Cross Coupling of Allylic Derivatives. 16.[1] Regiochemistry of Cross Coupling the Isomeric (*E,E*)-3,5-Heptadien-2-yl and (*E,E*)-2,5-Heptadien-4-yl Pivalates with Organocopper and Grignard Reagents

Ted L. Underiner and Harlan L. Goering*

Samuel M. McElvain Laboratories of Organic Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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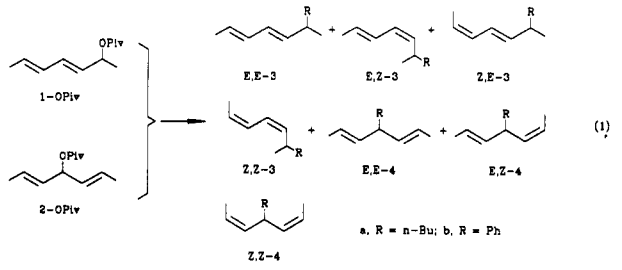
The regiochemistry of cross coupling the isomeric (*E,E*)-3,5-heptadien-2-yl and (*E,E*)-2,5-heptadien-4-yl pivalates (1-OPiv and 2-OPiv) with organocopper and Grignard reagents has been investigated. With $LiCuBu_2$, phenylcuprates, and Grignard reagents, the cross coupling is regioselective but not regiospecific and yields predominantly conjugated product. The starting pivalates do not rearrange under conditions for lithium cuprate cross-coupling reactions; however, 2-OPiv isomerizes to 1-OPiv in the presence of Grignard reagents (i.e., Mg(II)). For alkylation of 1-OPiv with butylcuprates, the degree of regiospecificity (γ-alkylation) increases in the order $LiCuBu_2$ < LiCu(CN)Bu < Bu_2CuMgI < *n*-BuMgI/1% CuCN. Mechanistic implications are discussed.

This paper reports an investigation of the regiochemistry of cross coupling (*E,E*)-3,5-heptadien-2-yl pivalate (1-OPiv) and (*E,E*)-2,5-heptadien-4-yl pivalate (2-OPiv) with organocopper reagents (eq 1). Of particular interest was



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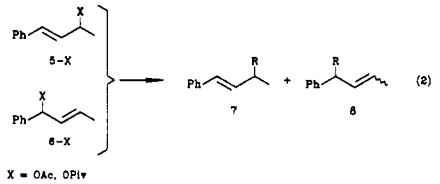
comparison of alkyl(sp^3)cuprates and aryl(sp^2)cuprates. Reactions investigated include stoichiometric cross coupling of 1-OPiv and 2-OPiv with butylcuprates ($LiCuBu_2$ and LiCu(CN)Bu) and phenylcuprates ($LiCuPh_2$ and LiCu(CN)Ph). Copper(I)-catalyzed cross-coupling reactions of butyl and phenyl Grignard reagents with the pivalates were also examined.

This investigation is similar to an earlier study of the α,γ-methylphenylallyl systems (5-X and 6-X),[3] in that in each case, coupling can lead to a conjugated (3 or 7) and an unconjugated (4 or 8) regioisomer. Because of the thermodynamic bias, nonregiospecific[2] coupling reactions lead mainly, or exclusively, to the conjugated product. Thus, under these conditions 5-X undergoes mainly α-coupling to give 7, whereas 6-X undergoes γ-coupling (eq 2). With 1-OPiv, the thermodynamically favored conjugated product 3 can result from either α- or ϵ-coupling. These two processes can be distinguished by deuterium labeling.[4,5]



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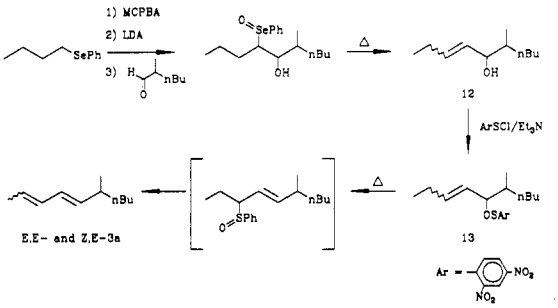
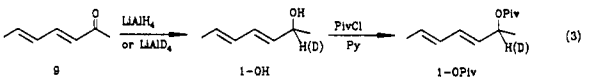
Scheme I. Synthesis of (*E,E*)-3a and (*Z,E*)-3a



Synthesis of 1-OPiv[6] (and α-D-1-OPiv) was accomplished by reduction[7] of (*E,E*)-3,5-heptadien-2-one (9)[8] with $LiAlH_4$ (or $LiAlD_4$) followed by esterification with pivaloyl chloride (eq 3).



