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Copper-Catalyzed Reactions of Organotitanium Reagents. Highly Selective S_N2'-Allylation and Conjugate Addition

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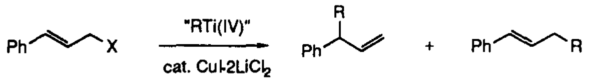
Abstract: In the presence of a catalytic amount of CuI·2LiCl, alkyltitanium ($RTi(O\text{-}i\text{-}Pr)_3$) and titanate reagents ($R_nTi(O\text{-}i\text{-}Pr)_{5\text{-}n}Li$) undergo highly selective S_N2'-alkylation reactions with allylic chlorides and allylic diethylphosphates in high yields. The regioselectivity of the reaction is as high as 99.8%. The reaction proceeds with excellent *anti*-stereoselectivity with respect to the nucleophile and the leaving group, and exhibits high 1,2-*anti*-diastereoselectivity with a δ-chiral allylic chloride. The catalytic copper reagent is also a mild agent to transfer an alkyl group to an enone in the presence of Me_3SiCl. The alkyltitanium-based catalytic reagent selectively reacts with an allylic phosphate rather than with an enone, while in the presence of a silicon activator, it reacts preferentially with the enone rather than with the phosphate. ^1H NMR studies on a mixture of Me_2CuLi and $TiCl(O\text{-}i\text{-}Pr)_3$ provided information on reagent composition.

The S_N2'-substitution reaction of an organocopper reagent with an allylic alcohol derivative is receiving an increasing amount of attention as a method for stereoselective transformation of a trigonal carbon to a tetrahedral carbon center on an acyclic carbon chain.[1,2] One general problem associated with this strategy for construction of stereogenic centers, however, has been the propensity of such reactions to divert to an alternative S_N2-substitution pathway. In this respect, standard Gilman reagents (R_2CuLi) are generally unreliable, and reagents based on combinations of copper and Lewis acidic metals–Cu/Mg,[3] Cu/Zn,[2,4] and Cu/Ti[2,5,6]–have been found to give consistently high S_N2' regioselectivity. The last combination which we initially described utilized stoichiometric quantities of copper,[2] and more recently catalytic amounts,[5] is an interesting reagent in several respects: (1) in light of renewed interest in catalytic organocopper chemistry;[7] (2) the recent transmetallations from group 4 organometallics to copper;[8] and (3) the role of Lewis acidic metals in S_N2'-selective allylation reactions. In this article, we report full details of our studies on the reactivity of organotitanium-based catalytic organocopper reagents, as well as NMR information as to the reagents composition.

Results and Discussion

Organotitanium compounds[9] show mild nucleophilic reactivities toward ketone and ester carbonyl groups yet behave as poor nucleophiles toward organic halides.[10] $n\text{-}BuTi(O\text{-}i\text{-}Pr)_3$ prepared from $TiCl(O\text{-}i\text{-}Pr)_3$ and n-BuLi (1 equiv each) is inert to allylic chloride (**1a**) at -70 °C in THF (Table I, entry 1). However, addition of a $CuBr{\cdot}SMe_2$ (6 mol%) to this mixture results in the formation of an alkylation product (**2**) in good yield and with 97% S_N2'-regioselectivity (entry 2). CuI·2LiCl (prepared by mixing CuI (6 mol%) and LiCl (12 mol%) in THF) showed enhanced yield and regioselectivity (entry 3). Similarly, the reaction of ate complexes, n-Bu$_2$Ti(O-i-Pr)$_3$Li and n-BuTi(O-i-Pr)$_4$Li,[11] (prepared from Ti(O-i-Pr)$_3$Cl and n-BuLi (2 equiv), and Ti(O-i-Pr)$_4$ and n-BuLi (1 equiv), respectively) gave **2** with excellent regioselectivity in higher yields (entries 4 and 5). While the reactions of these reagents with allylic bromides (**1b**) showed only ca. 2:1 S$_N$2'-regioselectivity (entry 6), those with cinnamyl phosphates (**1c**)[12] exhibited nearly complete S$_N$2'-regioselectivity. Thus, the reactions of n-Bu$_2$Ti(O-i-Pr)$_3$Li and n-BuTi(O-i-Pr)$_4$Li with **1c** proceeded equally smoothly at -70 °C to give the allylation product **2** quantitatively with 99.2% S$_N$2'-selectivity (entries 7 and 8). In view of the observed reactivities and selectivities, allylic chlorides and phosphates appear to be of comparable use, although the latter is of definite synthetic advantage in terms of availability and ease of preparation.[13] A related reagent, a combination of n-Bu$_2$Zn with CuI·2LiCl catalyst,[4] showed comparable regioselectivity. Notably, the reactions of n-BuCu (n-BuLi + CuI) and n-Bu$_2$CuLi·LiI (2 n-BuLi + CuI) with **1c** at -70 °C in THF showed only 73-77% S$_N$2'-regioselectivity (entries 10 and 11). The reaction of n-BuLi with **1a** in the presence of a catalytic amount of CuI·2LiCl gave a complex mixture. Thus, both titanium and copper metals are essential for the high regioselectivity.



