Synthesis of Farnesol Analogues through Cu(I)-Mediated Displacements of Allylic THP Ethers by Grignard Reagents

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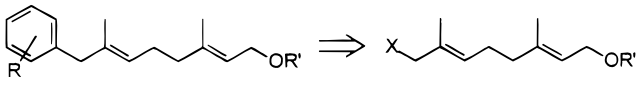
The synthesis of a family of farnesol analogues, incorporating aromatic rings, has been achieved in high yields through the development of a regioselective coupling of allylic tetrahydropyranyl ethers with organometallic reagents. The allylic THP group is displaced readily by Grignard reagents in the presence of Cu(I) halides but is stable in the absence of added copper. Thus, an allylic THP group can fulfill its traditional role as a protecting group or serve as a leaving group depending on reaction conditions. An improved synthesis of (2*E*,6*E*)-10,11-dihydrofarnesol also has been accomplished using this methodology, and some preliminary studies on the reactivity and regioselectivity of THP ether displacements were conducted. The farnesol analogues reported herein may be useful probes of the importance of nonbonding interactions in enzymatic recognition of the farnesyl chain and allow development of more potent competitive inhibitors of enzymes such as farnesyl protein transferase.

The family of GTP-binding proteins known as RAS plays an essential role in signal transduction pathways that regulate cell proliferation,[1−4] and mutations in RAS proteins are associated with approximately 30% of all human cancers.[1] Because a metabolic farnesylation reaction, catalyzed by the enzyme farnesyl protein transferase (FPTase), is essential for RAS-induced cellular transformations, an intense interest in farnesyl pyrophosphate analogues as potential chemotherapeutic agents has arisen.[5−7] However, farnesyl pyrophosphate is a substrate for many other enzymes, perhaps most notably squalene synthase, which suggests that selective inhibition of FPTase by terpene analogues is not a trivial goal.

Most research in this area has focused on replacing the biologically labile diphosphate "head" of farnesyl pyrophosphate with a more stable bioisosteric moiety.[8−13] Recent evidence suggests that modifications of the hydrophobic farnesyl "tail" might enhance the binding of farnesyl pyrophosphate analogues. For example, photoactive farnesyl pyrophosphate mimetics that incorporate stable ether-linked benzophenones into the terpenoid chain[14] gave a slight increase (1.5-fold) in the binding affinity for FPTase. In addition, the publication of a crystal structure for FPTase[15] revealed a hydrophobic pocket lined with aromatic amino acid residues that presumably accepts the terpenoid chain. These data support the design of novel, aromatic farnesyl "tails", compounds that may further illuminate the importance of nonbonding interactions in enzymatic recognition of the farnesyl chain.[16] Synthesis of such compounds could be approached through displacement of an allylic leaving group by an appropriate nucleophile, but constructing farnesol analogues (e.g., **1**) via this strategy would require reaction at one allylic position of a geraniol derivative (**2**) in the presence of a second allylic functional group that also might be displaced. One solution to this problem, based on an interesting Cu(I)-mediated displacement of allylic tetrahydropyranyl (THP) ethers by Grignard reagents, is the subject of this report.



1 2

Compounds of the general structure **2** are readily available through oxidation of geraniol derivatives with selenium dioxide.[17] For example, oxidation of geranyl acetate (**3**) with SeO_2 gives alcohol **4**, and this compound