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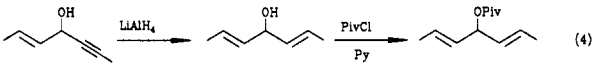
Lithium aluminum hydride reduction[9] of (*E*)-2-hepten-5-yn-4-ol (10)[10] (prepared by addition of lithium methylacetylide to crotonaldehyde) gives (*E,E*)-2,5-heptadien-4-ol (2-OH);[11] esterification with pivaloyl chloride yields 2-OPiv (eq 4).



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Two equivalents of organocopper reagent (either preformed cuprate or Grignard reagent containing catalytic amounts of copper(I)) were used in these cross-coupling reactions. Pre-formed homocuprate reactions were carried out in ether at −20 °C and then allowed to gradually warm to room temperature. Copper(I)-catalyzed Grignard reactions were carried out in ether at 0 °C and then allowed

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Table I. Product Distribution[a] for Reaction of 1-OPiv with Butyl- and Phenylcopper Reagents

reagent	(E,E)-3	(E,Z)-3 (conjugated)	(Z,E)-3	α:ε[b]	(E,E)-4 (unconjugated)	(E,Z)-4 (unconjugated)
$LiCuBu_2$	81.8	7.7	5.5	2.0:1	3.5	1.5
LiCu(CN)Bu	36.6	0.0	4.2	2.3:1	3.91	20.1
Bu_2CuMgI[c]	16.8	2.2	5.0	7.6:1	41.8	34.2
n-BuMgI						
1% CuCN	<1	0.0	<1		75.2	24.8
10% CuCl	13.8	1.7	<1	5.7:1	43.1	41.4
10% CuI	11.8	2.0	6.3	6.7:1	44.9	35.0
no copper	38.4	3.3	8.4	0.82:1	49.9	0.0
$LiCuPh_2$	100	0	0	1:0	0	0
LiCu(CN)Ph	100	0	0	1:0	0	0
$Ph_2CuMgBr$[d]	100	0	0	1:0	0	0
PhMgBr						
1% CuCN	100	0	0	1:0	0	0
10% CuCl	100	0	0	1:0	0	0
10% CuI	100	0	0	1:0	0	0
no copper	42.5	0	0	0.82:1	57.5	0

[a] Determined by capillary GC; (E,E)-**4a**:(E,Z)-**4a** and (E,E)-**3a**:(Z,E)-**3a** ratios determined by ^1H NMR; average of two determinations. [b] α-coupling to ε-coupling ratio determined by ^1H NMR; average of two determinations. [c] Prepared by adding 2 equiv of *n*-BuMgI to 1 equiv of CuI. [d] Prepared by adding 2 equiv of PhMgBr to 1 equiv of CuI.

Table II. Product Distribution[a] for Reaction of 2-OPiv with Butyl- and Phenylcopper Reagents

reagent	(E,E)-3	(E,Z)-3 (conjugated)	(Z,E)-3	(E,E)-4 (unconjugated)	(E,Z)-4 (unconjugated)
$LiCuBu_2$	87.8	8.9	0	2.1	1.2
LiCu(CN)Bu	67.4	32.6	0	0	0
$LiCuPh_2$	100	0	0	0	0
LiCu(CN)Ph	86.7	12.3	0	1.0	0

[a] Determined by capillary GC; (E,E)-**4a**:(E,Z)-**4a** ratio determined by ^1H NMR. Average values of two determinations.

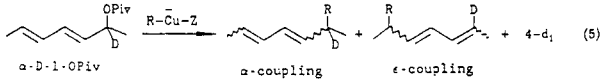
to slowly warm to room temperature. Coupling products were isolated by rotary thin layer chromatography; product distributions were found to be the same before and after isolation as determined by capillary GC.

Cross coupling of either **1**-OPiv or **2**-OPiv with organocopper reagents could yield two regioisomers (**3** and **4**) with a total of seven stereoisomers (eq 1); generally, less than the maximum number of isomers was observed.

Product distributions for cross coupling **1**-OPiv or **2**-OPiv with organocopper reagents were determined by capillary GC and are reported in Tables I and II. Base-line resolution could not be obtained for isomers (E,E)-**3a** and (Z,E)-**3a** or (E,E)-**4a** and (E,Z)-**4a**. The ^1H NMR spectra of preparative GC isolated samples proved effective for determining these stereoisomer ratios.

