The present catalytic system exhibits chemoselectivity toward allylation rather than the conjugate addition pathway. Reaction of **5** with chlorinated carvone (entry 14) took place exclusively on the allylic chloride moiety rather than with the enone, and less than 0.1% of side products was found on capillary GC analysis.[17] A more challenging example between an allylic phosphate and an enone is illustrated in Scheme I. Treatment of an equimolar mixture of cinnamyl phosphate (**2a**) and cyclohexenone (**3**) with 1.0 equiv of **6** and 5 mol % of CuI·2LiCl at −70 to −40 °C in THF resulted in the preferential reaction with the phosphate, affording the allylation product **1** in good yield. By contrast, *upon introduction of Me$_3$SiCl, the conjugate addition pathway is activated* and now competition between **2a** and **3** in the presence of Me$_3$SiCl[16] (1.1 equivalent) selectively gave the conjugate addition product **4**. The same competition reaction performed with Bu$_2$CuLi (1.0 equiv) at −70 °C exhibited much lower selectivities.

The nature of the reactive species in the present catalytic reaction is presently unclear. However, the following experiments for various butyl group transfer reagents indicated that both titanium and copper metals are essential for high regioselectivity. The regioselectivity of the common organolithium-based copper reagents is much lower. For instance, the reaction of BuCu (BuLi + CuI) with the phosphate **2a** at −70 °C for 6 h in THF showed only 77% S$_N$2′ selectivity (88% yield). Similarly, Bu$_2$CuLi (2BuLi + CuI) showed 73% selectivity (70% yield). The reaction of BuLi with **2a** in the presence of a catalytic amount of CuI·2LiCl was very complex. All butyltitanium reagents examined above were totally inert to cinnamyl chloride or phosphate at low temperatures, the copper catalyst thus being essential for the reaction.

In summary, by combining catalytic amounts of CuI·2LiCl with alkyltitanium reagents, a new reactive species is formed, which perhaps is acting as a low energy carrier of alkyl groups capable of selective synthetic transformations under mild conditions.

Acknowledgment. E.N. thanks the Nissan Foundation for financial support of the work.

Supplementary Material Available: Full experimental procedures and product identification (7 pages). Ordering information is given on any current masthead page.

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[17] The same reaction of Bu$_2$CuLi was quite complex as judged by GC analysis.

Configurationally Fixed α-Alkoxyorganocopper Reagents: 1,4-Addition of Cyclic Enantiopure Transferable Ligands with Complete Retention of Configuration

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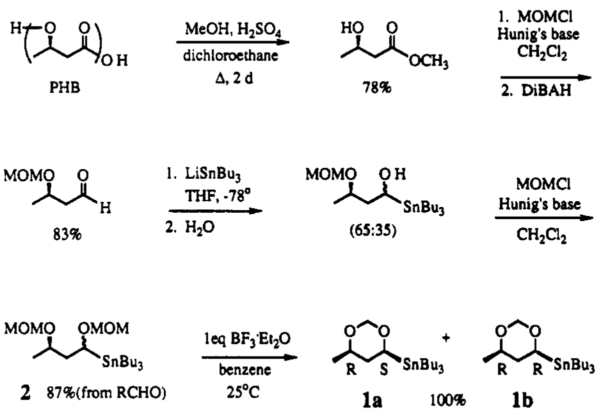
Summary: Optically active 4-lithio-1,3-dioxanes have been converted to the corresponding TMEDA–organocopper reagents and shown to undergo conjugate addition reactions to ethyl propiolate with complete retention of configuration.

Racemic α-alkoxyorganocuprates have been developed as useful reagents for the synthesis of homoaldol products[1] and as nucleophilic capped carbonyl ylide synthons.[2] Recently, we reported that enantiopure higher order cyano α-alkoxyorganocuprates could undergo conjugate addition reactions with retention of configuration; however, the acyclic optically active reagents also readily racemized during 1,4-addition reactions.[3] In this paper, we wish to report studies on cyclic enantiopure α-alkoxyorganocopper reagents derived from 4-(tributylstannyl)-1,3-dioxanes.

