Alkylation of Allylic Derivatives. 11.[1] Copper(I)-Catalyzed Cross Coupling of Allylic Carboxylates with Grignard Reagents

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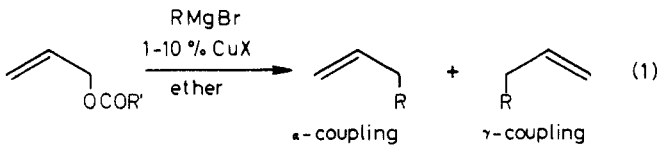
Reactions of allylic carboxylates with Grignard reagents containing catalytic amounts (1–10 mol %) of cuprous salts give high yields of cross-coupled products. With alkyl Grignard reagents, regiochemistry can be controlled by choice of cuprous salt. With cuprous halides, little regiospecificity is observed. There is a small excess of γ-coupling in unbiased systems such as 5-methyl-2-cyclohexenyl (1), 2-cyclohexenyl (3), and β-phenylallyl (5) carboxylates. With CuCN, complete regiospecificity (exclusive γ-coupling) is observed with all alkyl Grignard reagents in unbiased systems, and with *n*-butylmagnesium halide >97% γ-coupling results with α-methyl-γ-phenylallyl pivalate (7-OPiv) which is biased in favor of coupling at the α-position. In sharp contrast to alkyl Grignard reagents, phenyl and vinyl Grignard reagents containing CuCN show no regiospecificity.

We report that cross coupling of allylic carboxylates with Grignard reagents containing catalytic amounts (1–10 mol %) of cuprous salts (eq 1) is superior to conventional



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methods that involve stoichiometric quantities of preformed organocuprates.[2,3] Advantages of the catalytic method include control of regiochemistry by selection of cuprous salt used as catalyst and high yields based on organometallic reagent as well as on the allylic substrate. Also, Grignard reagents are generally easier to prepare than the alkyllithiums that are required for preparation of lithium organocuprates.

Although allylic carboxylates can be converted to cross-coupled products in high yields by the stoichiometric method, yields with respect to the organocopper reagent (and all precursors) are generally poor. This is because organocuprates are unstable and for optimum yields excess cuprate (usually at least 2 equiv) must be used to compensate for decomposition that accompanies the reaction.[2,3] On the other hand, with the catalytic method excellent yields (often "quantitative" conversions) are obtained with only a 10% excess of Grignard reagent. Moreover, these reactions can be carried out at room temperature without decomposition.

Copper(I)-catalyzed cross-coupling reactions of Grignard reagents have been reported for other allylic derivatives including ethers,[4] halides,[5] benzothiazoles,[6] and sulfides.[7,8] However, the dependence of regiochemistry on the cuprous salt used as catalyst has not been observed. Except for isolated experiments with a lactone[9] and two acetates,[4a,10] evidently allylic carboxylates have not been investigated.

Alkylation of allylic acetates with Grignard reagents containing 1–10 mol % cuprous salt is often accompanied by carbonyl attack. However, this side reaction can be eliminated in most cases by using the pivalate ester and in all cases using the mesitoate derivative. In earlier work we found that mesitoates are more effective than pivalates for preventing carbonyl attack.[2] Interference from carbonyl attack depends on the coupling reactivity of the allylic carboxylate.[1] With relatively unreactive systems, such as 2-cyclohexenyl carboxylates,[1] it is necessary to use the mesitoate to eliminate carbonyl attack with reactive Grignard reagents. Acyclic allylic systems are sufficiently reactive so that pivalates can be used in all cases without detectable carbonyl attack.

In this work we have investigated several allylic carboxylates and a variety of Grignard reagents. Most combinations give excellent yields of cross-coupling products. Moreover, we have discovered that with alkyl Grignard reagents, the regiochemistry of alkylation depends on the copper(I) salt even though this is present in only catalytic amounts. For example, with alkyl Grignard reagents the CuCN-catalyzed reaction is highly regiospecific and gives exclusive or predominating γ-alkylation. On the other hand, with cuprous halides there is little, if any, regiospecificity.

For mechanistic interpretation of regiochemical results it is essential to distinguish between regiospecificity and regioselectivity.[11] In this work we have used systems in which this distinction can be made. This can most simply be done with unbiased (symmetrical) allylic systems because in this case regioselectivity is eliminated.

Results for reaction of α-deuterio-*cis*-5-methyl-2-cyclohexenyl mesitoate (1-OTMB) with 2 equiv of *n*-BuMgBr containing 10 mol % CuCN or CuCl for 6 h at room temperature are shown under eq 2.[12] In each case the product (2) was isolated in ~65% yield. Subsequent experiments showed that under these conditions the reaction is prob-

(1) Previous paper in this series: Goering, H. L.; Kantner, S. S.; Seitz, E. P., Jr. *J. Org. Chem.* **1985**, *50*, 5495.
(2) Coering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422 and earlier papers in this series.
(3) (a) Levisalles, J.; Rudler-Chauvin, M.; Rudler, H. *J. Organomet. Chem.* **1977**, *136*, 103. (b) Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4256.
(4) (a) Claesson, A.; Sahlberg, C. *J. Organomet. Chem.* **1979**, *170*, 355. (b) Gendreau, Y.; Normant, J. F. *Tetrahedron* **1979**, *35*, 1517. (c) Normant, J. F.; Commercon, A.; Gendreau, Y.; Bourgain, M.; Villieras, J. *Bull. Soc. Chim. Fr.* **1979**, II-309.
(5) Ohbe, Y.; Matsuda, T. *Tetrahedron* **1973**, *29*, 2989.
(6) Calo, V.; Lopez, L.; Pesce, G.; Calianno, A. *J. Org. Chem.* **1982**, *47*, 4482.
(7) (a) Barsamti, P.; Calo, V.; Lopez, L.; Marchese, G.; Naso, F.; Pesce, G. *J. Chem. Soc. D* **1978**, 1085. (b) Calo, V.; Lopez, L.; Marchese, G.; Pesce, G. *Synthesis* **1979**, 885.
(8) For a recent review that includes this subject, see: Erdik, E. *Tetrahedron* **1984**, *40*, 641.
(9) Fujisawa, T.; Sato, T.; Kawashima, M.; Naruse, K.; Tamai, K. *Tetrahedron Lett.* **1982**, *23*, 3583.
(10) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82.
(11) The terms "regioselective" and "regiospecific" are used as defined in footnote 3 of: Goering, H. L.; Singleton, V. D., Jr. *J. Org. Chem.* **1983**, *48*, 1531.
(12) The solvent was ether in all cases except for reactions with vinyl Grignard reagents in which cases the solvent was a 50:50 mixture of ether and THF.

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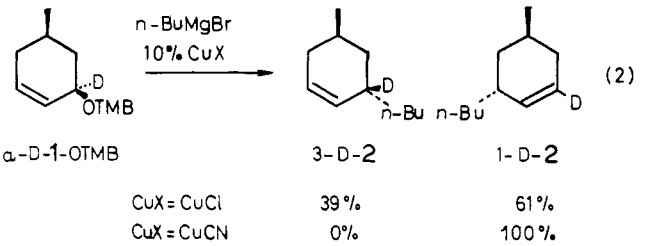
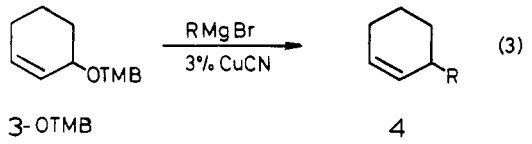


ably complete in a few minutes. This system is unbiased with regard to regiochemistry except for a small perturbation by the deuterium label which favors the isomer with the deuterium on a sp^3 carbon atom, the α-alkylation product in this case.[13]

Attempts to determine the configurational composition of **2** by capillary GC were unsuccessful. This composition was found to be 97% trans isomer by hydrogenation (PtO_2) to 1-*n*-butyl-3-methylcyclohexane and capillary GC analysis of the latter. This stereochemistry (>97% anti alkylation) is about the same as for stoichiometric alkylation of 1-OAc with $LiCuMe_2$[14] or LiCu(CN)Me.[2] Similar stereochemical results have been reported for cross coupling 2-cyclohexenyl methyl ethers with *n*-BuMgCl containing 5 mol % CuBr.[4b]

The results under eq 2 show that there is a remarkable difference in regiochemistry for catalysis by CuCl and CuCN. Partial regiospecificity (22% excess γ-alkylation) is observed with CuCl. However, exclusive γ-alkylation results with CuCN.[15]

To investigate the scope of the catalytic process, 2-cyclohexenyl mesitoate (**3**-OTMB) was reacted with a series of Grignard reagents containing 3 mol % CuCN (eq 3). Two equivalents of Grignard reagent were used in



these experiments and reaction mixtures were prepared and stirred for 5 h at 0 °C.[12] Yields of isolated products (**4**) are shown in Table I. Ranges are given for cases with two or more independent experiments. Except as noted, isolated products were shown to be homogeneous by capillary GC and were identified by IR and NMR spectra and GC retention times.