All reaction products except (Z,E)-**3a** have been characterized previously.[5,12] A binary mixture consisting of (E,E)-**3a** and (Z,E)-**3a** was prepared by Reich's 1,3-diene synthesis (Scheme I);[12] rotary TLC of this mixture provided a homogeneous sample of (Z,E)-**3a**, which was characterized spectroscopically. Oxidation of butyl phenyl selenide with MCPBA gives the corresponding selenoxide, which was sequentially treated with LDA and 2-methylhexanal. This affords β-hydroxy selenoxide **11**, which gives allyl alcohol **12** upon pyrolysis. Treatment of **12** with 2,4-dinitrobenzenesulfenyl chloride affords sulfenate ester **13**, which undergoes [2,3]-sigmatropic rearrangement to the isomeric allylic sulfoxide, which undergoes thermal elimination to give (E,E)- and (Z,E)-**3a**.

The deuterium distribution in the coupling product **3** arising from reacting α-D-**1**-OPiv with organocopper reagents (eq 5) was determined by ^1H NMR spectroscopy.



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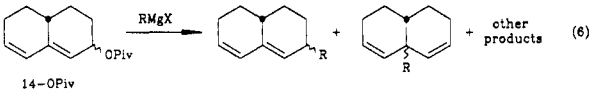
The coupling products **3** were isolated without fractionation by preparative GC, and integration of the vinyl and allylic protons in the ^1H NMR spectra measured the deuterium distribution and thus the regiochemistry of cross coupling. This proved to be a reliable and reproducible method. In most cases, direct determination of the deuterium distribution by ^2H NMR would have been cumbersome due to the small sample size obtained by preparative GC.

Cross coupling of **1**-OPiv with *n*-BuMgI and PhMgBr in the absence of cuprous salts occurs with little regioselectivity (i.e., nearly equal amounts of α-, γ-, and ε-substitution, Table I).[4] This is similar to the reactivity of 2,3,4,4a,5,6-hexahydro-2-naphthalenyl pivalate (**14**-OPiv)[13] with Grignard reagents (eq 6).[4] Reaction of **14**-OPiv with



(6)

Grignard reagents occurs remarkably fast and prevents isolation of copper(I)-catalyzed reaction of the ester with Grignard reagents.[4] Cross coupling of allylic carboxylates with Grignard reagents has been reported:[14] however, it has been found that these reactions are generally much slower than copper(I)-catalyzed Grignard reactions.[3b,4,15]

It was necessary to determine if copper(I)-catalyzed cross coupling of **1**-OPiv with Grignard reagents could be isolated. The cross-coupling reaction of PhMgBr with **1**-OPiv in the absence of cuprous salts produces a substantial

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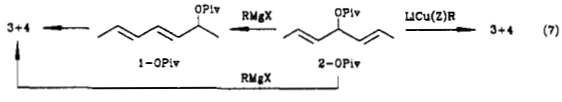
amount of unconjugated product (*E,E*)-**4b**. None of this isomer is observed in the copper(I)-catalyzed cross coupling of 1-OPiv with PhMgBr (Table I). Thus, the copper(I)-catalyzed reaction is much faster and cleanly isolated from the uncatalyzed reaction.

Uncatalyzed cross coupling of 1-OPiv with *n*-BuMgI gives nearly equal amounts of **3a** and **4a**, but CuCN-catalyzed cross coupling gives >98% **4a**. Therefore cross coupling of 1-OPiv with *n*-BuMgI is relatively slow in the absence of CuCN. That cross coupling of 1-OPiv with *n*-BuMgI/10% CuI is faster than uncatalyzed cross coupling was demonstrated by spiking an ethereal solution of 1-OPiv with dodecane as an internal standard, partitioning the resulting solution amongst two vials (one containing the appropriate amount of Cu(I)), treating each mixture with *n*-BuMgI, and measuring product formation as a function of time. After 20 min at 0 °C, the Cu(I)-catalyzed reaction was greater than 50% complete while the uncatalyzed reaction showed no detectable amount of product; after 1 h, the Cu(I) reaction was essentially complete, while the uncatalyzed reaction was only 9% complete. The relative ratio of **3a**:**4a** remained constant throughout the Cu(I)-catalyzed reaction; if an uncatalyzed reaction were competing, the ratio of **3a**:**4a** would increase. In addition, the ratio of α:ϵ-alkylation (Cu(I) catalyzed, 6.7:1; uncatalyzed, 0.87:1 vide infra) also indicates that the Cu(I)-catalyzed reaction is much faster than the uncatalyzed Grignard cross-coupling reaction.

It should be noted that although cross coupling of 1-OPiv with Grignard reagents is faster in the presence of Cu(I) than in its absence, the uncatalyzed reaction is still remarkably fast. For example, 5-OPiv is completely unreactive toward Grignard reagents after 4 h at room temperature (only a small amount of carbonyl attack is detected),[3b] while under identical conditions, 1-OPiv has undergone >75% conversion to coupling products.