Cohen and Matz reported the generation of cyclic α-lithio ethers by means of the reductive lithiation of α-phenylthio ethers.[4] Subsequent studies on 2-lithiotetrahydropyrans[5] revealed that equatorial lithio anions were configurationally stable while axial anions could undergo inversion at elevated temperatures. Rychnovsky and Mikus[6] have recently reported an extension of this chemistry to 4-lithio-1,3-dioxanes. As with the 2-lithiotetrahydropyrans,[5] the dioxane anions also undergo inversion at elevated temperatures from the kinetic (axial) isomer to the thermodynamic (equatorial) isomer. The cyclic lithio ethers could also be produced by transmetalation of the derived stannane[7] with retention of configuration.

Scheme I



To analyze the configurational stability of a cyclic α-alkoxyorganocopper derivative, stannane **1** was chosen as a common precursor for axial and equatorial organocopper reagents. The synthesis of **1** from poly(3(*R*)-hydroxybutyric acid) is shown in Scheme I. Conversion of the ester[8] to the aldehyde followed by condensation with lithio tributylstannylate was accomplished by known proce-

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[1] (a) Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron* **1989**, *45*, 495–506. (b) Linderman, R. J.; McKenzie, J. M. *Tetrahedron Lett.* **1988**, *29*, 3911–3914.

[2] Linderman, R. J.; Godfrey, A. *J. Am. Chem. Soc.* **1988**, *110*, 6249–6251.

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[4] Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900–6901.

[5] Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130–1131.

[6] Rychnovsky, S. D.; Mikus, D. E. *Tetrahedron Lett.* **1989**, *30*, 3011–3014.

[7] Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982–4984.

[8] Seebach, D.; Zuger, M. F. *Tetrahedron Lett.* **1984**, *25*, 2747–2750.

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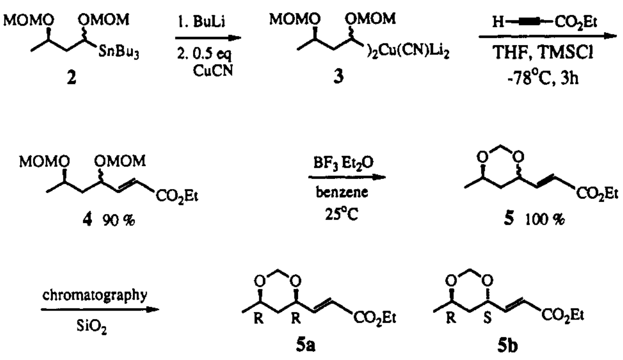
dures.[1] Treating **2** with 1 equiv of $BF_3{\cdot}Et_2O$ rapidly generated the diastereomeric dioxane derivatives **1a** and **1b** in quantitative yield.[9] The dioxanes were readily resolved by flash chromatography (SiO_2) leading to enantiopure **1a** and **1b**.

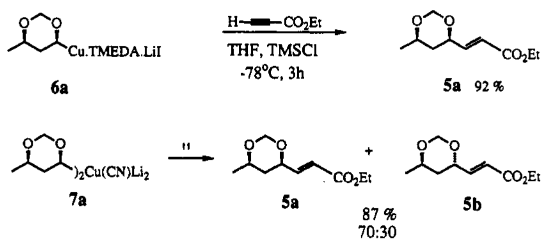
The configurational stability of the 4-lithio-1,3-dioxanes as a function of temperature was then investigated. The lithio species was generated in THF at -78 °C and quenched with Bu_3SnI[10] after 15 min at temperatures ranging from -78 to 0 °C. The products were analyzed by capillary GC and compared (by retention times) to the starting material. As in previous studies,[4-8] the lithio species generated from the equatorial isomer **1a** (4*S*,6*R*) was found to be configurationally stable, even at 0 °C.[11] The axial isomer generated from **1b** (4*R*,6*R*) was configurationally stable at -78 °C, but at higher temperatures began to invert to the more stable equatorial lithio species. For example, at -40 °C, 96% retention, at -20 °C, 65% retention, and at 0 °C, complete inversion of **1b** to **1a** was observed.