As shown in Table I, good yields of cross-coupling products were obtained in all cases except with allyl and vinyl Grignard reagents—yields with MeMgI and EtMgI were reduced by loss of the volatile products during isolation and purification. With the allyl-MgBr, at 0 °C there is immediate reduction of the CuCN and apparently no product is formed. The 66% yield was obtained by preparing a reaction mixture containing 25 mol % CuCN at −60 °C and allowing the solution to warm to 0 °C. With vinyl-MgBr the reaction stopped short of completion and only ~11% of the product was isolated. Addition of a second 3 mol % portion of CuCN raised the yield to 56%.

In other work[1] we found that the 2-cyclohexenyl system (**3**) is less reactive than acyclic allylic systems for alkylation of carboxylates with $LiCuMe_2$. Thus side reactions (e.g., carbonyl attack or decomposition of organocopper intermediates) would be expected to be more important in this system than in most other cases. From this we conclude that this catalytic cross-coupling process is general for allylic carboxylates as well as for Grignard reagents.

Table I. Yields of Isolated Products (4) for Cross Coupling Cyclohexenyl Mesitoate (3-OTMB) with Grignard Reagents Containing 3 mol % CuCN (eq 3)[a]

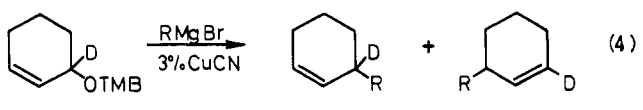
RMgBr	% yield of 4	RMgBr	% yield of 4
MeMgI	59–62	cyclohexyl-MgBr	75–87
EtMgI	68–69	PhMgBr	90–94
n-BuMgBr	85–87	*p*-anisyl-MgBr	82–95
i-BuMgBr	87	allyl-MgBr	0–66[c]
i-PrMgBr	75–88	vinyl-MgBr	11–56[d,e]
2-BuMgBr	89[b]	propen-2-yl-MgBr	60–63[d]

[a] Except as noted all reactions were carried out in ether at 0 °C. [b] Mixture (50:50) of two diastereomers. [c] No product obtained at 0 °C (85% recovery of **3**-OTMB). The 66% yield was obtained by preparing reaction mixture at −60 °C and allowing the stirred solution to warm to 0 °C. [d] Solvent was 50:50 mixture of ether and THF. [e] The higher yield (56%) was obtained by adding a second 3 mol % portion of CuCN.

2-Cyclohexenyl pivalate (**3**-OPiv) was reacted with 1.1 equiv of Grignard reagent containing 1 mol % CuCN to determine the minimum amount of Grignard reagent required for suitable yields. Reaction mixtures were prepared at 0 °C and the ether solutions stirred at room temperature for 1 h. The Grignard reagents involved (and yields of isolated products) were *i*-PrMgBr (78%), PhMgBr (93%), and *n*-BuMgBr (83–94%). These experiments show that the catalytic method, unlike stoichiometric procedures, gives good yields with respect to the organometallic reagent as well as the allylic substrate.

In work to be reported elsewhere we have found that the order of reactivity for the copper(I)-catalyzed reaction of a series of Grignard reagents with **3**-OPiv at 0 °C[12] is *t*-BuMgBr > *i*-PrMgBr > PhMgBr > *n*-BuMgBr. The difference in reactivity is substantial. With *t*-BuMgBr the reaction is complete about as soon as the reaction mixture is prepared and there is a ~40-fold difference in rate for *i*-Pr- and *n*-BuMgBr. Preliminary experiments indicate that even in unreactive allylic systems[1] acetates can be used with tertiary and secondary alkyl Grignard reagents without detectable carbonyl attack.

Results of regiochemical studies for reaction of α-deuterio-2-cyclohexenyl mesitoate (α-D-**3**-OTMB)[16] with several Grignard reagents containing CuCN are tabulated under eq 4.[15] These experiments involved 2 equiv of



RMgBr	% yield		
n-BuMgBr	93	0	100
i-PrMgBr	75	0	100
t-BuMgBr	87	0	100
PhMgBr	60–90	51–53	47–49
propen-2-yl-MgBr	63	54	46

Grignard reagent containing 3 mol % CuCN in ether at room temperature. Complete regiospecificity (exclusive γ-alkylation) is observed with all alkyl Grignard reagents in this unbiased system. However, the results are strikingly different for propen-2-yl-MgBr and PhMgBr. In these

(13) In other work we have found that in the α-deuterio- or γ-deuterio-2-cyclohexenyl system the deuterium thermodynamic isotope effect for equilibration of the allylic alcohols results in a deuterium sp^3/sp^2 ratio of 54/46.

(14) Goering, H. L.; Singleton, V. D., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854.

(15) The deuterium distribution in the alkylation product was determined by 30.6-MHz ^2H NMR as described in ref 2.

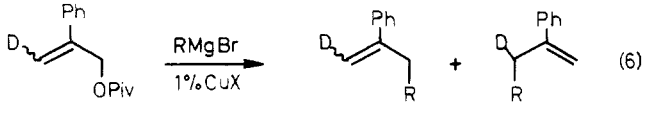
(16) Prepared from the corresponding deuterated alcohol; see: Kantner, S. S.; Humski, K.; Goering, H. L. *J. Am. Chem. Soc.* **1982**, *104*, 1693.

cases there is no regiospecificity and the deuterium distribution in the alkylation product corresponds to an equilibrium mixture of the two isomers.[13]

In other experiments it was shown that reaction of α-deuterio- and γ-deuterio-2-cyclohexenyl pivalate (3-OPiv) with PhMgBr containing 1 mol % CuCN gives products with the same deuterium distribution, as shown by eq 5. This confirms the complete loss of regiochemistry (randomization of allylic carbon atoms) with this reagent.

$$\alpha\text{-D- or } \gamma\text{-D-3-OPiv} \xrightarrow[1\%\ \mathrm{CuCN}]{\mathrm{PhMgBr}} 54\%\ \text{3-D-4} + 46\%\ \text{1-D-4} \quad (5)$$

Results for reaction of several Grignard reagents with γ-deuterio-β-phenylallyl pivalate (5), an unbiased acyclic system, are shown under eq 6. This ester was prepared



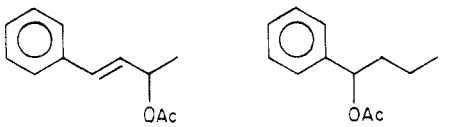
(6)

5 1-D-6 3-D-6

R	X	% yield		
n-Bu	CN	97	0	100
n-Bu	Cl	97	39	61
t-Bu	CN	76	0	100
i-Pr	CN	86	0	100
Ph	CN	80	47	53

from the corresponding deuterated alcohol.[17] These experiments involved reaction of 5 with 2 equiv of Grignard reagent containing 1% CuCN or CuCl in ether at room temperature for 1 h. Products were isolated in from 76% (*t*-BuMgBr) to 97% yields (*n*-BuMgBr). The results with this system are essentially the same as for the cyclohexenyl systems (1 and 3). Complete regiospecificity (γ-alkylation) is observed with all of the alkyl Grignard reagents in the presence of CuCN (but not with CuCl) and regiospecificity is completely lost with PhMgBr.

In other work[18] we investigated the stoichiometric alkylation of the isomeric *trans*-α,γ-methyl(phenyl)allyl acetates (7-OAc and 8-OAc) with *n*-Bu_2CuLi and found



7-OAc 8-OAc

that both acetates give the same product distribution, ~93% conjugate isomer (9, R = *n*-Bu) and ~7% unconjugated isomer (10, R = *n*-Bu). Thus because of a thermodynamic bias favoring formation of 9 the reaction is regioselective; however, there is no regiospecificity.[11] The results are similar for alkylation with Me_2CuLi and we presume that this is general for all lithium dialkylcuprates.

In this work we have used this system to investigate the regiochemistry of the catalytic reaction. Of particular interest were the reactions that are totally regiospecific in unbiased systems, viz. CuCN-catalyzed reactions with alkyl Grignard reagents. We also used this system to compare different cuprous salts.

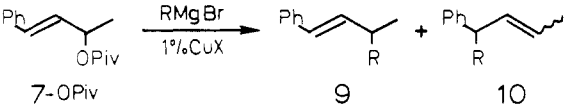
Results for reaction of *trans*-α-methyl-γ-phenylallyl pivalate (7-OPiv) with Grignard reagents containing 1 mol % cuprous salt (eq 7) are presented in Table II. In this

Table II. Product Distribution for Cross Coupling *trans*-α-Methyl-γ-phenylallyl Pivalate (7-OPiv) with Grignard Reagents Containing 1 mol % Copper(I) Salts (eq 7)[a]

		product distribtn, %[b]		
RMgBr	CuX	9	10	% yield[c]
n-BuMgBr	CuCN	2–3[d]	97–98	96–100[d]
n-BuMgBr	CuCl	89	11	78–96[e]
n-BuMgBr	CuBr	85	15	92
n-BuMgBr	CuI	86	14	86
n-BuMgBr	CuSCN	86	14	90
t-BuMgBr	CuCN	16–27[f]	73–84	81–91[f]
PhMgBr	CuCN	>99	<1	76

[a] Reactions involved 2 equiv of Grignard reagents in ether at room temperature. [b] Composition determined by capillary GC. [c] Yield of isolated products. [d] Range for four independent experiments. [e] Range for two independent experiments. [f] Range for five independent experiments.

highly reactive system,[1] carbonyl attack is not observed with the pivalate derivative.