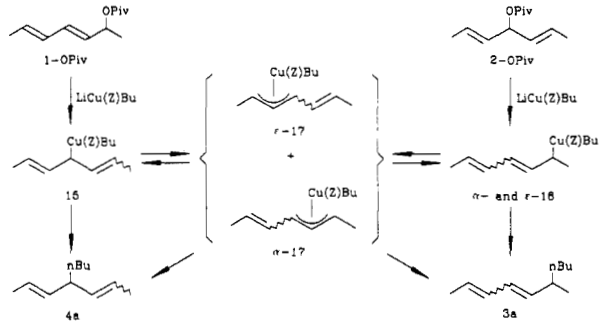
In the presence of Grignard reagents (i.e., magnesium ions), 2-OPiv isomerizes to 1-OPiv at a rate comparable to the copper(I)-catalyzed cross-coupling reaction of Grignard reagent with 2-OPiv; therefore, cross-coupling reactions of 2-OPiv with magnesium cuprates could not be studied (eq 7). Stirring 2-OPiv with a catalytic amount



of anhydrous $MgBr_2$ etherate in ether for 30 min was found to cause complete isomerization to 1-OPiv. Silica gel is even a strong enough Lewis acid to cause complete isomerization of 2-OPiv to 1-OPiv. For example, rotary chromatography of initial pure 2-OPiv on a silica gel plate with ether/pentane gives a single band. Analysis of this band's ^{1}H NMR spectrum showed that quantitative isomerization to 1-OPiv had occurred. Similar treatment of α-D-1-OPiv, however, returns discreetly labeled pivalate.

That isomerization of 2-OPiv to 1-OPiv occurs during cross-coupling reactions of 2-OPiv with magnesium cuprates was established as follows. Alkylation of 2-OPiv with Grignard (in the presence and absence of cuprous salts) was stopped short of completion, and the reaction mixture was subjected to diimide reduction. Analysis of the resulting mixture by capillary GC showed (in addition to hydrogenated alkylation products) hydrogenated 1-OPiv but no hydrogenated 2-OPiv. Hydrogenation of the reaction mixture was necessary since neither unsaturated pivalate survives capillary GC. Control experiments show that diimide reduction occurs with complete regiospecificity. Hydrogenation of the pivalates over palladium, however, proceeds with less regiospecificity, depending on how long 2-OPiv is in contact with the palladium catalyst.[16]

Scheme II. Mechanism for Alkylation of 1-OPiv and 2-OPiv with Butylcopper Reagents



Copper(I)-catalyzed cross coupling of 2-OPiv with Grignard reagents might be completely regiospecific, but isomerization of 2-OPiv to 1-OPiv prior to coupling conceals this observations. For example, cross coupling 2-OPiv with *n*-BuMgI/1% CuCN is expected to give 100% γ-alkylation (**3a**) based on thermodynamic bias favoring conjugated products and analogy with other systems (such as 6-OAc);[3] however, cross coupling yields 70% **3a** *and* 30% **4a**, presumably due to partial initial isomerization followed by γ-alkylation. A similar control experiment was performed to test the regiochemical integrity of 2-OPiv under $LiCuBu_2$ alkylating conditions. Alkylation of 2-OPiv with $LiCuBu_2$ was stopped after ≈50% completion, and after diimide reduction, GC analysis showed (in addition to hydrogenated alkylation products) only hydrogenated 2-OPiv and no hydrogenated 1-OPiv. That 1-OPiv could be detected if isomerization were to occur was demonstrated by reacting an 85:15 mixture of 2-OPiv/1-OPiv with $LiBuBu_2$ and quenching the reaction after ≈50% completion. After diimide reduction, GC analysis showed a 75:25 mixture of hydrogenated 2-OPiv/1-OPiv. Thus, 1-OPiv is slightly less reactive than 2-OPiv and should accumulate if isomerization precedes alkylation.

Cross Coupling of 1-OPiv and 2-OPiv with Butylcopper Reagents. The degree of regiospecificity (excess γ-alkylation) observed in cross coupling of 1-OPiv with butylcuprates increases in the order $LiCuBu_2$ < LiCu(CN)Bu < Bu_2CuMgI < *n*-BuMgI/1% CuCN (Table I). This is similar to the order observed for butylation of the α-methyl-γ-phenylallyl system (**5**)[3,15] as well as other systems.[5] Thus, cyanocuprates are more regiospecific than are dialkylcuprates, and magnesium cuprates are more regiospecific than lithium cuprates.[3,15]

