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Communications

Copper-Catalyzed Reactions of Organotitanium Reagents. Highly S_N2'- and Anti-Selective and Diastereo- and Chemoselective Alkylation of Allylic Chlorides and Phosphates

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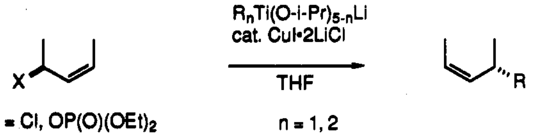
Summary: Organotitanium reagents undergo Cu(I)-catalyzed S_N2' substitution reactions with allylic chlorides and phosphates in a regio-, stereo-, and chemoselective manner: in the presence of Me_3SiCl or $Me_3SiOSO_2CF_3$, they undergo preferential conjugate addition to enones.

The S_N2' substitution reaction of an organocopper reagent with an allylic alcohol derivative is receiving increasing attention as a method for stereoselective transformation of a trigonal carbon to a tetrahedral carbon center on an acyclic carbon chain.[1] A general drawback of this strategy for construction of stereogenic centers has been the propensity of such reactions to divert to an alternative S_N2 substitution pathway.[2] We wish to report here that alkyltitanium reagents[3] undergo S_N2'-selective reactions with allylic phosphates in the presence of a Cu(I) catalyst (eq 1). The new catalytic organocopper reagents prepared by the Ti-to-Cu transmetalation[4] exhibits (1) excellent S_N2' regioselectivity, (2) anti selectivity with respect to the stereochemistry of the incoming nucleophile/leaving group pair, (3) excellent diastereoselectivity with respect to 1,2-asymmetric induction, and (4) useful chemoselectivity.[5]



(1)

Organotitanium compounds show mild nucleophilic reactivities toward ketone and ester carbonyl groups yet behave as poor nucleophiles toward organic halides.[6] In fact, n-BuTi(O-i-Pr)$_3$ (1.2 equiv) is inert to cinnamyl chloride (**2b**) at −70 °C in THF. However, addition of a THF solution of CuI (6 mol %) and LiCl (12 mol %) to this mixture results in the formation of an alkylation product (1) in good yield (Table I, entry 1; see also entry 9). The CuI·2LiCl combination was found to be a far more effective catalyst than $CuBr{\cdot}Me_2S$, which was used in our previous investigations.[7] Similarly, the reactions of ate

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[1] (a) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801 and references therein. (b) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091. (c) Denmark, S. L.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984. (d) Marino, J. P.; Viso, A. *J. Org. Chem.* **1991**, *56*, 1349.

[2] For pertinent references, see: Underiner, T. L.; Paisley, S. D.; Schmitter, J.; Lesheski, L.; Goering, H. L. *J. Org. Chem.* **1989**, *54*, 2369 and references therein.

[3] Reetz, M. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986.

[4] Previous examples of transmetalation approaches in catalytic organocopper chemistry. (a) From Mg: Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308. (b) Mn: Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 3541. (c) Zn: Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5155. In stoichiometric organocopper chemistry. (d) Zn: Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (e) Sn: Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641. (f) Al: Ireland, R. E.; Wipf, P. *J. Am. Chem. Soc.* **1990**, *55*, 1425. (g) Zr: Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440.

[5] Review: Nakamura, E. *Synlett*. In press.

[6] However, it is a good reagent for *electrophilic* S_N1 alkylation owing to the Lewis acidity of the metal. See also: p 204 in ref 3.

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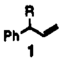
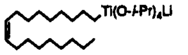
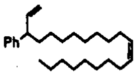
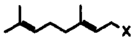
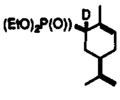
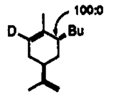
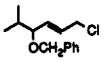
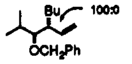
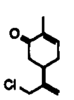
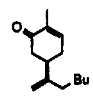
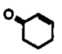
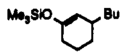
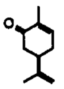
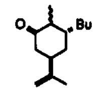
Table I. Copper-Catalyzed S_N2' Allylation and Conjugate Addition of Organotitanium Reagents[a]