(7)

7-OPiv 9 10

With *n*-BuMgBr, the CuCN-catalyzed reaction is highly regiospecific and gives 97–98% γ-alkylation even though this system is biased in favor of the α-alkylation product. This process is substantially more regiospecific than stoichiometric alkylation of 7-OPiv with *n*-BuCu(CN)Li which heretofore was the method of choice for regiospecific γ-alkylation of allylic carboxylates.[2,3,19]

On the other hand, there is very little regiospecificity with the other cuprous salts. The product distribution, 85–89% α-alkylation and 11–15% γ-alkylation, shows only slightly more γ-alkylation than the nonregiospecific stoichiometric alkylation of 7-OAc with *n*-Bu_2CuLi (~7% γ-alkylation).[18] The remarkable difference in regiochemistry for CuCN and the other cuprous salts evidently is not observed for cross-coupling reactions of allylic ethers.[4c]

This biased system provides the proper scale for comparing the regiospecificity for different alkyl Grignard reagents which are completely regiospecific in the unbiased systems. The data in Table II show that the CuCN-catalyzed reaction is more regiospecific with *n*-BuMgBr than with *t*-BuMgBr. As in the unbiased systems, the reaction with PhMgBr shows no regiospecificity. In this case regioselectivity favors the conjugated product (9, R = Ph) to a somewhat greater extent than nonregiospecific alkylations of 7-OAc with alkylcuprates (93–95%, 9).[18]

Comparison of the present regiochemical results with those for stoichiometric alkylations with R_2CuLi[14,18] and $RCu(CN)Li$[2,19] in these systems suggests that the active species for the RMgBr–CuCN combination is RCu(CN)MgBr (eq 8) and that for catalysis with the other cuprous salts is $R_2CuMgBr$ (eq 9 and 10). Clearly, the CuCN bond

$$\mathrm{RMgBr} + \mathrm{CuCN} \rightarrow \mathrm{RCu(CN)MgBr} \quad (8)$$

$$\mathrm{RMgBr} + \mathrm{CuX} \rightarrow \mathrm{RCu} + \mathrm{Mg(X)Br} \quad (9)$$

$$\mathrm{RMgBr} + \mathrm{RCu} \rightarrow \mathrm{R_2CuMgBr} \quad (10)$$

remains intact for many catalytic cycles. From other work,[20] metal–metal exchange would not be expected with

(17) Jousseaume, B.; Duboudin, J.-G. *J. Organomet. Chem.* **1975**, *91*, C1; **1979**, *168*, 1.
(18) Goering, H. L.; Seitz, E. P., Jr.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5304.
(19) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986.
(20) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1983**, *48*, 546.

Table III. Product Distribution for Stoichiometric and Catalytic Alkylation of *trans*-α-Methyl-γ-phenylallyl Pivalate (7-OPiv) with *n*-Butyl Reagents[a]

expt	reagent	product distribtn, %[b] 9	10	% yield[c]
1[d]	BuCu(CN)Li	50	50	65
2[e]	BuCu(CN)MgBr	2.2	97.8	74
3[f]	BuMgBr/CuCN (100:1)	2.6	97.4	99
4[e,g]	Bu_2CuLi	94	6	86
5[e]	$Bu_2CuMgBr$	85	15	78
6[f]	BuMgBr/CuCl (100:1)	89	11	96

[a] All reactions carried out in ether. Reaction temperature −10 °C for expt 1, 2, and 5 and 0 °C for other cases. [b] Compositions determined by capillary GC. [c] Yield of isolated products. [d] Cuprate/ester ratio was 5. [e] Cuprate/ester ratio was 2. [f] Grignard reagent/ester ratio was 2. [g] Data taken from ref 18 and are for acetate instead of pivalate.

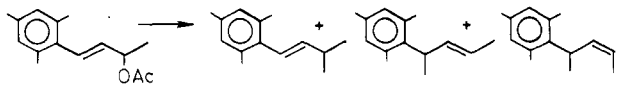
CuCN (i.e., RMgBr + CuCN ⇌ RCu + Mg(CN)Br). The present results show that there is no bromide–cyanide exchange either (Br^- + CuCN ⇌ CuBr + CN^-) even though the Br:CN ratio is high.

According to this proposal, with the other cuprous salts there is immediate metal–metal exchange (eq 9) followed by conversion of the intermediate alkylcopper to the dialkylcuprate (eq 10).

In support of this view are the results for stoichiometric alkylations of 7-OPiv with *n*-BuCu(CN)MgBr (*n*-BuMgBr:CuCN = 1:1) and *n*-$Bu_2CuMgBr$ (*n*-BuMgBr:CuCl = 2:1) shown in Table III. The regiochemistry for stoichiometric alkylation with *n*-BuCu(CN)MgBr (expt 2) is the same as that for the CuCN-catalyzed reaction (expt 3). Unlike with CuCN, no reaction occurs with *n*-BuMgBr:CuCl (1:1). In this case only the insoluble *n*-BuCu is formed (eq 9). The regiochemistry for alkylation with *n*-$Bu_2CuMgBr$ (expt 5) is also very similar to that for the CuCl-catalyzed reaction (expt 6).

Product distributions for stoichiometric alkylations of 7-OPiv with *n*-BuCu(CN)Li and *n*-Bu_2CuLi are included in Table III. Comparison of experiment 1 with 2, and 4 with 5, shows that magnesium cuprates are more regiospecific (excess γ-alkylation) than lithium cuprates. Other workers have also noticed this difference for stoichiometric alkylations of allylic carboxylates.[21]

In another experiment it was found that alkylation of 7-OPiv with a 1:1 mixture of *n*-BuCu(CN)Li and $MgBr_2 \cdot Et_2O$ gives the same product distribution as *n*-BuCu(CN)MgBr, i.e., 2.5% **9** and 97.5% **10**. In earlier work[2] we investigated the regiochemistry of alkylation of γ-(2,4,6-trimethylphenyl)-α-methylallyl acetate (11-OAc) with $LiCuMe_2$ and LiCu(CN)Me and observed the product distributions shown under eq 11. In this work we have found that addition of 1 equiv of $MgBr_2 \cdot Et_2O$ to the LiCu(CN)Me prior to reaction results in a substantial increase in regiospecificity and increases the amount of γ-alkylation from 43% to 92% as indicated under eq 11.



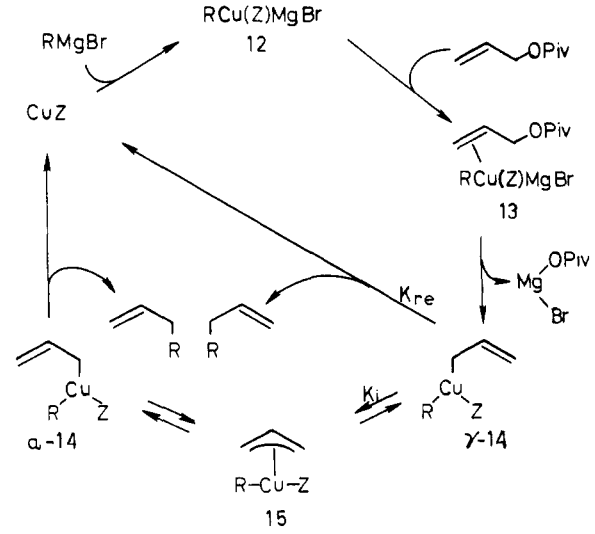
11-OAc

$LiCuMe_2$	97.5	2.5	--
LiCu(CN)Me	57	35	8
LiCu(CN)Me:$MgBr_2$	8	72	20

(11)

(21) Liu, H. J.; Ho, L.-K. *Can. J. Chem.* **1983**, *61*, 632.

Scheme I. Catalytic Cycle for Copper(I)-Catalyzed Cross Coupling of Allylic Carboxylates with Grignard Reagents



The reason for the difference in reactivity[7b,8,22] and regiochemistry for magnesium and lithium cuprates is not clear. This may result from a difference in the state of aggregation or solubility.

For some reason the cuprates involved in the catalytic process (excess Grignard reagent) are more reactive than preformed cuprates. To account for this difference it has been proposed[4a] that so-called higher order cuprates,[23] $R_3Cu(MgX)_2$, are formed in the presence of excess Grignard reagents and that trialkylcopper(I) dianions (R_3Cu^{-2}) are the active species. However, in an important recent study it has been shown by ^7Li NMR spectroscopy that Me_2CuLi in the presence of excess MeLi does not form higher order cuprates in either ether or THF and is simply a mixture of the dimethylcuprate and free methyllithium.[24] This finding is compatible with our earlier observations[18] that alkylation of allylic carboxylates with dialkylcuprates is invariably accompanied by carbonyl attack if excess alkyllithium is present, i.e. RLi:RCu ratio >1. From this we conclude that higher order cuprates are not involved in the catalytic reactions and that the active species are Gilman reagents generated as shown by eq 8–10.