Cuprous iodide and cuprous chloride catalyzed cross-coupling reactions of 1-OPiv with *n*-BuMgI favor γ-alkylation. Both reagents derived from these cuprous halides give the same product distribution (i.e., the same amount of α-, γ-, and ϵ-alkylation) as that obtained with Bu_2CuMgI. This suggests that Bu_2CuMgX is the reactive cuprate in the Cu(I)-catalyzed reactions.[3,15]

Regiochemical studies using α-D-1-OPiv indicate that α-butylation is favored over ϵ-butylation for every butylcuprate studied (Table I). Similar behavior was observed before in the naphthalenyl system (14-OPiv).[4] A mechanism consistent with this data, which is similar to one proposed earlier,[4,5] is shown in Scheme II. Stereochemical constraints require the π-system of the newly formed C_α–C_β double bond in the initial conformation of **15** to be aligned with the newly formed C_γ–Cu bond, and this permits facile $\sigma \rightarrow \pi \rightarrow \sigma$ isomerization (**15** → α-**16**). The

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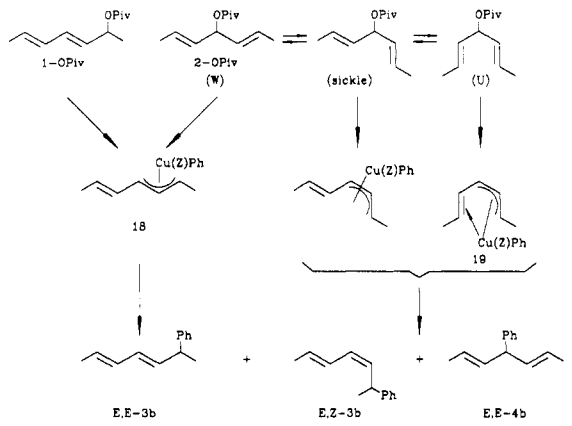
Scheme III. Mechanism for Phenylation of 1-OPiv and 2-OPiv with $LiCuPh_2$ and LiCu(CN)Ph



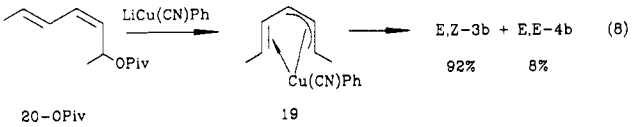
remote C_δ–C_ϵ double bond has no such constraints and may or may not be properly aligned for $\sigma \rightarrow \pi \rightarrow \sigma$ isomerization (**15** $\rightarrow$ ϵ-**16**). Thus, the γ-σ-allylcopper(III) intermediate **15** has three options: reductively eliminate to give **4a**, isomerize ($\sigma \rightarrow \pi \rightarrow \sigma$) to α-**16**, and/or wait for the remote double to become aligned before isomerizing ($\sigma \rightarrow \pi \rightarrow \sigma$) to ϵ-**16**. Apparently the last process is slower than the first two for all cases except cross coupling with $LiCuBu_2$. In this case reductive elimination by **15** (to give **4a**) is apparently slower than isomerization to ϵ-**16**; however, isomerization of **15** to α-**16** is still the predominant pathway. Thus, the regiospecificity of cross-coupling depends on the relative rates of these processes.

Alkylation of **2**-OPiv with $LiCuBu_2$ gives nearly the same product distribution as **1**-OPiv; thus, the reaction is essentially nonregiospecific (Tables I and II). This suggests that a π-allylcopper(III) complex (**17**) is a common intermediate (Scheme II).[3] Alkylations with LiCu(CN)Bu, however, are partially regiospecific, and presumably, $\sigma \rightarrow \pi$ isomerization (**15** $\rightarrow$ **17**) is slow relative to reductive elimination (Scheme II).[3-5]

Cross Coupling of 1-OPiv and 2-OPiv with Phenylcopper Reagents. Phenylation of **1**-OPiv gives only (*E,E*)-**3b** regardless of the phenylcopper reagent (Table I). Furthermore this product arises from exclusive α-substitution. As reported earlier, reaction of **14**-OPiv with $LiCuPh_2$ or LiCu(CN)Ph also gives primarily α-coupling product.[4] These results are consistent with a mechanism proposed earlier,[4,5] which is shown in Scheme III. Cross coupling of **1**-OPiv with phenylcopper reagents evidently proceeds via an initial π-allylcopper(III) intermediate (**18**) and not a γ-σ-allylcopper(III) intermediate.[4,5] Reductive elimination at the α-position to give conjugated product **3** would be expected to be more favorable than at the γ-position, in which case unconjugated product **4** is formed.[4]

Phenylation of **2**-OPiv with $LiCuPh_2$ gives only (*E,E*)-**3b** but coupling with LiCu(CN)Ph gives (*E,E*)-**3b** and (*E,Z*)-**3b** and a small amount of (*E,E*)-**4b**. This mixture is presumably due to several possible reactive conformations for **2**-OPiv, namely, a *W*, *sickle*, and *U* conformation.[17] Prior coordination of the cuprate to both double bonds[18] would enforce a *U* conformation and presumably gives a π-allylcopper(III) chelate complex (**19**),[19] which ultimately gives rise to (*E,Z*)-**3b** and (*E,E*)-**4b** (Scheme III). Why this is more important with LiCu(CN)Ph than with $LiCuPh_2$ is not certain.