(1)

1a: X = Cl
b: X = Br
c: X = P(O)(OEt)$_2$

2 **3**

Table I. Reaction of Titanium Reagents with Cinnamyl Derivatives.

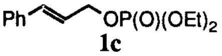
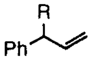
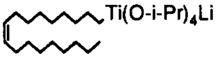
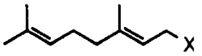
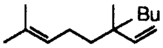
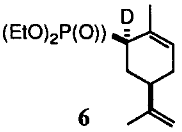
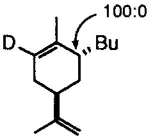
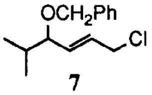
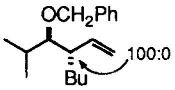
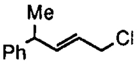
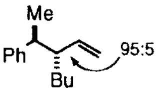
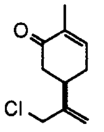
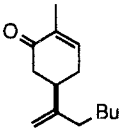
entry	"RTi"	catalyst[a]	X	yield (%)	% S$_N$2'
1	n-BuTi(O-i-Pr)$_3$	none	**1a**: Cl	no reaction	
2	n-BuTi(O-i-Pr)$_3$	CuBr·SMe$_2$	**1a**: Cl	57	97
3	n-BuTi(O-i-Pr)$_3$	CuI·2LiCl	**1a**: Cl	66	99.7
4	n-Bu$_2$Ti(O-i-Pr)$_3$Li	CuI·2LiCl	**1a**: Cl	88	99.8
5	n-BuTi(O-i-Pr)$_4$Li	CuI·2LiCl	**1a**: Cl	74	99.5
6	n-Bu$_2$Ti(O-i-Pr)$_3$Li	CuI·2LiCl	**1b**: Br	85	54
7	n-Bu$_2$Ti(O-i-Pr)$_3$Li	CuI·2LiCl	**1c**: OP(O)(OEt)$_2$	91	99.2
8	n-BuTi(O-i-Pr)$_4$Li	CuI·2LiCl	**1a**: Cl	96	99.9
9	n-Bu$_2$Zn	CuI·2LiCl	**1a**: Cl	97	99.3
10	n-BuCu·LiI	none	**1c**: OP(O)(OEt)$_2$	88	77
11	n-Bu$_2$CuLi·LiI	none	**1c**: OP(O)(OEt)$_2$	70	73

[a] 6-7.5 mol% of catalyst was used.

Some representative results of the S$_N$2'-allylation with this new catalytic organocopper reagent are shown in Table II. The high S$_N$2' selectivity was consistently observed for long chain alkyl titanium reagents[14] (entries 2 and 3), while methyltitanate showed diminished selectivity (entry 1).[15] Generally, the reactions were carried out at -70 °C except for the reaction of MeTi(O-i-Pr)$_4$Li and for the cases where a quaternary carbon center is created (entries 4-6, final warming to -20~0 °C): the S$_N$2'-selectivity may be lower in these cases. The reaction with the phosphate of deuterium-labelled (-)-cis-carveol (**6**, entry 7) proceeded with 99% S$_N$2'-

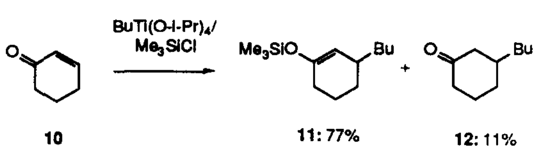
regioselectivity and >98.7% *anti*-stereochemistry[16] (as to the incoming cuprate and the leaving group) as judged by comparison with authentic samples by 270 MHz ^1H NMR and capillary GC.