In addition to enhanced reactivity, the cross coupling to decomposition ratio is more favorable for cuprates generated in the catalytic process and this results in improved yields, especially with regard to the organometallic partner. We believe that the composition of cuprates in the catalytic and stoichiometric reactions is probably the same and that the different properties result from differences in aggregation. In one case the cuprate is present in very low concentrations in a catalytic cycle and in the other the total amount of preformed cuprate is present at the outset. Put another way, in the catalytic reaction the relatively thermally unstable cuprates are consumed as generated and the organometallic reagent is a stable Grignard reagent.

A mechanism that correlates the present results is shown in Scheme I. The cuprate (**12**) at the top of the catalytic cycle is generated as shown by eq 8 or 10. Thus, Z = CN if the catalyst is CuCN (eq 8) and Z = R with other cup-

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rous salts (eq 10). The main features of this scheme are the same as those proposed earlier for stoichiometric alkylations with alkylcuprates.[1,2] Olefin–cuprate π complexation to give **13** followed by oxidative addition with complete allylic rearrangement leads to the σ-allylcopper(III) complex (γ-**14**).[25] The overall regiochemistry of cross coupling is determined by the relative rates at which γ-**14** undergoes reductive elimination (k_{re}) (regiospecific γ-coupling) and isomerization (k_i) to the π-allyl complex (**15**) which results in loss of regiochemistry. When Z = CN, reductive elimination results in formation of stable CuCN together with the γ-cross-coupling product. In this case the k_{re}/k_i ratio for **14** is large and regiospecificity (excess γ-coupling) is observed. If Z = R, reductive elimination gives relatively unstable R–Cu together with product. In this case allylic rearrangement of **14** by the $\sigma \rightleftarrows \pi$ mechanism becomes important and loss of regiospecificity is observed. Under stoichiometric conditions with R_2CuLi, the k_i/k_{re} ratio is so high that almost complete equilibration of α- and γ-**14** occurs prior to reductive elimination and regiospecificity is almost completely lost.[18,25b]

According to this proposal, when the ligand (R) in γ-**14** is phenyl or vinyl the k_i/k_{re} ratio is large even if Z = CN. In these cases the σ-allyl complex (**14**) undergoes extensive, if not complete, equilibration prior to reductive elimination. We have no explanation for why $k_{re} \gg k_i$ with alkyl ligands and $k_i \gg k_{re}$ when the ligand is vinyl or phenyl. Or can we explain the difference in regiochemistry for lithium and magnesium cuprates. Our mechanistic proposals do not include the metallic counterion of the cuprates. According to our mechanistic proposals, for some unknown reason, the k_{re}/k_i ratio is higher when magnesium(II) is present than when only lithium(I) is present. This may have something to do with states of aggregation of intermediates or with configurations of the d^8 square-planer copper(III) complexes (**14**).

Experimental Section

General Methods. All reactions were carried out under a positive pressure of dry nitrogen. Magnesium "turnings for Grignard reactions" (Fischer Scientific Company) was used without purification. Cuprous chloride[26] and cyanide[27] were prepared by published procedures. Commercial cuprous bromide (Alfa) was used without purification. Cuprous iodide was purified by a known method[28] and the thiocyanate was purified by the same method except that CuSCN and KSCN were used instead of the iodide salts. Commercial anhydrous ether (Mallinckrodt), magnesium bromide etherate (Aldrich), and all of the organic halides (Aldrich) were used without purification. Tetrahydrofuran was distilled from Na/benzophenone ketyl and stored under dry nitrogen. Pyridine and dichloromethane were dried by distillation from calcium hydride and stored under nitrogen. Grignard reagents and alkyllithium solutions were standardized by titration with 2-butanol using *o*-phenanthroline as an indicator.[29] Vinylmagnesium bromide was purchased from Aldrich as a 1 M THF solution. Propen-2-ylmagnesium bromide was prepared in THF.[30] Other Grignard reagents were prepared in ether. All equipment was thoroughly cleaned and dried before use. Boiling points and melting points are uncorrected.

Mass spectra were obtained with an AEI MS-902 high-resolution instrument. Proton NMR spectra were obtained with a JEOLCO MH-100, Brucker WP200 SY, or Brucker WH270 instrument. Proton-decoupled ^2H and ^{13}C NMR spectra were obtained with a JEOLCO FX-200 spectrometer operating at 30.6 MHz (^2H) or 50.1 MHz (^{13}C). Deuterium chemical shifts are reported in ppm relative to internal $CDCl_3$ (set to 7.24 ppm). Chemical shifts for ^{13}C are referenced to the center peak of the $CDCl_3$ triplet (77.0 ppm).

Materials. ***cis*-5-Methyl-2-cyclohexenyl mesitoate (1-OTMB)** was prepared by reacting **1-OH**[31] with a 20% excess of mesitoyl chloride[32] in 2.5 equiv of dry pyridine at room temperature. After stirring overnight the excess acid chloride was quenched with 5 drops of water and the solution was stirred 15 min. The reaction mixture was diluted with 5 mL of water and extracted with pentane (4 × 10 mL). The organic extract was washed with cold dilute aqueous $CuSO_4$ (3×), saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. After purification by chromatography (silica gel, hexane/ether eluent), 1-OTMB was obtained as a light yellow oil: IR (neat) 3030 (w), 2950 (m), 2920 (m), 2870 (m), 2830 (w), 1715 (s), 1650 (w), 1610 (m), 1575 (m), 1275 (s); NMR (δ, CCl_4) 6.63 (s, 2 H), 5.7–5.3 (m, 3 H), 2.17 (s, 6 H), 2.11 (s, 3 H), 2.1–1.0 (m, 5 H), 0.93 (d, 3 H, J = 6 Hz); high-resolution mass spectrum, calcd for $C_{17}H_{22}O_2$ m/e 258.1619, found m/e 258.1620. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.11; H, 8.65.

α-Deuterio-*cis*-5-methyl-2-cyclohexenyl mesitoate (α-D-1-OTMB) was prepared from the corresponding alcohol (α-D-1-OH)[31] by the same method.

2-Cyclohexenyl mesitoate (3-OTMB) was prepared from 2-cyclohexenol (**3-OH**)[16] by the method described above and had the following: bp 136 °C (0.2 mm); IR (neat) 3020–2820 (m), 1720 (s), 1615 (s), 1450 (m), 1435 (m), 1270 (s), 1175 (s), 1085 (s), 1060 (m), 1050 (m), 1010 (w), 915 (m), 855 (m); NMR (δ, $CDCl_3$) 6.82 (s, 2 H), 5.98 (dt, 1 H, J = 10, 3.6 Hz), 5.85 (d, 1 H, J = 10 Hz), 5.53 (br s, 1 H), 2.29 (s, 6 H), 2.25 (s, 3 H), 1.6–2.1 (m, 6 H); ^{13}C NMR (δ, $CDCl_3$) 138.8, 134.8, 132.7, 128.7 (×2), 125.4, 68.5, 28.3, 24.7, 20.9, 19.5, 18.8; high-resolution mass spectrum, calcd for $C_{16}H_{20}O_2$ m/e 244.1463, found m/e 244.1464.

α-Deuterio-2-cyclohexenyl mesitoate (α-D-3-OTMB) was prepared from α-D-2-cyclohexenol (α-D-**3-OH**)[16] by the same method and had the following: bp 141–147 °C (0.2 mm); IR (neat) 3030–2830 (m), 2070 (w), 1720 (s), 1610 (m), 1430 (m), 1280 (s), 1170 (s), 1090 (s), 1075 (s), 910 (m), 850 (m); NMR (δ, $CDCl_3$) 6.83 (s, 2 H), 5.99 (dt, 1 H, J = 10.2, 3.6 Hz), 5.84 (d, 1 H, J = 10.2 Hz), 2.30 (s, 6 H), 2.27 (s, 3 H), 1.5–2.1 (m, 6 H); ^{13}C NMR (δ, $CDCl_3$) 169.6, 138.8, 134.8, 132.8, 128.2 (×2), 125.3, 28.2, 24.8, 20.9, 19.5, 18.7; ^2H NMR (δ, $CHCl_3$) 5.55 (97%), 5.07 (3%) [The latter signal results from contamination with 3% cyclohexyl mesitoate.]; high-resolution mass spectrum, calcd for $C_{18}H_{19}DO_2$ m/e 245.1525, found m/e 245.1524.