Reaction of the higher order cyano α-alkoxyorganocuprate reagent[1] **3** derived from diastereomeric **2** with ethyl propiolate at -78 °C gave the 1,4-addition product **4** as a mixture of diastereomers in 90% yield. Only the *E* isomer was obtained. No kinetic resolution of the racemic anionic center (Cl) was noted in this reaction. The addition product was then converted to the dioxane derivative **5** in quantitative yield by treatment with $BF_3{\cdot}Et_2O$. The unsaturated ester diastereomers were easily resolved by chromatography to the enantiopure **5a** (4*R*,6*R*) and **5b** (4*S*,6*R*) diastereomers (Scheme II). The optical purity of **5a** and **5b** was readily assessed by capillary GC analysis.

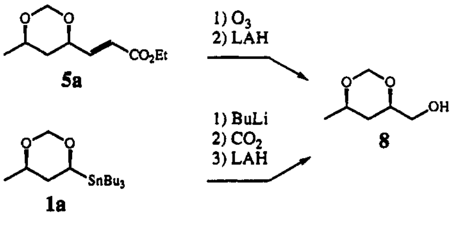
Generation of the α-alkoxyorganocopper reagent using TMEDA·CuI from both enantiopure dioxane stannanes **1a** and **1b** was straightforward.[12] The TMEDA-copper reagent **6a** derived from enantiopure **1a** was then added to ethyl propiolate to provide **5a** as a single isomer in 92% yield. An analogous reaction with TMEDA-copper reagent **6b** provided **5b** as a single isomer in 90% yield. Therefore, **1a** and **1b** undergo Sn-Li and Li-Cu transmetalation and conjugate addition without any detectable racemization. When the higher order cyano cuprate reagent **7a** was generated from **1a** and reacted with ethyl propiolate at -78 °C, only partial retention of configuration was observed; the reaction gave both **5a** and **5b** in a 70:30 ratio, respectively.[14] An analogous reaction with higher order cyano cuprate reagent **7b** also gave both **5a** and **5b** in a 30:70 ratio, respectively. At higher reaction temperatures, the yields of **5a** or **5b** dramatically decreased in both the organocopper and organocuprate reactions.

Scheme II





The possibility that racemization was taking place in the higher order cuprate reaction mixture via deprotonation of the γ-proton of **5** was ruled out. When **5a** was added to a higher order cyano α-alkoxyorganocuprate reaction mixture under the same conditions (THF, 5 equiv TMSCl, 3 h, -78 °C) no trace of **5b** was observed by GC in the crude product mixture after workup. Determination of retention of absolute configuration for the conjugate addition reaction was accomplished by conversion of **5a** and **1a** to a common intermediate **8**. Ozonization of **5a** followed by reductive workup with lithium aluminum hyride gave **8** in 56% yield. Likewise, **1a** was transmetalated at -78 °C in THF and subjected to a steady stream of carbon dioxide for 15 min.[15] The crude acid was reduced with lithium aluminum hydride to produce **8** in a 62% overall yield.



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(9) All new compounds exhibited satisfactory spectral data and correct combustion analyses.

(10) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201-1202.

(11) However, at temperatures above -20 °C, the yield was greatly diminished, presumably due to competitive deprotonation of the solvent by the lithio species.