In an earlier report,[5] we proposed that intermediate **19** was involved in cross coupling of **20**-OPiv with phenylcuprates (eq 8). In this instance, conjugated product



(8)

((*E,Z*)-**3b**) is favored over unconjugated product ((*E,E*)-**4b**) by slightly more than a factor of 11.[5] In the present case, cross coupling of **2**-OPiv with LiCu(CN)Ph gives only 12% of (*E,Z*)-**3b** and 1% of (*E,E*)-**4b**, presumably because 13% of the reaction occurs from the *U* conformation of **2**-OPiv (leading to 13% **19**). Reductive elimination of **19** is expected to yield an 11:1 mixture of (*E,Z*)-**3b** and (*E,E*)-**4b** based on the previous finding;[5] the product mixture reported in Table II is consistent with the intermediacy of **19**.

In conclusion, **1**-OPiv behaves more like an allylic system with a vinyl substituent than a conjugated allylic dienyl system. In organocopper cross-coupling reactions, the influence on reactivity of a conjugated double bond in an allylic system is very similar, in most cases, to the influence of a conjugated phenyl ring. The chemistry of cross-coupling reactions of these allylic dienyl systems is predictable, based on analogy with simple allylic systems. The regiospecificity of cross coupling is determined by the relative rates of isomerization of the initial σ-allylcopper(III) intermediates verses reductive elimination. Regiospecificity is higher for magnesium alkylcuprates[3b] than for the corresponding lithium alkylcuprates, and higher for cyanoalkylcuprates than for the corresponding dialkylcuprates. There is no regiospecificity for reactions involving phenylcuprates.

Experimental Section

General Methods. All reactions were carried out under a positive pressure of dry nitrogen. Grignard reagents and cuprous salts were prepared and purified as described earlier.[3b,15] *n*-BuLi (2.5 M in hexane) and PhLi (2.0 M in 7:3 cyclohexane/ether) were purchased from Aldrich Chemical Company.

The instrumentation used in this work has been described;[5] proton NMR spectra were obtained at 200 MHz. *J* values are in hertz.

(*E,E*)-3,5-Heptadien-2-yl 2,2-dimethylpropanoate (1-OPiv)[6] was prepared in the standard way[4] from the corresponding alcohol[7,20] and pivaloyl chloride in 94% yield: bp 95–97 °C (20 mm); IR (neat) 3020 (m), 2980 (s), 2940 (s), 2920 (m), 2880 (m), 1760 (s), 1490 (s), 1470 (m), 1370 (m), 1290 (s), 1170 (s), 1150 (s), 1050 (s), 1000 (s), 950 (m); NMR (δ, $CDCl_3$) 6.19 (ddd, 1 H, J = 14.6, 10.4, 0.5), 6.02 (ddq, 1 H, J = 14.5, 10.4, 1.4), 5.72 (dq, 1 H, J = 14.5, 6.7), 5.53 (ddd, 1 H, J = 14.6, 6.6, 0.5), 5.34 (app p, 1 H, J = 6.6), 1.76 (d, 3 H, J = 6.7), 1.29 (d, 3 H, J = 6.6), 1.19 (s, 9 H); high resolution mass spectrum, calcd for $C_{12}H_{20}O_2$ m/e 196.1464, found m/e 196.1464.

[2-^{2}H]-(*E,E*)-3,5-Heptadien-2-yl 2,2-dimethylpropanoate (α-D-1-OPiv)[6] was prepared in the usual manner from pivaloyl chloride and the corresponding alcohol (α-D-1-OH), which was obtained by $LiAlD_4$ reduction[7] of (*E,E*)-3,5-heptadien-2-one.[8]

(*E*)-2-Hepten-5-yn-4-ol (10).[10] Approximately 7 g (175 mmol) of methyl acetylene was condensed in a flask (−78 °C) and dissolved in 20 mL of dry ether before 44 mL of 2.85 M *n*-BuLi was added. This mixture was warmed to 0 °C and then recooled to −78 °C before a solution of 7.00 g (100 mmol) of crotonaldehyde in 25 mL of ether was added. The resulting homogeneous solution was warmed to room temperature overnight before being poured

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into a solution of ice-cold 10% NH_4Cl. The aqueous layer was discarded and the ether fraction was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Solvent was removed by fractional distillation and 5.4 g (49%) of **10** was obtained by distillation: bp 65–68 °C (0.5 mm); NMR (δ, $CDCl_3$) 5.87 (dqd, 1 H, J = 15.2, 6.4, 1.1), 5.61 (ddq, 1 H, J = 15.2, 6.2, 1.5), 4.78 (br s, 1 H), 1.94 (br s, 1 H), 1.89 (d, 3 H, J = 2.0), 1.73 (ddd, 3 H, J = 6.4, 1.5, 1.1).