2-Cyclohexenyl pivalate (3-OPiv), α-deuterio-2-cyclohexenyl pivalate (α-D-3-OPiv), and γ-deuterio-2-cyclohexenyl pivalate (γ-D-3-OPiv) were prepared from **3-OH**, α-D-**3-OH**, and γ-D-**3-OH**[16] and pivaloyl chloride by the method described above for preparation of mesitoate derivatives. After purification **3-OPiv** had the following: bp 94–97 °C (15 mm); IR (neat) 3030–2820 (m), 1810 (w), 1720 (s), 1475 (m), 1450 (w), 1390 (w), 1360 (w), 1280 (s), 1050 (s), 1010 (m), 920 (m), 720 (m); NMR (δ, $CDCl_3$) 5.93 (ddt, 1 H, J = 10.1, 1.0, 3.6 Hz), 5.66 (ddt, 1 H, J = 10.1, 3.5, 2.0 Hz), 5.22 (br s, 1 H), 2.0–2.1 (m, 2 H), 1.6–2.0 (m, 4 H), 1.19 (s, 9 H); ^{13}C NMR (δ, $CDCl_3$) 177.4, 131.8, 125.6, 67.2, 27.9, 26.8 (×3), 24.6, 18.6; high resolution mass spectrum, calcd for $C_{11}H_{18}O_2$ m/e 182.1307, found m/e 182.1310. Capillary GC (175 ft, UCON LB550-X, 135 °C) showed this sample contained ~3% cyclohexyl pivalate. This contaminant is inert under the conditions of the cross-coupling reactions and thus has no effect on the results.

α-D-**3-OPiv** had ^2H NMR (δ, $CHCl_3$): 5.13. γ-D-**3-OPiv** had ^2H NMR (δ, $CHCl_3$): 5.90. High-resolution mass spectrum: calcd for $C_{11}H_{17}DO_2$ m/e 183.1368, found 183.1370.

3-Deuterio-2-phenyl-2-propenyl pivalate (5) was prepared from 3-deuterio-2-phenyl-2-propen-1-ol[17] and pivaloyl chloride in pyridine in the usual manner. After purification, **5** had the following: bp 80–82 °C (0.4 mm); IR (neat) 3060 (w), 3040 (w),

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3000 (w), 2950 (m), 2910 (m), 2885 (w), 2850 (w), 1730 (s), 1720 (s), 1495 (w), 1477 (s), 1457 (m), 1443 (m), 1397 (m), 1365 (w), 1280 (s), 1145 (s), 1030 (m), 975 (w), 860 (w), 765 (m), 470 (w), 698 (m); NMR (δ, $CDCl_3$) 7.2–7.65 (m, 5 H), 5.51 (d, 0.7 H, J = 3.3 Hz), 5.35 (d, 0.5 H, J = 1.1 Hz), 4.97 (s, 2 H), 1.18 (s, 9 H); ^2H NMR (δ, $CHCl_3$) 5.60 (34%), 5.41 (66%); high-resolution mass spectrum, calcd for $C_{14}H_{17}DO_2$ m/e 219.1364, found m/e 219.1369.

α-Methyl-γ-phenylallyl pivalate (7-OPiv) was prepared from α-methyl-γ-phenylallyl alcohol[18] and pivaloyl chloride in dry pyridine by the usual method. After distillation, bp 109 °C (1.2 mm), the colorless oil solidified and had the following: mp 41–42.5 °C; IR (neat) 2970, 2925, 1732, 1493, 1480, 1459, 1450, 1398, 1370, 1282, 1165, 1150, 1044, 968, 750, 695; NMR (δ, CCl_4) 7.46–7.04 (m, 5 H), 6.56 (d, 1 H, J = 15.2 Hz), 6.11 (dd, 1 H, J = 15.2, 6 Hz), 5.46 (m, 1 H), 1.38 (d, 3 H, J = 7.2 Hz), 1.24 (s, 9 H); high-resolution mass spectrum, calcd for $C_{15}H_{20}O_2$ m/e 232.1462, found 232.1463. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.80; H, 8.90.

Copper(I)-Catalyzed Reaction of *n*-Butylmagnesium Bromide with α-Deuterio-*cis*-5-methyl-2-cyclohexenyl Pivalate (α-D-2-OTMB). In a typical experiment a flask equipped with a magnetic stirrer and septum was charged with 54 mg (0.6 mequiv) of CuCN. After flushing with dry nitrogen, 2 mL of anhydrous ether was added and the suspension was chilled to −10 °C. An ether solution of 6 mmol of *n*-BuMgBr (prepared from 987 mg of *n*-BuBr and 146 mg of Mg in 8 mL of ether) was added through a cannula, and after stirring the mixture 10 min, a solution of 778 mg (3 mmol) of α-D-1-OTMB in 2 mL of ether was added. The cooling bath was removed and the mixture was stirred at room temperature for 6.5 h after which the reaction was quenched with 2 mL of aqueous NH_4Cl. The resulting mixture was filtered, the precipitate washed with ether, and the ether solution was dried ($MgSO_4$). Removal of the solvent by fractionation followed by column chromatography (silica gel, pentane/ether) and vacuum distillation gave 289 mg (63% yield) of clear mobile oil, bp 58–60 °C (7.4 mm). This product (**2-d_1**) had the following: IR (neat) 3020 (m), 2945 (s), 2910 (s), 2900 (s, sh), 2860 (s), 2840 (s, sh), 2820 (m), 2240 (w), 1640 (w), 1465 (m), 1455 (m), 1430 (w), 1375 (m), 895 (w), 730 (w), 710 (w); NMR (δ, $CDCl_3$) 5.63 (br s, 1 H), 2.20–1.90 (br m, 2 H), 1.90–1.68 (br m, 1 H), 1.68–1.50 (m, 9 H), 1.05–0.70 (m, 3 H), 0.93 (d, 3 H, J = 7.5 Hz); high-resolution mass spectrum, calcd for $C_{11}H_{19}D$ m/e 153.1622, found m/e 153.1628. The distribution of deuterium in the product was determined as described earlier.[2]

Capillary GC of the above product gave a single peak and we were unable to resolve *cis*- and *trans*-3-*n*-butyl-5-methylcyclohexene by this method. In other work[33a] we confirmed that cis and trans isomers of the saturated analogue, 3-*n*-butyl-1-methylcyclohexane, are separated by capillary GC (UCON, 94 ft, LB-550-X, 100 °C).[33b] Hydrogenation of 90 mg of the above olefinic product in 4 mL of acetic acid over PtO_2 gave a mixture of 97% *trans*- and 3% *cis*-3-*n*-butyl-1-methylcyclohexane. These stereoisomers were identified by comparison with authentic samples.[33a]

The same procedure was used for the CuCl-catalyzed reaction of *n*-BuMgBr with α-D-1-OTMB. The results of these experiments are shown under eq 2.

Reaction of 2-Cyclohexenyl Mesitoate (3-OTMB) with Grignard Reagents Containing 3 mol % CuCN. In a typical experiment a flask equipped with a septum and stirring bar was flushed with dry nitrogen and charged with 45–55 mg (~0.6 mmol) of CuCN and 70 mL of dry ether. A solution of 20 mmol of *n*-BuMgBr in 20 mL of ether was added and the resulting mixture was stirred a few minutes at 0 °C after which a solution of 2.44 g (10 mmol) of 3-OTMB in 10 mL of ether was added with a syringe. The resulting reaction mixture was stirred for 4 h at room temperature and then quenched with water and extracted with 5% HCl, 10% NaOH (2 × 15 mL), and saturated $NaHCO_3$. After drying ($MgSO_4$) the ether was removed by fractionation and product distilled under reduced pressure. The same procedure was used for the other Grignard reagents in Table I except allyl- and vinylmagnesium bromide. Later experiments showed that yields and regiochemistry are unchanged if the CuCN is reduced to 1 mol % relative to Grignard reagent or if the Grignard reagent is added to a stirred suspension of CuCN in an ether solution of the ester.

Reaction with vinylmagnesium bromide (1 M in THF) with 3 mol % CuCN gave only an 11% yield of 3-vinylcyclohexene. Addition of a second 50-mg portion of CuCN after 2 h increased the yield to 57% (20% of unreacted 3-OTMB was recovered).

Addition of ethereal allylmagnesium bromide to a suspension of CuCN in ether at 0 °C results in immediate formation of a black precipitate, presumably Cu(O). Increasing the amount of CuCN to 25 mol % on the basis of Grignard reagent, lowering the mixing temperature to −55 °C, and allowing the reaction mixture to warm to 0 °C over a period of 45 min resulted in a 66% yield of 3-allylcyclohexene. Results of these experiments are summarized in Table I.

Reaction of α-D-3-OTMB with Grignard Reagents Containing 1 mol % CuCN. These reactions were carried out in the same manner as above except that the amount of CuCN was reduced to 1 mol % and the reaction time was 2 h instead of 4 h. Results of these experiments are shown under eq 4. With *i*-Pr-, *n*-Bu-, and *t*-BuMgBr only 1-D-4 was observed by ^2H NMR (signals at 5.2 (R = *i*-Pr), 5.66 (R = *n*-Bu), and 5.75 (R = *t*-Bu)). As little as 1% 3-D-4 would have been detected.