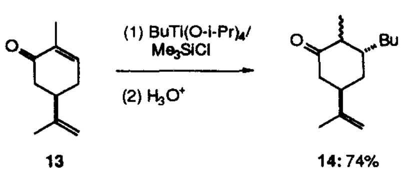
Table II. Copper-Catalyzed S_N2'-Allylation Reactions.

entry	"RTi"	substrate	yield (%)	% S_N2'	product
1	$MeTi(O\text{-}i\text{-}Pr)_4Li$	 **1c**	74	85	
2	$n\text{-}HexTi(O\text{-}i\text{-}Pr)_4Li$		75	~100	
3			66	~100	
4	$n\text{-}BuTi(O\text{-}i\text{-}Pr)_3$	**4**: X = Cl	61	96	
5	$n\text{-}Bu_2Ti(O\text{-}i\text{-}Pr)_3Li$		100	95	
6	$n\text{-}BuTi(O\text{-}i\text{-}Pr)_4Li$	**5**: X = $OP(O)(OEt)_2$	99	96	
7	$n\text{-}Bu_2Ti(O\text{-}i\text{-}Pr)_3Li$	 **6**	92	99.0	
8	$n\text{-}Bu_2Ti(O\text{-}i\text{-}Pr)_3Li$	 **7**	92	99	
9	$n\text{-}Bu_2Ti(O\text{-}i\text{-}Pr)_3Li$	 **8**	91	99.2	
10	$n\text{-}Bu_2Ti(O\text{-}i\text{-}Pr)_3Li$	 **9**	96	not applicable	

The diastereoselectivity of 1,2-asymmetric induction was also found to be very high with this new reagent. Thus, $n\text{-}Bu_2Ti(O\text{-}i\text{-}Pr)_3Li$ underwent 100% diastereoselective reaction with the δ-alkoxy substituted allylic chloride **7** (entry 8). This result confirms our previous observation[2] that *anti*-diastereoselectivity is insensitive to the nature of the copper nucleophile. The reaction with δ-phenyl substituted allylic chloride **8** also showed diastereoselectivity as high as 95% (entry 9).[17]

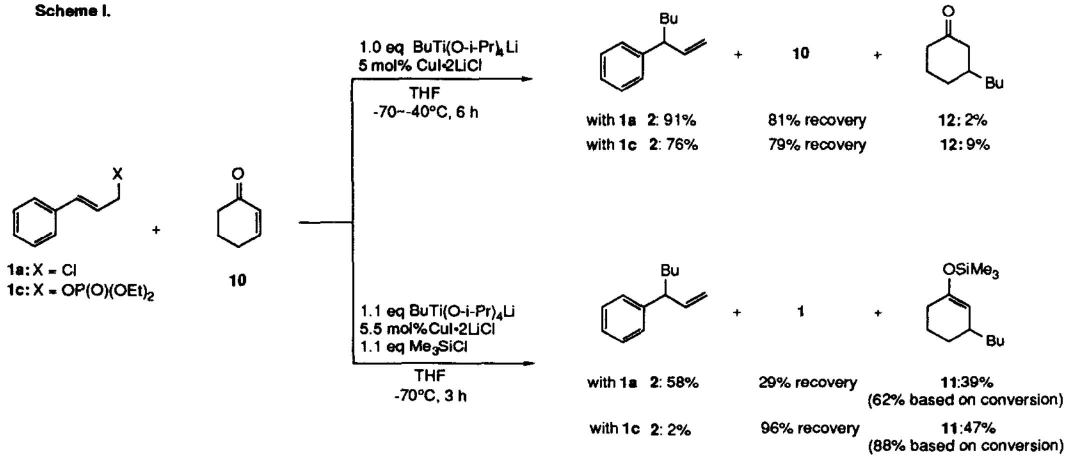
In the presence of Me_3SiCl,[18] these catalytic copper reagents serve as mild Michael donors for conjugate additions to enones, as shown below. A more reactive accelerator, such as $Me_3SiOSO_2CF_3$,[19] may be necessary for otherwise sluggish enones.