(*E*,*E*)-2,5-Heptadien-4-ol (2-OH)[11] was prepared by adding 500 mg (12.8 mmol) of $LiAlH_4$ in portions to a stirred solution of 2.40 g (21.8 mmol) of the above **10**[10] in 30 mL of ether and refluxing the resulting mixture for 48 h.[9] Standard aqueous workup and distillation afforded 2.04 g (85%) of **2**-OH: bp 58–59 °C (6 mm); NMR (δ, $CDCl_3$) 5.69 (dqd, 2 H, J = 15.3, 6.2, 0.9), 5.52 (ddq, 2 H, J = 15.3, 6.5, 1.5), 4.52 (br t, 1 H, J = 6.5), 1.71 (ddd, 6 H, J = 6.2, 1.5, 0.5), 1.65 (br s).

(*E*,*E*)-2,5-Heptadien-4-yl 2,2-dimethylpropanoate (2-OPiv) was prepared in the standard way from the above **2**-OH and pivaloyl chloride in 94% yield: IR (neat) 3020 (w), 2990 (s), 2940 (s), 2800 (m), 1740 (s), 1480 (m), 1450 (m), 1275 (s), 1150 (s), 960 (s), 920 (m); NMR (δ, $CDCl_3$) 5.75 (dqd, 2 H, J = 15.2, 6.2, 1.0), 5.62 (t, 1 H, J = 6.4), 5.48 (ddq, 2 H, J = 15.2, 6.4, 1.6), 1.70 (dd, 6 H, J = 6.2, 1.6), 1.19 (s, 9 H); high resolution mass spectrum, calcd for $C_{12}H_{20}O_2$ m/e 196.1464, found m/e 196.1465.

General Procedure for Cross Coupling of 1-OPiv with Grignard Reagents in the Presence and Absence of Copper(I). The pivalate (1 mmol) was dissolved in 6 mL of dry ether and an appropriate amount of cuprous salt (0–10% with respect to Grignard reagent, see Tables I and II) was added. The resulting mixture was cooled to the indicated temperature, and a 2 molar equiv excess of an ethereal solution of Grignard reagent (≈2 M) was added. After standard workup,[4] products were isolated by rotary TLC.

General procedure for cross coupling of 1-OPiv and 2-OPiv with $LiCuR_2$ and LiCu(CN)R is the same as reported earlier.[4]

Determination of the deuterium distribution in coupling products 3 derived from α-D-1-OPiv was done as described previously.[5] Integration of the methine resonances in the ^1H NMR spectrum proved a convenient and reproducible method for determining the deuterium distribution. Duplicate runs gave identical results (±2%), and control experiments indicated that 2% was the lower limit of detection.

(*E*,*E*)-6-Phenyl-2,4-heptadiene ((*E*,*E*)-3b):[12] NMR (δ, $CDCl_3$) 7.1–7.5 (m, 5 H), 5.9–6.1 (m, 2 H), 5.5–5.8 (m, 2 H), 3.48 (app p, J = 6.9), 1.73 (d, 3 H, J = 6.0), 1.36 (d, 3 H, J = 7.1).