(1) Barbacid, M. *Annu. Rev. Biochem.* **1987**, *56*, 779−827.
(2) Lowy, D. R.; Willumsen, B. M. *Annu. Rev. Biochem.* **1993**, *62*, 851−891.
(3) Bos, J. L. *Cancer Res.* **1989**, *49*, 4682−4689.
(4) Chang, E. H.; Furth, M. E.; Scolnick, E. M.; Lowy, D. R. *Nature* **1982**, *297*, 479−483.
(5) Willumsen, B. M.; Norris, K.; Papageorge, A. G.; Hubbert, N. L.; Lowy, D. R. *EMBO J.* **1984**, *3*, 2581−2585.
(6) Jackson, J. H.; Cochrane, C. G.; Bourne, J. R.; Solski, P. A.; Buss, J. E.; Der, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 3042−3046.
(7) Hancock, J. F.; Magee, A. I.; Childs, J. E.; Marshall, C. J. *Cell* **1989**, *57*, 1167−1187.
(8) Patel, D. V.; Schmidt, R. J.; Biller, S. A.; Gordon, E. M.; Robinson, S. S.; Manne, V. *J. Med. Chem.* **1995**, *38*, 2906−2921.
(9) Kang, M. S.; Stemerick, D. M.; Zwolshen, J. H.; Harry, B. S.; Sunkara, P. S.; Harrison, B. L. *Biochem. Biophys. Res. Commun.* **1995**, *217*, 245−249.
(10) Magnin, D. R.; Biller, S. A.; Dickson, J. K., Jr.; Logan, J. V.; Lawrence, R. M.; Chen, Y.; Sulsky, R. B.; Ciosek, C. P., Jr.; Harrity, T. W.; Holibois, K. G.; Kunselman, L. K.; Rich, L. C.; Slusarchyk, D. A. *J. Med. Chem.* **1995**, *38*, 2596−2605.
(11) Pompliano, D. L.; Rands, E.; Schaber, M. D.; Mosser, S. D.; Anthony, N. J.; Gibbs, J. B. *Biochemistry* **1992**, *31*, 3800−3807.
(12) Valentijn, A. R. P. M.; van den Berg, O.; van der Marel, G. A.; Cohen, L. H.; van Boom, J. H. *Tetrahedron* **1995**, *51*, 2099−2108.
(13) Holstein, S. A.; Cermak, D. M.; Wiemer, D. F.; Lewis, K.; Hohl, R. J. *Bioorganic & Medicinal Chemistry* **1998**, *6*, 687−694.
(14) Gaon, I.; Turek, T. C.; Distefano, M. D. *Tetrahedron Lett.* **1996**, *37*, 8833−8836.
(15) a) Park, H.; Boduluri, S. R.; Moomaw, J. F.; Casey, P. J.; Beese, L. S. *Science* **1997**, *275*, 1800−1804. (b) Long, S. B.; Casey, P. J.; Beese, L. S. *Biochemistry* **1998**, *37*, 9612−9618.
(16) For syntheses of other modified farnesols, see: Gibbs, R. A.; Krishnan, V. *Tetrahedron Lett.* **1994**, *35*, 2509−2512. (b) Gibbs, R. A.; Krishnan, V.; Dolence, J. M.; Poulter, C. D. *J. Org. Chem.* **1995**, *60*, 7821−7829. (c) Mu Y. Q.; Gibbs R. A.; Eubanks, L. M.; Poulter, C. D. *J. Org. Chem.* **1996**, *61*, 8010−8015. (d) Zahn, T. J.; Ksebati, M. B.; Gibbs, R. A. *Tetrahedron Lett.* **1998**, *39*, 3991−3994.
(17) SeO_2 oxidation of geraniol protected with THP, TBDPS, or benzyl groups gave modest yields, while oxidation of geranyl acetate gave >55% yield. For the oxidation procedure cf: Sharpless, K. B.; Umbreit, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 5526−5528.

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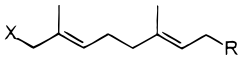
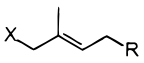
has been converted to the corresponding bromide **5** by reaction with *N*-bromosuccinimide and dimethyl sulfide.[18] Unfortunately, reaction of compound **5** with phenylmagnesium bromide in the presence of copper(I) iodide gave primarily the diaryl compound **6**. In an effort to circumvent the double displacement, the related compound **9** was prepared by reaction of the geranyl THP ether **7** with SeO_2 to afford alcohol **8** and subsequent reaction with acetic anhydride. Surprisingly, reaction of compound **9** with C_6H_5MgBr and Cu(I)I also gave compound **6** as the major product, suggesting that under these conditions displacement of an allylic THP ether may be as facile as the displacement of an allylic acetate or bromide.[19,20]