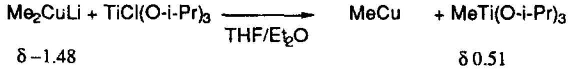


The reagent exhibits chemoselectivity toward the allylation reaction rather than the conjugate addition pathway. The reaction of $n\text{-}Bu_2Ti(O\text{-}i\text{-}Pr)_3Li$ with the chlorinated carvone (Table II, entry 10) took place exclusively at the reactive allylic chloride site rather than on the enone group, and less than 0.1% of side products was found on capillary GC analysis.[20] More difficult competition between an allylic phosphate (**1c**) and an enone is illustrated in Scheme I. Treatment of an equimolar mixture of cinnamyl phosphate (**1c**) and cyclohexenone (**10**) with 1.0 equivalent of $n\text{-}BuTi(O\text{-}i\text{-}Pr)_4Li$ and 5 mol% CuI·2LiCl at -70~-40 °C in THF resulted in the preferential reaction with the phosphate affording the allylation product **2** in good yield. Similarly, cinnamyl chloride (**1a**) reacted more competitively than cyclohexenone. In contrast, *Me_3SiCl selectively activates the conjugate addition pathway.* Thus, competition between **2a** and **3** in the presence of Me_3SiCl (1.1 equiv) afforded predominantly the conjugate addition product **11**. However, cinnamyl chloride (**1a**) is still slightly more reactive than the enone **10** even in the presence of the chlorosilane, and the competition experiment for **1a** and **10** gave a nearly 1:1 mixture of the alkylation (**1**) and the conjugate addition products in excellent combined yield. The same competition reactions (for **1c**) performed with $n\text{-}Bu_2CuLi$ (1.0 equiv) at -70 °C exhibited much lower selectivities of little practical value.

Scheme I.



The synthetic scope of the new catalytic copper reagent based on organotitanium chemistry has been described above. In this paragraph are summarized the NMR studies on the nature of a stoichiometric, mixed copper/titanium reagent, Me_2CuLi + $TiCl(O\text{-}i\text{-}Pr)_3$.[2] The ^1H NMR signal of the Gilman reagent, Me_2CuLi, appears at δ -1.48 ppm in ether/THF at -40 °C. Upon addition of one equivalent of $TiCl(O\text{-}i\text{-}Pr)_3$, this signal disappears, and one major signal at δ 0.51 ppm appears together with three minor signals (δ 0.19, 0.08, and -1.23 ppm with 42, 58, 41% intensity, respectively, relative to the δ 0.51 signal). The peak at δ 0.51 was a single dominant peak for an equimolar mixture of $TiCl(O\text{-}i\text{-}Pr)_3$ and MeLi together with the minor signals at δ 0.19 and 0.08 (20 and 10% relative intensities).[21] The signal at δ -1.23, which may be assigned as MeCu(X)Li (X = I or Cl),[22] was not observed in the MeLi/$TiCl(O\text{-}i\text{-}Pr)_3$ mixture. The methyl signal of $MeTi(O\text{-}i\text{-}Pr)_3$ in CCl_4 has been reported to appear at δ 0.57 ppm.[23] The reaction of Me_2CuLi with $TiCl(O\text{-}i\text{-}Pr)_3$ produces a sizable amount of thick yellow precipitate which is most probably polymeric MeCu. These results indicate that one of the methyl groups on Me_2CuLi has been transferred completely to titanium.[24] This mixture of $Me_2CuLi/TiCl(O\text{-}i\text{-}Pr)_3$ has been found to be a highly S_N2'-selective reagent which compares favorably with the present catalytic reagent. It must be noted, however, that RCu·LiI and $RTi(O\text{-}i\text{-}Pr)_3$ alone are either non-selective or unreactive reagents when used in these reaction (vide supra). In the present analysis, we found only a single signal (at δ -1.23) which can be attributed to a methyl group on copper. This species (MeCu(X)Li, $Me(X)CuTi(O\text{-}i\text{-}Pr)_3$ or other combinations) may well be responsible for the observed chemistry.



$$\underset{\delta\,-1.48}{Me_2CuLi + TiCl(O\text{-}i\text{-}Pr)_3} \xrightarrow[THF/Et_2O]{} MeCu \quad + \underset{\delta\,0.51}{MeTi(O\text{-}i\text{-}Pr)_3} \qquad (2)$$

The results of the reactivity analysis and the NMR analysis are summarized as follows. (1) Organotitanium reagents are unreactive toward allylating agents. (2) However, they become highly reactive reagents in the presence of a copper catalyst. (3) RCu and R_2CuLi reagents themselves show poor S_N2'-regioselectivity, and thus are likely to be the actual reactive species in the catalytic process. (4) Stoichiometric transmetallation takes place in a direction from copper to titanium, and the titanium alkyls in the catalytic reagent may thus only act as a weak alkyl transfer reagent to copper. Although we are far from drawing a firm conclusion as to the reason for the excellent S_N2'-regioselectivity of these new catalytic reagents, it is tempting to invoke the possibility that a minute amount of a copper/titanium complex acts as a highly selective reactive species. In such an event, fine tuning of the reactivities may be possible by changing the nature of the Lewis acidic metal.