(*E*)-6-Methyl-3-decen-5-ol (12). Following the procedure of Reich and co-workers,[12] 605 mg (2.98 mmol) of MCPBA (85%) was added in portions to a solution of 640 mg (3.00 mmol) of butyl phenyl selenide[12] in 8 mL of THF at −15 °C. After 20 min, the solution was cooled to −78 °C, and 6.6 mL of 1 M LDA (THF) was added. After 5 min, a solution of 336 mg (2.95 mmol) of 2-methylhexanal in 2 mL of THF was added. After 30 min, a solution containing 1 mL of THF, 0.3 mL of HOAc, and 0.3 mL of H_2O was added and the cold mixture was quickly poured into 25 mL of refluxing hexane containing 0.5 mL of diisopropylamine. After 5 min, the mixture was poured into ice-cold saturated $NaHCO_3$, and the aqueous layer was extracted with 2 × 100 mL of ether. The combined ether layers were washed with 5% HCl, $NaHCO_3$, and brine and dried over $MgSO_4$. Allylic alcohol **12** (323.2 mg, 65%) was removed from residual diphenyl diselenide by rotary TLC (pentane/ether–silica gel): IR (neat) 3400 (br s), 2960 (s), 2930 (s), 2880 (s), 1470 (m), 1390 (m), 1020 (m), 980 (s); NMR (δ, $CDCl_3$) 5.68 (dt, 1 H, J = 15.4, 7.0), 5.45 (br dd, 1 H, J = 15.4, 7.0), 3.90 (br s, 1 H), 2.05 (app septet, 1 H, J = 6.1), 0.8–1.6 (m, 18 H, including δ 1.01, t, J = 6.8); high resolution mass spectrum, calcd for $C_{11}H_{22}O$ m/e 170.1671, found m/e 170.1670.

(*Z*,*E*)- and (*E*,*E*)-6-Methyl-2,4-decadiene ((*Z*,*E*)- and (*E*,*E*)-3a[5]**).** Following the procedure of Reich and co-workers,[12] 740 mg (3.16 mmol) of 2,4-dinitrobenzenesulfenyl chloride was added to a solution of 188.9 mg (1.11 mmol) of the above allylic alcohol **12** in 15 mL of 1,2-dichloroethane containing 347 mg (3.44 mmol) of NEt_3, and the mixture was rapidly heated to reflux for 2 h. The resulting mixture was poured into 30 mL of pentane and filtered, and solvent was removed by rotary evaporation. Elution through a plug of silica gel with pentane gave 130 mg of a colorless oil, which consisted of a 2.1:1 mixture of (*E*,*E*)-**3a** and (*Z*,*E*)-**3a**. Determination of the stereoisomer ratio was accomplished by integration of (*Z*,*E*)-**3a**'s vinyl resonance at δ 6.28 and (*E*,*E*)-**3a**'s vinyl resonance at δ 6.00 in the ^1H NMR spectrum of the mixture. (*E*,*E*)-**3a** was easily separated from (*Z*,*E*)-**3a** by rotary TLC (pentane/$AgNO_3$–silica gel). (*Z*,*E*)-**3a**: IR (neat) 3010 (w), 2950 (s), 2860 (s), 2840 (m), 1470 (m), 1460 (m), 990 (m), 970 (w), 950 (w); high resolution mass spectrum, calcd for $C_{11}H_{20}$ m/e 152.1566, found m/e 152.1566; NMR spectrum including decoupling experiments led to the assignment of (*Z*,*E*)-**3a** (δ, $CDCl_3$) 6.28 (dd, 1 H, J = 15.0, 10.8), 5.96 (ddd, 1 H, J = 10.8, 10.7, 1.0), 5.37 (dq, 1 H, J = 10.7, 7.1), 5.35 (dd, 1 H, J = 15.0, 7.7), 2.18 (m, 1 H), 1.74 (dd, 3 H, J = 7.1, 1.0), 1.4 (m, 6 H), 1.00 (d, 3 H, J = 7.1), 0.89 (t, 3 H, J = 6.9).

Diimide Reduction[21] **of 1-OPiv and 2-OPiv** in diglyme at 80 °C proceeded regiospecifically to yield the respective saturated pivalates in 90% yields.

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Registry No. 1-OPiv, 126156-59-0; **2**-OPiv, 126156-60-3; **2**-OH, 91001-08-0; (*E*,*E*)-**3a**, 119819-20-4; (*Z*,*E*)-**3a**, 126156-62-5; (*E*,*Z*)-**3a**, 119819-21-5; (*E*,*E*)-**3b**, 68099-29-6; (*E*,*Z*)-**3b**, 126156-63-6; (*E*,*E*)-**4a**, 119819-18-0; (*E*,*Z*)-**4a**, 119819-19-1; (*E*,*E*)-**4b**, 119819-22-6; **10**, 63124-69-6; **12**, 126156-61-4; $LiCuBu_2$, 24406-16-4; LiCu(CN)Bu, 41742-63-6; Bu_2CuMgI, 51340-42-2; *n*-BuMgI, 1889-20-9; $LiCuPh_2$, 23402-69-9; LiCu(CN)Ph, 41742-64-7; $Ph_2CuMgBr$, 58938-91-3; PhMgBr, 100-58-3; CuCN, 544-92-3; CuCl, 7758-89-6; CuI, 7681-65-4; methylacetylene, 74-99-7; crotonaldehyde, 4170-30-3; butyl phenyl selenide, 28622-61-9; 2-methylhexanal, 925-54-2.

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