The indicated results for PhMgBr were reproducible and the same for reactions carried out at 0 °C and room temperature. In other experiments it was found that the same deuterium distribution (~53% 3-D-4 and ~47% 1-D-4) results from reaction of α-D- and γ-D-3-OPiv with PhMgBr. The ^2H NMR signals for 4-d_1 are 3.5 ppm for 3-D-4 and 6.0 ppm for 1-D-4.

Cross-Coupling Products for Reaction of 2-Cyclohexenyl Mesitoate or Pivalate (3-OTMB and 3-OPiv) with Grignard Reagents. The products (4) of the reactions summarized in Table I were as follows.

3-Methylcyclohexene:[34,35] bp 49–50 °C (135 mm); IR (neat) 3030 (s), 2970–2830 (s), 1645 (w), 1455 (m), 1370 (m), 1315 (w), 1115 (w), 990 (w), 975 (w), 860 (m), 720 (s), 700 (w), 670 (m); NMR (δ, $CDCl_3$) 5.63 (ddd, 1 H, J = 10.0, 3.3, 2.3 Hz), 5.52 (dd, 1 H, J = 10.0, 1.8 Hz), 2.15–2.25 (br s, 1 H), 1.9–2.0 (m, 2 H), 1.65–1.85 (m, 2 H), 1.45–1.60 (m, 1 H), 1.10–1.25 (m, 1 H), 0.96 (d, 3 H, J = 7.3 Hz); ^{13}C NMR (δ, $CDCl_3$) 133.5, 126.3, 31.4, 30.2, 25.1, 21.7, 21.5; high-resolution mass spectrum, calcd for C_7H_{12} m/e 96.0939, found m/e 96.0939.

3-Ethylcyclohexene:[35] bp 60–62 °C (63 mmHg); IR (neat) 3000 (s), 2960–2820 (s), 1645 (m), 1455 (s), 1375 (s), 1285 (w), 1260 (w), 1245 (w), 1145 (w), 1110 (m), 980 (m), 880 (s), 720 (s), 690 (m), 660 (s); NMR (δ, $CDCl_3$) 5.70 (d, 1 H, J = 10.9 Hz), 5.56 (d, 1 H, J = 10.9 Hz), 1.9–2.05 (m, 3 H), 1.65–1.9 (m, 2 H), 1.1–1.65 (m, 4 H), 0.91 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (δ, $CDCl_3$) 132.0, 126.6, 37.0, 29.1, 28.8, 25.5, 21.6, 11.3; high-resolution mass spectrum, calcd for C_8H_{14} m/e 110.1096, found m/e 110.1109.

3-Vinylcyclohexene:[36] bp 30 °C (17 mm); IR (neat) 3080 (m), 3020 (s), 2830–3000 (s), 1640 (s), 1450 (m), 1440 (m), 1420 (w), 1000 (s), 920 (s), 730 (s); NMR (δ, $CDCl_3$) 5.7–5.9 (m, 2 H), 5.5–5.65 (d, 1 H), 4.95–5.1 (m, 1 H), 2.8 (br s, 1 H), 1.9–2.1 (m, 2 H), 1.35–1.9 (m, 5 H); high-resolution mass spectrum, calcd for C_8H_{12} m/e 108.0939, found m/e 108.0939.

3-(2-Propyl)cyclohexene:[35] bp 47 °C (15 mm); IR (neat) 3020 (m), 2830–2970 (s), 1470 (m), 1450 (w), 1390 (m), 1370 (m), 730 (s), 660 (m); NMR (δ, $CDCl_3$) 5.69 (dd, 1 H, J = 10.7, 2.5 Hz), 5.59 (d, 1 H, J = 10.7 Hz), 1.95 (br s, 3 H), 1.4–1.85 (m, 3 H), 1.15–1.40 (m, 2 H), 0.89 (d, 3 H, J = 6.8 Hz), 0.87 (d, 3 H, J = 6.8 H); ^{13}C NMR (δ, $CDCl_3$) 130.8, 127.4, 41.9, 32.4, 25.8, 25.5, 22.3, 19.6, 19.4; high-resolution mass spectrum, calcd for C_9H_{16} m/e 124.1252, found m/e 124.1252.

3-Allylcyclohexene:[37] bp 25 °C (25 mm); NMR (δ, $CDCl_3$) 5.5–5.9 (m, 3 H), 4.95–5.1 (m, 2 H), 1.9–2.25 (m, 5 H), 1.6–1.9 (m,

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2 H), 1.4–1.6 (m, 1 H), 1.15–1.35 (m, 1 H); high-resolution mass spectrum, calcd for C_9H_{14} m/e 122.1095, found m/e 122.1083.

3-*n*-Butylcyclohexene:[4c,35] bp 76 °C (17 mm); IR (neat) 3010 (m), 2930–2840 (s), 1640 (w), 1605 (w), 1450 (m), 1370 (w), 1255 (m), 1160 (w), 1070 (m), 710 (m), 660 (m); NMR (δ, $CDCl_3$) 5.64 (br d, 1 H, J = 11.0 Hz), 5.57 (d, 1 H), 1.9–2.1 (m, 3 H), 1.6–1.85 (m, 2 H), 1.4–1.6 (m, 1 H), 1.2–1.4 (m, 7 H), 0.9 (br t, 3 H); ^{13}C NMR (δ, $CDCl_3$) 132.4, 126.5, 36.2, 35.2, 29.2 (×2), 25.4, 22.9, 21.6, 14.0; high-resolution mass spectrum, calcd for $C_{10}H_{18}$ m/e 138.1408, found m/e 138.1409.

3-Propen-2-ylcyclohexene:[38] bp 60 °C (20 mm); IR (neat) 3070 (m), 3020 (s), 2960–2830 (s), 1640 (s), 1450 (s), 1370 (s), 1305 (w), 1290 (w), 1290 (w), 1230 (w), 1160 (w), 1140 (w), 1050 (w), 960 (w), 900 (s), 895 (s), 730 (m), 690 (m), 650 (m); NMR (δ, $CDCl_3$) 5.77 (dd, 1 H, J = 10.1, 2.36 Hz), 5.57 (dd, 1 H, J = 10.1, 2.17 Hz), 4.76 (s, 1 H), 4.72 (s, 1 H), 2.75 (br s, 1 H), 1.95–2.05 (m, 2 H), 1.65–1.9 (m, 5 H), 1.4–1.65 (m, 2 H); high-resolution mass spectrum, calcd for C_9H_{14} m/e 122.1096, found m/e 122.1096.

3-(2-Methylpropyl)cyclohexene:[39] bp 66 °C (17 mm); NMR (δ, $CDCl_3$) 5.69 (d, 1 H, J = 10.1 Hz), 5.52 (d, 1 H, J = 10.1 Hz), 2.05–2.2 (m, 1 H), 1.9–2.05 (m, 2 H), 1.65–1.85 (m, 3 H), 1.45–1.60 (m, 1 H), 1.05–1.25 (m, 3 H), 0.89 (d, 3 H, J = 6.5 Hz), 0.87 (d, 3 H, J = 6.5 Hz); ^{13}C NMR (δ, $CDCl_3$) 132.4, 126.4, 46.1, 32.9, 29.5, 25.6, 25.1, 23.0, 22.6, 21.6; high-resolution mass spectrum, calcd for $C_{10}H_{18}$ m/e 138.1408, found 138.1419.

3-(2-Butyl)cyclohexene:[39] bp 70 °C (17 mm); [This product was shown to be a 50:50 mixture of the two diastereomers by ^1H and ^{13}C NMR spectroscopy.]; NMR (δ, $CDCl_3$) 5.69 (m, 1 H), 5.53 (d, 1 H), 2.1 (br s, 1 H), 1.95 (br s, 2 H), 1.1–1.8 (m, 7 H), 0.7–0.9 (m, 6 H); ^{13}C NMR (δ, $CDCl_3$) 131.8, 130.4, 127.5, 127.2, 40.5, 40.0, 39.2 (×2), 26.8, 26.4, 25.6, 24.4, 22.6 (2×), 22.5 (2×), 15.9, 15.4, 12.0 (×2); high-resolution mass spectrum, calcd for $C_{10}H_{18}$ m/e 138.1408, found m/e 138.1409.

3-(*tert*-Butyl)cyclohexene:[35,40] bp 64 °C (17 mm); NMR (δ, $CDCl_3$) 5.70 (m, 2 H), 1.7–2.0 (m, 5 H), 1.4–2.6 (m, 1 H), 1.1–1.3 (m, 1 H), 0.87 (s, 9 H); ^{13}C NMR (δ, $CDCl_3$) 126.5, 125.2, 43.2, 29.9, 24.4 (×3), 22.5, 21.7, 20.1; high-resolution mass spectrum, calcd for $C_{10}H_{18}$ m/e 138.1408, found m/e 138.1409.