Conclusion

These new catalytic organocopper reagents prepared by the Ti-to-Cu transmetalation exhibit (1) excellent S_N2'-regioselectivity in allylation, (2) *anti*-selectivity with respect to the stereochemistry of the incoming and leaving groups, (3) good diastereoselectivity insofar as 1,2-asymmetric induction is concerned, and (4) selective switching of reaction pathways between allylation and conjugate addition. Neither an organocopper nor titanium reagents show the observed selectivities by itself, and the experimental evidence implies the formation of a new titanium/copper complex reagent. The alkyltitanium based catalytic copper combination and related reagents will serve as new "low energy carriers" of alkyl groups for selective synthetic transformations under mild conditions.

Experimental Section

General. All the reactions dealing with air or moisture sensitive compounds were carried out in a dry reaction vessel under nitrogen. Routine chromatographic purification was achieved with Merck Kieselgel 60 (230-400 mesh) with hexane/AcOEt as eluent. Routine ^{1}H NMR (90, 200, 270, and 500 MHz) and ^{13}C NMR were measured for a CDCl$_3$ solution on JEOL EX-90, FX-200, GSX-270 and GSX-500 instruments. ^{1}H NMR spectra are reported in parts per million from internal tetramethylsilane, ^{13}C NMR spectra from CDCl$_3$ (77.0 ppm). IR spectra were recorded on a JASCO IR-800; absorptions are reported in cm^{-1}. Gas chromatographic (GC) analysis was performed on a Shimadzu 8A or 14A machine equipped with glass capillary columns. Low-temperature NMR experiments were conducted on a JEOL GSX-500 instrument. The spectra were recorded for an ether/THF solution with THF-d_8 as an internal lock and were referenced to ether (methyl proton = 1.90 ppm).

Material. Ethereal solvents were distilled from benzophenone ketyl under nitrogen immediately before use. All commercially available reagents were either distilled or recrystallized before use. MeLi (Aldrich) was titrated with diphenylacetic acid before use. CuI was purified by recrystallization from NaI, and dried in vacuo at 150 °C for 10 min before use. Allylic phosphates were prepared according to literature procedures.[13]

Typical Procedure for Preparation of a ^{1}H NMR Sample. To a suspension of dry CuI (1.5 mmol, 285 mg) in THF (4.5 mL) was added MeLi (1.48 M in ether, 3.0 mmol, 2.0 mL) at -78 °C. The reaction mixture was stirred at 0 °C until it became clear, and then cooled to -78 °C. This solution (0.23 M) was used as the Me$_2$CuLi source for all samples. The Me$_2$CuLi solution (0.5 mmol, 2.2 mL) was transferred with a cooled syringe to another cooled flask. A hexane solution of Ti(O-i-Pr)$_3$Cl (1.61 M, 0.5 mmol, 0.31 mL) was added at -78 °C, and the whole mixture was transferred to a 5 mm NMR tube via a cooled cannula. After addition of THF-d_8 (0.25 mL) as an internal lock, spectra were recorded in a pre-cooled NMR probe.

Preparation of a 1.0 M THF solution of CuI·2LiCl. A mixture of CuI (1.00 mmol, 190 mg) and LiCl (2.00 mmol, 85 mg) was dried by heating in vacuo at 150 °C, and dissolved in about 1 mL of THF to prepare a 1.0 M solution. This solution was used as the CuI·2LiCl source for the copper-catalyzed reactions.