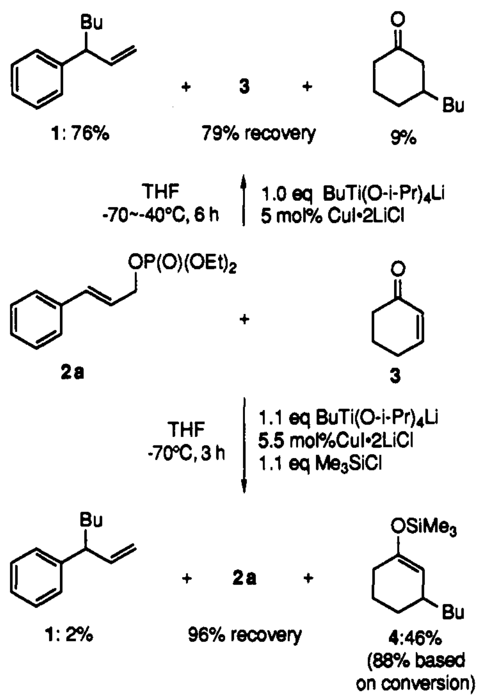
entry	"RTi"	electrophile	% yield[b]	% S_N2'[c]	product
1	BuTi(O-*i*-Pr)$_3$	 **2a** X = Cl	66	>99.8	 **1**
2	Bu$_2$Ti(O-*i*-Pr)$_3$Li		88	>99.7	
3	Bu$_2$Ti(O-*i*-Pr)$_3$Li	X = Br	85	54	
4	BuTi(O-*i*-Pr)$_4$Li	**2b** X = OP(O)(OEt)$_2$	96	>99.9	
5	Bu$_2$Ti(O-*i*-Pr)$_3$Li		91	>99.2	
6	MeTi(O-*i*-Pr)$_4$Li		74	85	
7	HexTi(O-*i*-Pr)$_4$Li		75	~100	
8			66	~100	
9	BuTi(O-*i*-Pr)$_3$	 X = Cl	61	96	
10	Bu$_2$Ti(O-*i*-Pr)$_3$Li		100	95	
11	BuTi(O-*i*-Pr)$_4$Li	X = OP(O)(OEt)$_2$	99	96	
12	Bu$_2$Ti(O-*i*-Pr)$_3$Li		92	99	
13	Bu$_2$Ti(O-*i*-Pr)$_3$Li		92	98.7	
14	Bu$_2$Ti(O-*i*-Pr)$_3$Li		96[d]	–	
15	BuTi(O-*i*-Pr)$_4$Li/ Me$_3$SiCl		77 (+11)[e]	–	
16	BuTi(O-*i*-Pr)$_4$Li/ Me$_3$SiOTf		74[e]	–	

[a] All reactions were carried out with 1.2–1.5 equiv of the titanium reagents in the presence of 6–7.5 mol % CuI·2LiCl in THF at −70 °C for 6 h (except for entries 6–11, 14, and 15, −78–0 °C). [b] Yield is based on pure isolated material except in entry 12 (GC yield). [c] The isomer ratio was determined by capillary GC analysis except in entry 12, wherein the S_N2' ratio was determined by 270-MHz ^{1}H NMR analysis of the olefinic proton, and the stereochemistry was determined by GC analysis. [d] The reaction was free of side products (<0.1% by capillary GC). [e] The yield of the desilylated conjugate adduct.

complexes *n*-Bu$_2$Ti(O-*i*-Pr)$_3$Li (**5**) and *n*-BuTi(O-*i*-Pr)$_4$Li (**6**)[8] gave **1** with excellent regioselectivity in higher yields (cf. entry 2). While the reactions of these reagents with allylic bromides showed only ca. 2:1 S_N2' regioselectivity (entry 3), those with allylic phosphates[9] exhibited nearly complete S_N2' regioselectivity (entries 4 and 5). Thus, the reactions of **5** and **6** with cinnamyl phosphate (**2a**) proceeded equally smoothly at −70 °C to give the allylation product **1** in high yield with >99.8% S_N2' selectivity. Thus, while allylic chlorides and phosphates appear to be of comparable use, the latter is of synthetic advantage in terms of availability and ease of preparation.[10]

Other representative results of the S_N2' allylation are shown in Table I.[11] The high S_N2' selectivity was generally observed for long-chain alkyl groups[12] (entries 7 and 8), while a methyl group showed diminished selectivity (entry 6).[13] Generally, the reactions were carried out at −70 °C except for the reaction of MeTi(O-*i*-Pr)$_4$Li, and for the cases where a quaternary carbon center is created (entries 9–11, final warming to −20–0 °C): the S_N2' selectivity may be slightly lower in these cases. The reaction with the phosphate of deuterium-labeled (−)-*cis*-carveol (entry 12) proceeded with 99% S_N2' regioselectivity and >98.7% anti stereochemistry[14] as judged by comparison with authentic samples by NMR and capillary GC.