3-Phenylcyclohexene:[41] bp 106 °C (17 mm); NMR (δ, $CDCl_3$) 7.1–7.4 (m, 5 H), 5.9 (m, 1 H), 5.7 (d, 1 H), 3.39 (br s, 1 H), 1.9–2.1 (m, 3 H), 1.4–1.8 (m, 3 H); ^{13}C NMR (δ, $CDCl_3$) 130.1, 128.5, 128.0 (×2), 127.5 (×2), 127.0, 125.8, 41.8, 32.5, 24.9, 21.1; high-resolution mass spectrum, calcd for $C_{12}H_{14}$ m/e 158.1095, found m/e 159.1096.

3-(4-Methoxyphenyl)cyclohexene:[42] bp 160 °C (17 mm); NMR (δ, $CDCl_3$) 7.13 (d, 2 H, J = 8.6 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 5.86 (d, 1 H), 5.69 (dd, 1 H, J = 10.1, 2.0 Hz), 3.79 (s, 3 H), 3.35 (br s, 1 H), 1.9–2.1 (m, 3 H), 1.4–1.8 (m, 3 H); ^{13}C NMR (δ, $CDCl_3$) 157.8, 138.6, 130.5, 128.4 (×2), 127.9, 113.6 (×2), 55.0, 40.9, 32.6, 25.0, 21.1; high-resolution mass spectrum, calcd for $C_{13}H_{16}O$ m/e 188.1201, found m/e 188.1200.

3-Cyclohexylcyclohexene:[43] bp 113 °C (15 mm); NMR (δ, $CDCl_3$) 5.68 (dd, 1 H, J = 10.7, 2.3 Hz), 5.60 (d, 1 H, J = 10.7 Hz), 1.95 (m, 3 H), 1.65 (br s, 7 H), 0.95–1.60 (m, 8 H); ^{13}C NMR (δ, $CDCl_3$) 128.2, 124.4, 40.2, 38.3, 27.7, 27.3, 24.2 (×2), 23.2, 22.9, 19.7; high-resolution mass spectrum, calcd for $C_{12}H_{20}$ m/e 164.1565, found m/e 164.1565.

Reaction of 2-Cyclohexenyl Pivalate (3-OPiv) with 10% Excess Grignard Reagent Containing 0.9 mol % CuCN. In a typical experiment a flask was flushed with dry nitrogen and charged with 4.3 mg (0.048 mmol) of CuCN, 0.88 g (4.8 mmol) of 3-OPiv, and 17 mL of anhydrous ether. Standardized *n*-BuMgBr (7.8 mL, 5.2 mmol) was added at room temperature. The 3-OPiv/BuMgBr/CuCN ratio was 100:110:1 and [CuCN] = 0.002 M. Stirring was continued for 1 h followed by isolation as described above, GC analysis of the crude product, and distillation. Under these conditions ~30% carbonyl attack (to give cyclohexenol and tertiary alcohol) occurs with MeMgBr but none was observed with the other Grignard reagents. The GC yields (determined from peak areas of the ester and product) for various reagents was as follows: *i*-PrMgBr (100%), *n*-BuMgBr (79–92% increased to 98–100% at 0 °C), PhMgBr (100%). Yield of isolated products ranged from 78% to 94%.

Reactions of 3-Deuterio-2-phenyl-2-propenyl Pivalate (5) with Grignard Reagents Containing 1 mol % CuCN or CuCl. In a typical experiment, 6.6 mg (0.073 mmol) of CuCN and 805 mg (3.70 mmol) of **5** were placed in a reaction vessel. The flask was purged with dry nitrogen after which 28 mL of ether and 7 mmol of *t*-BuMgBr in 8 mL of ether were added at room temperature. After being stirred for 1 h, the reaction was worked up in the usual way. Alkyl Grignard reagents gave only the γ-coupling product (3-D-**6**) (^2H signal at 2.4–2.6 ppm). A vinyl deuterium signal could not be detected—as little as 1% should be detectable. With PhMgBr integration of the ^2H spectrum showed the product distribution to be 54% 3-D-**6** (^2H signal at 3.85 ppm) and 46% 1-D-**6** (^2H signal 5.5 and 5.08 ppm).

Cross-Coupling Products for Reaction of 3-Deuterio-2-phenyl-2-propenyl Pivalate (5) with Grignard Reagents. 3-Deuterio-4,4-dimethyl-2-phenyl-1-pentene (3-D-**6**, R = *t*-Bu): IR (neat) 3080 (m), 3050 (m), 3020 (m), 2860–2950 (s), 1620 (s), 1600 (m), 1575 (m), 1495 (m), 1470 (s), 1445 (m), 1395 (m), 1365 (m), 1240 (m), 1220 (m), 900 (s), 760 (s), 740 (s), 700 (s); NMR (δ, $CDCl_3$) 7.25–7.5 (m, 5 H), 5.24 (d, 1 H, J = 2.1 Hz), 5.01 (d, 1 H, J = 2.1 Hz), 2.46 (s, 1.2 H), 0.80 (s, 9 H); ^2H NMR (δ, $CHCl_3$) 2.52. Spectral properties in agreement with those published for unlabeled **6** (R = *t*-Bu).[44]

3-Deuterio-4-methyl-2-phenyl-1-pentene (3-D-6, R = *i*-Pr):[44] bp 110 °C (20 mm); IR (neat) 3060 (m), 3040 (m), 3010 (m), 2940–2850 (s), 1620 (m), 1595 (w), 1565 (w), 1485 (s), 1455 (s), 1435 (m), 1375 (s), 1360 (s), 1025 (m), 890 (s), 770 (s), 735 (m), 695 (s); NMR (δ, $CDCl_3$) 7.2.7.5 (m, 5 H), 5.26 (d, 1 H, J = 1.7 Hz), 5.02 (s, 1 H), 2.38 (dd, 1.2 H, J = 7.2, 1.0 Hz), 1.66 (dq, 1 H, J = 7.2, 6.6 Hz), 0.87 (d, 6 H, J = 6.6 Hz); ^2H NMR (δ, $CHCl_3$) 2.57; ^{13}C NMR (δ, $CDCl_3$) 147.8, 141.5, 128.1 (2×), 127.1, 126.2 (×2), 113.3, 45.2, 26.3, 22.3 (×2); high-resolution mass spectrum, calcd for $C_{12}H_{15}D$ m/e 161.1314, found m/e 161.1314.

2,3-Diphenyl-1-propene-*1*/*3*-*d* (mixture of 1-D- and 3-D-6, R = Ph): bp 107 °C (0.5 mm); IR (neat) 3080 (s), 3020 (s), 2900 (m), 1630 (m), 1600 (s), 1570 (w), 1500 (s), 1460 (s), 1080 (m), 1040 (s), 910 (s), 790 (s), 780 (s), 740 (s), 730 (s), 700 (s); NMR (δ, $CDCl_3$) 7.15–7.5 (m, 10 H), 5.49 (d, 0.85 H, J = 0.8 Hz), 5.02 (m, 0.7 H), 3.83 (s, 1.45 H); ^2H NMR (δ, $CHCl_3$) 5.55 (13%), 5.08 (33%), 3.85 (54%). The spectral properties agree with those published for unlabeled **6** (R = Ph).[45]

3-Deuterio-2-phenyl-1-pentene (3-D-6, R = *n*-Bu): IR (neat) 3060 (m), 3040 (m), 3005 (m), 2930 (s), 2900 (s), 2840 (s), 1623 (m), 1598 (w), 1570 (w), 1490 (w), 1480 (w), 1465 (m), 1455 (m), 1440 (m), 1377 (w), 1075 (w), 1030 (m), 895 (s), 773 (s), 466 (m), 695 (s); NMR (δ, $CDCl_3$) 7.65–7.10 (m, 5 H), 5.22 (d, 1 H, J = 1.6 Hz), 5.01 (t, 1 H, J = 1.6 Hz), 2.48 (br m, 1 H), 1.55–1.10 (m, 6 H), 0.88 (br t, 3 H); high-resolution mass spectrum, calcd for $C_{13}H_{17}D$ m/e 175.1466, found m/e 175.1469. This product also identified by comparison of capillary GC retention time (UCON, 94 ft, LB-550-X, 160 °C) with that of an authentic sample synthesized by the Wittig reaction.

Reaction of *trans*-α-Methyl-γ-phenylallyl Pivalate (7-OPiv) with Grignard Reagents Containing 1 mol % Cuprous Salts. In a typical experiment a flask equipped with a stirring bar and septum was charged with 3.6 mg (0.04 mmol) of CuCN and flushed with nitrogen. Anhydrous ether (1 mL) was added and the suspension was cooled to −10 °C after which 4.0 mmol of *n*-BuMgBr (prepared from 658 mg of *n*-BuBr and 97 mg of Mg in 4 mL of ether) was added via a cannula. The mixture was allowed to stir at −10 °C for 10 min after which a solution of 465 mg (2 mmol) of 7-OPiv in 2 mL of ether was added. The cooling bath was removed and the reaction mixture was stirred for 4 h

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at room temperature and the reaction was quenched and worked up as described above. The composition of the product (**10**/**9** ratio) was determined by capillary GC (UCON, 94 ft, LB-550-X, 130 °C).[18] The results are shown in Table II.