A Typical Procedure: 3-Phenyl-1-heptene. To a solution of TiCl(O-i-Pr)$_3$ (1.64 M in hexane, 0.146 mL) in THF (0.6 mL) was added n-BuLi (1.64 M in hexane, 0.4 mmol, 0.24 mL) at -70 °C. A THF solution of CuI·2LiCl (1 M, 0.012 mmol) was added at this temperature to the orange solution, which then turned brown. Cinnamyl chloride (0.2 mmol, 0.035 mL) was added, and the reaction mixture was stirred for 6 h at -70 °C. After addition of hexane saturated with water, the reaction mixture was passed through a pad of silica gel. GC analysis (HR-1, 0.25 mm I.D. x 30 m, 100 °C) of the filtrate indicated an S$_N$2'/S$_N$2 ratio of 99.5:0.5 (retention times; 7.4 min and 10.7 min, respectively). Purification of the crude product by silica gel column chromatography afforded 31 mg (88%) of the allylation products. The product was identified by comparison (TLC, GC, and ^{1}H NMR) with an authentic sample.[4]

Physical Properties of Allylation Product (for experiment details, see Table III): 3-Phenyl-1-butene. IR (neat) 1640, 1600, 1500, 1460, 1020, 1000, 920, 760, 700; ^{1}H NMR (270 MHz, CDCl$_3$) δ 1.35 (d, J = 6.8 Hz, 3H), 3.45 (dt, J = 6.8, 6.8 Hz, 1H), 5.01 (d, J = 10.0 Hz, 1H), 5.03 (d, J = 16.8 Hz, 1H), 6.00 (ddd, J = 6.8, 10.0, 16.8 Hz, 1H), 7.12~7.35 (m, 5H). GC analysis (HR-1, 0.25 mm I.D. x 30 m, 70 °C): S$_N$2'/S$_N$2 = 84.8:15.2 (retention times; 4.4 min and 7.9 min, respectively).

(12*Z*)-3-Phenylheneicosa-1,12-diene. IR (neat) 1635, 1600, 1490, 1460, 1450, 990, 910, 750, 720, 700; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.88 (t, J = 6.7 Hz, 3H), 1.10~1.45 (m, 24H), 1.73 (br q, J = 6.3 Hz, 2H), 1.93~2.10 (m, 4H), 3.24 (q, J = 7.1 Hz, 1H), 5.02 (d, J = 11.8 Hz. 1H), 5.03 (d, J = 16.0 Hz, 1H), 5.36 (t, J = 5.5 Hz, 2H), 5.96 (ddd, J = 7.2, 11.8, 16.0 Hz, 1H), 7.15~7.35 (m, 5H). Anal. calcd for C$_{27}$H$_{44}$: C, 87.97; H, 12.03. Found: C, 87.77; H, 12.22.

3-Phenyl-1-nonene. IR (neat) 1635, 1600, 1490, 1465, 1450, 1380, 990, 910, 755, 700; ^{1}H NMR (270 MHz, CDCl$_3$). δ 0.86 (t, J = 6.8 Hz, 3H), 1.10~1.38 (m, 8H), 1.69 (q, J = 7.4 Hz), 3.23 (q, J = 7.4 Hz, 1H), 5.01 (d, J = 10.8 Hz, 1H), 5.02 (d, J = 16.0 Hz), 5.95 (ddd, J = 7.4, 10.8, 16.0 Hz, 1H), 7.14~7.36 (m, 5H). Anal. calcd for C$_{15}$H$_{22}$: C, 89.04; H, 10.96. Found: C, 88.90; H, 10.85.

2,6-Dimethyl-6-ethenyl-2-decene. The characteristic ^{1}H NMR signal of the terminal olefinic protons of the S_N2' product was diagnostic for the identification in comparison with an authentic sample.[4] ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 0.95 (s, 3H), 1.10~1.33 (m, 8H), 1.58 (s, 3H), 1.67 (s, 3H), 1.87 (dt, J = 7.0, 7.1 Hz, 2H), 4.88 (d, J = 17.5 Hz, 1H), 4.97 (d, J = 11.0 Hz, 1H), 5.08 (d, J = 7.1 Hz, 1H), 5.79 (dd, J = 11.0, 17.5 Hz, 1H). GC analysis (HR-1, 0.25 mm I.D. x 30 m, 100 °C): S_N2'/S_N2 = 99.5:0.5 (retention times; 8.8 min and 11.9 min, respectively).

(3*R, 4*R**)-3-Benzyloxy-4-ethenyl-2-methyl-5-decene.** IR (neat) 1470, 1455, 1110, 1070, 975, 920, 720, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 1.25~1.38 (m, 4H), 1.86 (sep, J = 6.8 Hz, 1H), 1.98~2.05 (m, 2H), 3.00 (br q, J = 5.7 Hz, 1H), 3.08 (t, J = 5.7 Hz, 1H), 4.52 (d, J = 11.3 Hz, 1H), 4.63 (d, J = 11.3 Hz, 1H), 5.03~5.09 (m, 2H), 5.41 (m, 2H), 5.94~6.03 (m, 1H), 7.23~7.40 (m, 5H). GC analysis (HR-1, 0.25 mm I.D. x 30 m, 140 °C): *anti*-S_N2'/S_N2 = 98.7:1.3 (retention time; 14.4 min and 18.7 min, respectively).