Scheme I



The diastereoselectivity was also found to be very high in terms of 1,2-asymmetric induction. Thus, **5** afforded a single product upon reaction with a δ-benzyloxy-substituted allylic chloride (entry 13). This result confirms our previous observations[1b] that the anti diastereoselectivity is insensitive to the nature of the copper nucleophile.

In the presence of Me$_3$SiCl,[15] the catalytic Cu(I)/RTi(O-*i*-Pr)$_4$Li combination effects conjugate addition to an enone (entry 15). With less reactive enones (entry 16), a better activating additive, Me$_3$SiOSO$_2$CF$_3$,[16] may be necessary.

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(7) Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5155. See also: ref 1b.

(8) (a) See p 88 in ref 3, and Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. (b) Bu$_2$Ti(O-*i*-Pr)$_3$Li was prepared from 2BuLi and ClTi(O-*i*-Pr)$_3$, and BuTi(O-*i*-Pr)$_4$ from BuLi and Ti(O-*i*-Pr)$_4$.

(9) Use of allylic phosphates in copper chemistry based on Grignard reagent: Bourgain-Commerçon; M.; Normant, J.-F.; Villieras, J. *J. Chem. Res., Synop.* **1977**, 183. Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. I* **1984**, 969. Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett.* **1991**, 251. Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kato, Y.; Kurozumi, S.; Noyori, R. *Tetrahedron* **1990**, *46*, 6689.

(10) Prepared by phosphorylation with diethyl phosphonochloridate and pyridine or by the action of the chloride on a lithium alkoxide. Cf. Miller, J. A.; Wood, H. C. S. *J. Chem. Soc. C* **1968**, 1837.

(11) **General Experimental Procedure.** To a solution of Ti(O-*i*-Pr)$_4$ (1.5 mmol) in 3 mL of dry THF under nitrogen was added 1.5 mmol of BuLi in hexane at −70 °C. A 1 M THF solution (75 μL) of CuI solubilized with 2LiCl was added to the orange solution, which turned brown. An allylic phosphate (1.0 mmol) was added and the mixture was stirred for 6 h at −70 °C. Addition of wet hexane followed by filtration through silica gel gave the desired alkylation product.

(12) Available from the corresponding lithium reagents: Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. Negishi, E.-i.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

(13) Benzyl-, allyl-, and phenyltitanium reagents have so far been found to give only moderate regioselectivity either with CuI·2LiCl or with CuCN·2LiCl.

(14) Itoh, A.; Ozawa, S.; Oshima, K.; Sasaki, S.; Yamamoto, H.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2357. See also: Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318.

(15) (a) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

(16) Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627.

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_3SiCl*, the conjugate addition pathway is activated* and now competition between **2a** and **3** in the presence of Me_3SiCl[15] (1.1 equivalent) selectively gave the conjugate addition product **4**. The same competition reaction performed with Bu_2CuLi (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_N2' selectivity (88% yield). Similarly, Bu_2CuLi (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_2CuLi 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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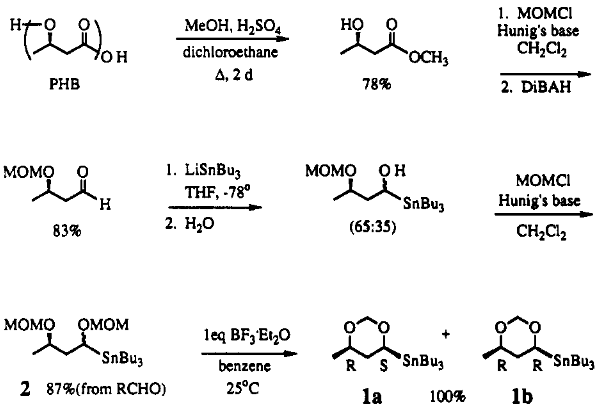
Summary: Optically active 4-lithio-1,3-dioxanes have been converted to the corresponding TMEDA–organocopper reagents and shown to undergo conjugate addition reactions to ethyl propiolate with complete retention of configuration.

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.

[3] Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1990**, *55*, 5428–5430.

[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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