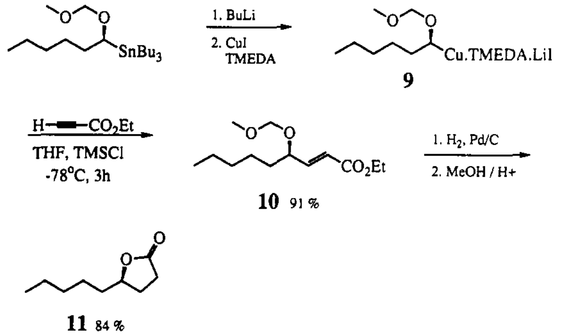
(12) A general procedure for the TMEDA/CuI organocopper[13] reactions is as follows: In a 100-mL round-bottom flask stannane **1a** (3.91 g, 10 mmol) was dissolved in 40 mL of THF under a nitrogen atmosphere. The solution was cooled to -78 °C followed by addition of *n*-butyllithium (4.6 mL, 2.57 M, 12 mmol) via syringe and then stirred for an additional 10 min. To a second 250-mL round-bottom flask containing 1.9 g (10 mmol) of copper (I) iodide (Aldrich, 99.999%) suspended in 40 mL of THF was added 1.7 mL (11 mmol) of tetramethylethylenediamine (TMEDA, freshly distilled from calcium hydride). The resulting dark, homogeneous CuI/TMEDA solution was then cooled to -78 °C and the transmetalated α-alkoxylithio species added via cannula, followed by rinsing the flask with an additional 5 mL of THF at -78 °C and transferral to the CuI/TMEDA flask via cannula. The organocopper reagent was allowed to stir at -78 °C for 20 min. Freshly distilled TMSCl (2.7 g, 3.1 mL, 25 mmol) was then added to the copper species at -78 °C. After stirring for 5 min, at -78 °C, ethyl propiolate (0.98 g, 1 mL, 10 mmol, in 10 mL THF) was added via syringe. The reaction mixture was allowed to stir for 3 h at -78 °C and was then quenched by adding 20 mL of saturated aqueous ammonium chloride. The biphasic mixture was allowed to warm to room temperature and stir vigorously for 2 h. The mixture was then diluted with 300 mL of ether, and the layers were separated. The organic phase was extracted sequentially with 100 mL of a 1:1 mixture of 0.1 N hydrochloric acid/saturated aqueous ammonium chloride, 50 mL of saturated aqueous sodium bicarbonate, and 50 mL of saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate and concentrated in vacuo. Gas chromatographic analysis of the crude product revealed greater than 99% trans isomer. The crude material was purified by flash chromatography on silica gel using 15% ethyl acetate/petroleum ether.

(13) For the preparation of alkylcopper reagents using TMEDA/CuI, see: Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27-30.

(14) Retention of configuration remained constant (70%) at temperatures from -78 °C to -20 °C; above -20 °C none of the conjugate addition product was observed.

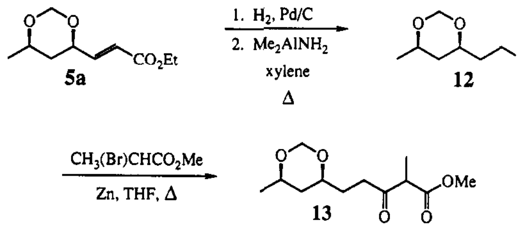
(15) The transmetalation of enantiopure acyclic α-alkoxystannanes and reaction with CO_2 has been shown to occur with complete retention of configuration: Chong, J. M.; Chan, P. C.-M. *Tetrahedron Lett.* **1990**, *31*, 1985-1988. For additional reactions of enantiopure α-alkoxylithio anions see ref 10.

Since the cyclic α-alkoxy TMEDA–organocopper reagent was shown to give the 1,4-addition product **5** with complete retention of configuration, the acyclic α-alkoxy TMEDA organocopper reagent **9** was also investigated. The organocopper reagent was prepared from the corresponding stannane of 98% ee. Addition to ethyl propiolate provided heptenoate **10** in 98% yield. Hydrogenation and acidic methanolysis directly produced pelargono lactone.[3] Unfortunately, the lactone was obtained in only 18% ee.[16] Therefore, generation of acyclic α-alkoxyorganocopper reagents in lieu of the higher order cuprate[3] does not circumvent the problem of racemization.