5-(1-Hexen-2-yl)-2-methyl-2-cyclohexen-1-one. IR (neat) 1680, 1640, 1450, 1430, 1365, 1110, 895; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3H), 1.20~1.49 (m, 4H), 1.79 (s, 3H), 2.03 (t, J = 6.9 Hz, 2H), 2.20~2.75 (m, 5H), 4.80 (s, 1H), 4.83 (s, 1H), 6.73~6.79 (m, 1H). Anal. calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.75. Found: C, 81.31; H, 10.92. GC analysis of the crude product (HR-1, 0.25 mm I.D. x 30 m, 130 °C): A single peak except a trace amount of the starting material appeared at 13.6 min.

***cis*-3-Butyl-5-isopropenyl-2-methylcyclohexene-1-d.** To a solution of $TiCl(O\text{-}i\text{-}Pr)_3$ (1.64 M in hexane, 0.146 mL) in THF (0.6 mL) was added n-BuLi (1.64 M in hexane, 0.4 mmol, 0.24 mL) at -70 °C. A THF solution of CuI·2LiCl (1 M, 0.012 mmol) was added to the orange solution which then turned brown. cis-Carveol diethylphosphate (**6**: 0.2 mmol, 58 mg), which was 99% deuterium labelled on its methyne connected to the phosphate group, was added and the reaction mixture was stirred for 6 h at -70 °C. After addition of hexane saturated with water, the reaction mixture was passed through a pad of silica gel. GC analysis (HR-1, 0.25 mm I.D. x 30 m, 140 °C) of the filtrate indicated a minimum 99.5% purity of the product. The integrated area of the cyclohexenyl olefinic proton in the product indicated that the reaction proceeded with 99% S_N2'-selectivity. Purification of the crude product by silica gel column chromatography afforded 34 mg (92%) of the allylation product. IR (neat) 1640, 1450, 1375, 1260, 885; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.04 (t, J = 6.8 Hz, 3H), 1.30~2.39 (m involving two s at δ 1.81 and 1.87, 9H), 4.84 (s, 1H), 5.30 (br s, 0.02H).

3-Butyl-1-trimethylsiloxy-1-cyclohexene. To a solution of $Ti(O\text{-}i\text{-}Pr)_4$ (1.1 mmol, 0.33 mL) in THF (2.0 mL) was added BuLi (1.64 M, 1.1 mmol, 0.67 mL) at -70 °C. A THF solution of CuI·2LiCl (1 M, 0.055 mmol) was added to the orange solution which then turned brown. After addition of Me_3SiCl (1.1 mmol, 0.15 mL), cyclohexenone (**10**: 1.0 mmol, 96 μL) was added and reaction mixture was stirred for 3 h at -70 °C. The reaction mixture was quenched with H_2O/hexane and passed through a pad of silica gel. Purification by silica gel column chromatography afforded 173 mg (77%) of enol silyl ether **11**[18a] and 16 mg (11%) of 3-butylcycloheane (**12**).

3-Butyl-5-isopropenyl-2-methylcyclohexanone (14). To a solution of $Ti(O\text{-}i\text{-}Pr)_4$ (1.5 mmol, 0.45 mL) in THF (3.0 mL) was added BuLi (1.64 M, 1.5 mmol, 0.91 mL) at -70 °C. A THF solution of CuI·2LiCl (1 M, 0.075 mmol) was added to the orange solution which then turned brown. After addition of Me_3SiOTf (1.5 mmol, 0.29 mL), carvone, (**13**: 1.0 mmol, 156 μL) was added and reaction mixture was stirred at -70 °C for 3h, at 0 °C for 1 h. The reaction mixture was quenched with H_2O/hexane and passed through a pad of silica gel. Purification by silica gel column chromatography afforded 154 mg (74%) of product. IR (neat) 1705, 1640, 1460, 1450, 1215, 895; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.85~2.69 (m involving t at δ 0.91, J = 6.9 Hz, s 1.03, s 1.05, and s 1.74, 22H), 4.73 (s, 1.5H). 4.76 (s, 1.5H). Anal. calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.87; H, 11.91.

