogen. The resulting MeCu was washed several times at −78 °C with 10-mL portions of dry ether to remove lithium halide. Finally, the methylcopper was suspended in 8 mL of dry ether and 2 mmol of halide-free MeLi was added. Warming to 0 °C gave a clear solution of $LiCuMe_2$. Lithium dimethylcuprate was also prepared by using powdered CuI or Me_2SCuBr[22] instead of $(Bu_2S)_2CuI$. The different preparations gave the same results. Also, $LiCuMe_2$ prepared from ethereal MeLi (Ventron, 1:1 LiBr complex) gave the same results as the above halide-free $LiCuMe_2$.

Alkylation of (−)-*cis*-5-Methyl-2-cyclohexenyl Acetate ((−)-*cis*-4-OAc) with Lithium Dimethylcuprate. In a typical experiment 154 mg (1 mmol) of the above (−)-*cis*-4-OAc, $[\alpha]^{25}_D$ −2.7% ($CHCl_3$),[18] was added to 2 mmol of freshly prepared ethereal $LiCuMe_2$ in a centrifuge tube at 0 °C. The mixture was kept at 0 °C for 8 after which 1 mL of water was added. Methane was evolved and a reddish precipitate formed. After centrifuging, the supernatant liquid was decanted and concentrated, and the product (*trans*-5) was isolated by preparative GC (100 ft XF-1150 on Chromosorb W, 60 °C). Isolated yields ranged from 30% and 40%. Analysis by capillary GC (100 ft SE-30, 50 °C) showed the product to be 99.5% *trans*-5 and 0.5% *cis*-5. Capillary GC of the starting (−)-*cis*-4-OAc (300 ft Ucon LB-2000, 80 °C) showed the acetate to be homogeneous except for a trace (~1.0%) of the trans isomers. Results of this and a similar experiment are given in Table I. That the trace amount of *cis*-5 in the product does not contribute to the observed rotation was established as follows. Fractions containing up to 3% *cis*-5 were obtained by preparative GC. Fractions containing 1% and 3% *cis*-5 had rotations within experimental error of each other and the bottom value in Table I.

In a control experiment, 2 mmol of 35% optically pure (−)-*cis*-4-OAc was reacted with 1 mmol of $LiCuMe_2$ as described above. The unreacted acetate was recovered by preparative GC (10 ft FFAP on Chromosorb W, 70 °C). The optical purity of the recovered (−)-*cis*-4-OAc was found to be unchanged (35%) by direct determination with the chiral NMR shift reagent, Eu(hfbc)$_3$.[12] This experiment shows that *cis*-4-OAc retains its optical configuration under conditions of the reaction with $LiCuMe_2$. Thus loss of configuration for the *cis*-4-OAc → *trans*-5 occurs during the reaction.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE 8108535).

Registry No. (−)-*cis*-4-OAc, 85317-77-7; (−)-*cis*-4-OH, 69685-64-9; (+)-*trans*-5, 85317-78-8; (−)-*trans*-5, 69685-66-1; Eu(hfbc)$_3$, 34788-82-4; $(Bu_2S)_2CuI$, 35907-81-4; MeLi, 917-54-4; MeCu, 1184-53-8; lithium dimethylcuprate, 15681-48-8.

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High Dilution via Solid–Liquid Phase-Transfer Catalysis. A Practical Approach to the Synthesis of Macrolides[1]

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We report herein an extremely simple and effective procedure for preparing macrolides based on the solid–liquid phase-transfer catalysis principle.[2-4] Our method involves the use of tetrabutylammonium bromide (1) to solubilize and activate the conjugate base of ω-bromocarboxylic acids in toluene (Scheme I). When catalytic quantities of 1 are employed, high dilution conditions are simulated and excellent yields of macrolide are readily obtained.[5]

Attempted intramolecular displacement of 1.0 mmol of potassium 12-bromododecanoic acid *suspended* in 10 mL of toluene at 90 °C, in the absence of a phase-transfer catalyst, resulted in no detectable reaction after 3 h. In contrast, a similar mixture containing 8 mg of 1 produced a 95% yield (GLC) of 12-hydroxydodecanoic acid lactone. Upon filtration, solvent removal, and chromatographic purification, a 95% isolated yield of the macrolide was obtained. When higher concentrations of the soluble

Scheme I

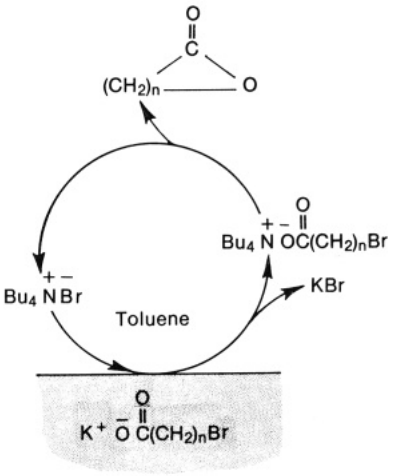
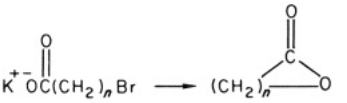


Table I. Biphase Cyclization of ω-Bromocarboxylic Acids[a]



n	ring size	$Bu_4N^+Br^-$, 10^3 M	time, h	yield,[b] %
5	7	2.5	3	92
7	9	1.5	24	26[c]
11	13	2.5	3	95 (95)[d]
		10.0	3	94
		58.0	3	85
		100.0	3	73
14	16	2.5	3	92
15	17	2.5	3	94

[a] Reaction of 0.1 mmol of potassium ω-bromocarboxylic acid suspended in 1.0 mL of anhydrous toluene in the presence of 1 at 90 °C. [b] GLC yield. [c] Yield remained unchanged upon further heating. [d] Isolated yield from a 1.0-mmol-scale reaction.

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