In other experiments it was found that the results are the same if the Grignard reagent is added to a suspension of CuCN in an ether solution of 7-OPiv at room temperature and the reaction quenched in 1 h.

Cross-Coupling Products for Reactions of *trans*-α-Methyl-γ-phenylallyl Pivalate (7-OPiv) with Grignard Reagents. Products resulting from reaction of 7-OPiv with *n*-BuMgBr, **9** and **10** (R = *n*-Bu), were described previously.[18]

(*E*)- and (*Z*)-1,3-diphenyl-1-butene (9, R = Ph) were obtained as a mixture (*E*:*Z* = 66:34) by the Wittig reaction of 2-phenylpropionaldehyde (Aldrich) and benzylidinetriphenylphosphorane. The isomers were separated by preparative GC (Carbowax 20M, 4 ft, 200 °C) and shown to be homogeneous by capillary GC (61 ft, UCON, LB 550-X, 180 °C). Spectral properties agreed with published data.[48]

(*E*)- and (*Z*)-1-phenyl-3,4,4-trimethyl-1-pentene (9, R = *t*-Bu) were prepared as a mixture (*E*:*Z* = 94:6) by the Wittig reaction of 2,3,3-trimethylbutanal[47] and benzylidinetriphenylphosphorane. This composition was determined by capillary GC (UCON, LB 550, 175 ft, 135 °C). Homogeneous samples were obtained by preparative GC (Carbowax 20M, 4 ft, 175 °C). The *E* isomer (**9**, R = *t*-Bu) had spectral properties in agreement with published values.[48] *Z* isomer: IR (neat) 1600 (m), 1480 (s), 1460 (s), 1370 (s), 1240 (m), 980 (m), 920 (m), 785 (s), 765 (s), 695 (s); NMR (δ, $CDCl_3$) 7.15–7.4 (m, 5 H), 6.40 (d, 1 H, *J* = 11.7 Hz), 5.62 (dd, 1 H, *J* = 11.7, 11.0 Hz), 2.57 (dq, 1 H, *J* = 11.0, 6.9 Hz), 0.99 (d, 3 H, *J* = 6.9 Hz), 0.84 (s, 9 H); high-resolution mass spectrum, calcd for $C_{14}H_{20}$ *m*/*e* 188.1565, found 188.1570.

(*E*)- and (*Z*)-4-phenyl-5,5-dimethyl-2-hexene (10, R = *t*-Bu) were obtained as an *E*/*Z* mixture by the Wittig reaction of 2-phenyl-3,3-dimethylbutanal and ethylidinetriphenylphosphorane. The aldehyde was prepared as follows. Reduction of methyl 2-phenyl-3,3-dimethylbutanoate[49] with LAH gave 2-phenyl-3,3-dimethylbutanol: mp 73–74 °C; NMR (δ, $CDCl_3$) 7.2–7.4 (m, 5 H), 4.03 (m, 2 H), 2.68 (dd, 1 H, *J* = 6.5, 7.7 Hz), 0.90 (s, 9 H). Oxidation of the alcohol with PCC[50] gave 2-phenyl-3,3-dimethylbutanal:[51] NMR (δ, $CDCl_3$) 10.0 (d, 1 H, *J* = 3.2 Hz), 7.2–7.4 (m, 5 H), 3.28 (d, 1 H, *J* = 3.2 Hz), 1.03 (s, 9 H). A homogeneous sample of the Wittig reaction product (mixture of (*E*)- and (*Z*)-**10**, R = *t*-Bu) was obtained by preparative GC (Carbowax 20 M, 4 ft, 175 °C). We were unable to resolve this mixture by capillary GC (QF-1, 300 ft, 135 °C). The 270-MHz NMR spectrum indicated a 7:3 mixture of *E*:*Z* isomers. The major component had (δ, $CDCl_3$) 7.1–7.5 (m, 5 H), 5.88 (ddq, 1 H, *J* = 15, 9.8, 1.6 Hz), 5.46 (dq, 1 H, *J* = 15, 6.4 Hz), 2.96 (d, 1 H, *J* = 9.8 Hz), 1.67 (dd, 3 H, *J* = 6.4, 1.6 Hz), 0.86 (s, 9 H). This corresponds to the published spectrum for (*E*)-**10**, R = *t*-Bu).[48] The minor component ((*Z*)-**10**, R = *t*-Bu) had (δ, $CDCl_3$) 7.1–7.5 (m, 5 H), 5.75–6.0 (m, not resolved from isomer), 5.56 (dq, 1 H, *J* = 10.6, 6.8 Hz), 3.37 (d, 1 H, *J* = 10.3 Hz), 1.57 (dd, 3 H, *J* = 6.8, 1.8 Hz), 0.88 (s, 9 H). Selective decoupling of the δ 1.67 methyl signal for the major isomer resulted in simplification of the vinyl signals to δ 5.88 (dd, *J* = 15, 9.9 Hz), 5.46 (d, *J* = 15 Hz). Similarly, decoupling the δ 1.57 methyl signal of the minor isomer resulted in collapse of the 5.56 signal to a doublet (*J* = 10.5 Hz). The downfield vinyl signal for the minor isomer could not be resolved from that for the major isomer.

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Registry No. 1-OTMB, 76807-00-6; α-D-1-OTMB, 102853-25-8; 1-OH, 22049-46-3; α-D-1-OH, 102853-30-5; *cis*-**2**, 73964-41-7; *trans*-**2**, 73964-47-3; α-D-**2**-OTMB, 102853-32-7; **3**-OPIV, 102147-31-9; **3**-OTMB, 102853-22-5; **3**-OH, 822-67-3; α-D-**3**-OTMB, 102853-26-9; α-D-**3**-OPIV, 102853-27-0; γ-D-**3**-OPIV, 102853-28-1; α-D-**3**-OH, 55282-88-7; γ-D-**3**-OH, 73741-72-7; **4** (R = Et), 2808-71-1; **4** (R = Pr-*i*), 3983-08-2; **4** (R = Me), 591-48-0; **4** (R = Bu), 3983-07-1; **4** (R = Bu-*i*), 4104-56-7; **4** (R = 2-Bu), 15232-91-4; **4** (R = cyclohexyl), 1808-09-9; **4** (R = Ph), 15232-96-9; **4** (R = *p*-anisyl), 52316-10-6; **4** (R = allyl), 15232-95-8; **4** (R = vinyl), 766-03-0; **4** (R = propen-2-yl), 15232-95-8; 1-D-**4** (R = *i*-Pr), 102853-41-8; 1-D-**4** (R = Bu), 102853-33-8; 1-D-**4** (R = *t*-Bu), 102853-34-9; 1-D-**4** (R = OTMB), 102853-35-0; 3-D-**4** (R = OTMB), 102853-26-9; **5**, 102853-29-2; 1-D-**6** (R = OH), 102853-31-6; 1-D-**6** (R = Ph), 102853-38-3; 3-D-**6** (R = Ph), 102853-39-4; 3-D-**6** (R = Bu), 102853-40-7; 3-D-**6** (R = Bu-*t*), 102853-36-1; 3-D-**6** (R = Pr-*i*), 102853-37-2; **7**-OH, 17488-65-2; **7**-OPIV, 102918-88-7; (*E*)-**9** (R = Bu), 79594-10-8; (*E*)-**9** (R = Bu-*t*), 66628-94-2; (*Z*)-**9** (R = Bu-*t*), 102918-89-8; (*E*)-**9** (R = Ph), 7302-01-4; (*Z*)-**9** (R = Ph), 7302-00-3; (*E*)-**10** (R = Bu-*t*), 66628-95-3; (*Z*)-**10** (R = Bu-*t*), 102853-24-7; **10** (R = Bu), 92776-47-1; **10** (R = Bu-*t*), 102853-23-6; MeMgI, 917-64-6; EtMgI, 10467-10-4; BuMgBr, 693-03-8; *i*-BuMgBr, 920-39-8; *i*-PrMgBr, 920-39-8; 2-BuMgBr, 922-66-7; cyclohexyl-MgBr, 931-50-0; PhMgBr, 100-58-3; *p*-anisyl-MgBr, 13139-86-1; allyl-MgBr, 1730-25-2; vinyl-MgBr, 1826-67-1; propen-2-yl-MgBr, 1730-25-2; *t*-BuMgBr, 2259-30-5; BuCu(CN)Li, 41742-63-6; BuCu(CN)MgBr, 102869-95-4; Bu_2CuLi, 24406-16-4; $Bu_2CuMgBr$, 54360-69-9; MeCH(Ph)CHO, 93-53-8; $PhCH{=}PPh_3$, 16721-45-2; $Me_3CCH(Me)CHO$, 17408-48-9; $Me_3CCH(Ph)CHO$, 86429-26-7; $MeCH{=}PPh_3$, 1754-88-7; mesitoyl chloride, 938-18-1; pivaloyl chloride, 3282-30-2.

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