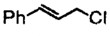
Table III. Various S_N2' Reactions.

substrate mmol (mg)	RLi mmol	titanium salt mmol	$CuI{\cdot}2LiCl$[a] mmol (mol%)	temp (time) °C (h)	product mg (%yield)[b]
1c 0.2 (54)	BuLi 0.3	$Ti(O\text{-}i\text{-}Pr)_4$ 0.3	0.012 (6)	-70 (6)	34 (96)
1c 1.0 (270)	MeLi 1.5	$Ti(O\text{-}i\text{-}Pr)_4$ 1.5	0.075 (7.5)	-70 (6)	97 (74)
1c 1.0 (270)	$C_{18}H_{36}Li$[d] 1.5	$Ti(O\text{-}i\text{-}Pr)_4$ 1.5	0.075 (7.5)	-70~rt (4)	243 (66)
1c 1.0 (270)	$C_6H_{13}Li$[d] 1.5	$Ti(O\text{-}i\text{-}Pr)_4$ 1.5	0.075 (7.5)	-70~rt (4)	152 (75)
4 0.2 (34)	BuLi 0.48	$TiCl(O\text{-}i\text{-}Pr)_3$ 0.24	0.012 (6)	-70~0 (2)	38 (100)
7 0.2 (48)	BuLi 0.48	$TiCl(O\text{-}i\text{-}Pr)_3$ 0.24	0.012 (6)	-70 (6)	48 (92)
9 0.2 (37)	BuLi 0.48	$TiCl(O\text{-}i\text{-}Pr)_3$ 0.24	0.012 (6)	-70 (6)	(96)[c]

[a] A THF solution (1 M) was used. [b] Isolated yield. [c] GC yield. [d] Prepared from corresponding iodide and 2 equiv of t-BuLi.

A Typical Procedure for Competition between Cinnamyl Phosphate and Cyclohexenone. To a solution of $Ti(O\text{-}i\text{-}Pr)_4$ (1.0 mmol, 0.30 mL) in THF (2.2 mL) was added BuLi (1.65 M, 1.0 mmol, 0.60 mL) at -70 °C. A THF solution of $CuI{\cdot}2LiCl$ (1 M, 0.05 mmol) was added to the orange solution which then turned brown. A mixture of cinnamyl phosphate (**1c**: 1.0 mmol, 270 mg) and cyclohexenone (**10**: 1.0 mmol, 0.096 mL) was added at -70 °C and the reaction mixture was warmed to -20 °C over 6 h. After addition of hexane saturated with water, the reaction mixture was passed through a pad of silica gel. GC analysis (HR-1, 0.25 mm I.D. x 30 m, 70~300 °C) of the filtrate with an internal standard ($C_{11}H_{24}$) indicated the presence of the 1,4-adduct (**12**, 9.3%) and the recovery of the enone (**10**, 79%). Purification of the product mixture by silica gel column chromatography afforded 132.1 mg (76%) of the allylation product (**2**). The data are summarized in Table IV.

Table IV. Competition Reaction between Cyclohexenone and Cinnamyl Derivatives[a].

substrate (mmol)	$BuTi(O\text{-}i\text{-}Pr)_4Li$ mmol	additive mmol	time h	yield (%)	yield (%)
1c:  (1.0) **10**: cyclohexenone (1.0)	1.0	$CuI{\cdot}2LiCl$ 0.05	6	**2**: 132 (76)[b] **12**: (9)[c]	**1c**: (17)[c] **10**: (79)[c]
	1.1	$CuI{\cdot}2LiCl$, Me_3SiCl 0.055, 1.1	3	**2**: (2)[c] **11**: 107 (47)[b]	**1c**: 259 (96)[b] **10**: (46)[c]
1a:  (1.5) **10**: cyclohexenone (1.5)	1.5	$CuI{\cdot}2LiCl$ 0.075	4	**2**: 238 (91)[b] **12**: (2)[c]	**1a**: 8 (3)[b] **10**: (81)[c]
	1.5	$CuI{\cdot}2LiCl$, Me_3SiCl 0.075, 1.5	4	**2**: 151 (58)[b] **11**: 133 (39)[b]	**1a**: 66 (29)[b] **10**: (38)[c]

[a] All reactions were carried out at -70 °C except the first entry (-70~-40 °C). [b] Isolated yield. [c] GC yield.

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