The racemization of enantiopure higher order acyclic α-alkoxyorganocuprates was related to the formation of byproducts arising from oxidative dimerization.[3] Interestingly, the organocopper reagents derived from **1a** and **1b** showed no tendency toward dimerization. One other example of a 1,4-addition reaction of an enantiopure organocopper reagent with retention of configuration has been reported.[18] These data indicate that cyclic higher order cuprates and organocopper species are chemically distinct.[19] The mechanistic details of 1,4-addition reactions of organocopper and cuprate reagents remain unclear.[20] One can only speculate that racemization processes for charged cyclic cuprate species are unavailable for cyclic neutral copper(I) reagents in 1,4-addition reactions.[21] The racemization of acyclic copper(I) reagents may be related to a lower energy barrier toward pyramidal inversion; however, the actual mechanism is unknown.

Asymmetric synthesis using the organocopper reagents can be realized. For example, β-keto ester **13** is similar to a known intermediate in the synthesis of (−)-methyl nonactate.[22] Hydrogenation of **5a** and direct conversion of the ester to nitrile **12**[23] was accomplished in 95% overall yield. A modified Blaise reaction[24] then provided **13** in 85% yield (54% overall yield from methyl 3-hydroxybutyrate). An analogous gem-dimethylketal derivative has been converted to (−)-methyl nonactate in two steps.[22]



Acknowledgment. B.D.G. thanks the Burroughs Wellcome Fund for fellowship support. R.J.L. thanks American Cyanamid for an American Cyanamid Academic Award (1989).

Supplementary Material Available: Complete spectral and analytical data for all new compounds (3 pages). Ordering information is given on any current masthead page.

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[16] **11** $[\alpha]_D$ observed +8.3°, c = 2.4(CH_2Cl_2) [lit[17] +44.6°, c = 2.4 (CH_2Cl_2)].

[17] Font, J.; Cardellach, J.; Ortuno, R. M. *J. Heterocycl. Chem.* **1984**, *21*, 327–331.

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[19] For a discussion of the possible solution structure of higher order cyano cuprates see: Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4052–4054.

[20] For lead references to mechanistic studies see refs 3 and 18.

[21] The addition of cyclic higher order cyano α-alkoxyorganocuprates derived from glycosyl stannanes to epoxides with retention of configuration has recently been reported: Prandi, J.; Audin, C.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 769–771.

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[23] Weinreb, S. M.; Wood, J. L.; Khatani, N. A. *Tetrahedron Lett.* **1979**, 4907–4910.

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Highly Stereoselective S$_E$′ Additions of α-Alkoxy Allylstannanes to Chiral Aldehydes. Synthesis of a C-1–C-9 Subunit of Tylonolide

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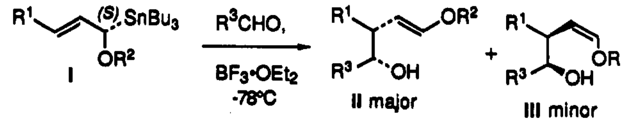
Summary: The racemic α-alkoxy allylic stannane **RS4** adds to the 2*S* aldehyde **24** to afford the homoaldol adduct **25** (45%) derived exclusively from the *S* enantiomer **S4** along with isomerized (*R*)-γ-alkoxy allylstannane **26** of >80% ee (50%) and unreacted aldehyde (40%). Use of the nonracemic α-alkoxy allylstannane **28** (1:1 mixture of diastereomers) in excess leads to the homoaldol adduct **29**, which is transformed in two steps to lactol ether **31**, an intermediate in Nicolaou's synthesis of *O*-micinosyl tylonolide.

We have shown that enantioenriched α-alkoxy allylic stannanes undergo stereospecific anti S$_E$′ additions to achiral aldehydes to afford homoaldol products II and III in high yield.[1] With simple unhindered aldehydes the syn *E* diastereomer II is favored, whereas certain intramolecular applications lead to the syn *Z* isomer III as the major product.[2] The present report describes preliminary



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[1] Marshall, J. A.; Gung, W. Y. *Tetrahedron* **1989**, *45*, 1043.

[2] Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 1657. Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 3899. Marshall, J. A.; Markwalder, J. A. *Tetrahedron Lett.* **1988**, *29*, 4811.

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