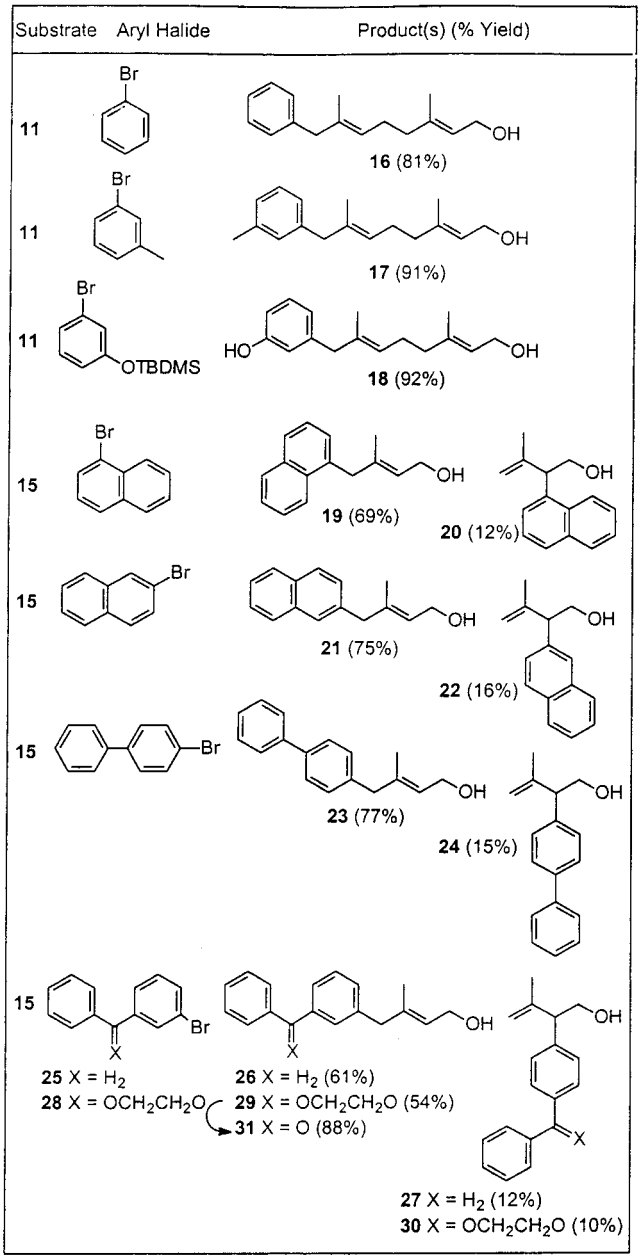
3 X = H; R = OAc
4 X = OH; R = OAc
5 X = Br; R = OAc
6 X = C_6H_5; R = C_6H_5
7 X = H; R = OTHP
8 X = OH; R = OTHP
9 X = OAc; R = OTHP
10 X = OTHP; R = OAc
11 X = OTHP; R = OH



12 X = H; R = OAc
13 X = OH; R = OAc
14 X = OTHP; R = OAc
15 X = OTHP; R = OH

Displacement of allylic THP ethers ultimately allowed the regioselective synthesis of a series of aromatic farnesol analogues. One appropriate substrate for the displacement was prepared by conversion of THP ether **10**[21] to alcohol **11** by reduction with $LiAlH_4$ or by basic hydrolysis. A parallel reaction series was used to convert prenyl acetate (**12**) to the known alcohol **13** and then to the desired THP ethers **14** and **15**.[22] Compounds **11** and **15** were examined in Grignard coupling reactions with several different organometallic species without attempting protection of the free hydroxyl group. Instead, an excess of the Grignard reagent was employed, presumably leading to formation of a C-1 alkoxide in situ. In all cases, efficient coupling was observed under these conditions (Table 1). When compound **11** was treated with an excess of the reagents derived from bromobenzene or *m*-bromotoluene, the coupled products **16** and **17** were obtained in high yields. With the TBDMS-protected *m*-bromophenol, coupling also proceeded smoothly, and treatment of the initial product with TBAF gave phenol **18** in 92% overall yield. Coupling of the smaller THP ether **15** with larger naphthyl and biphenyl reagents was examined to obtain coupled products approximating the length of the farnesyl chain. In this series, the desired compounds (**19**, **21**, and **23**) were always the major reaction products, and each was obtained in good yield, but in all three cases, a small amount of S_N2' coupling

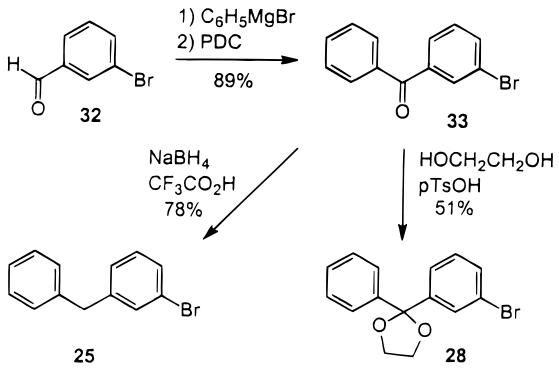
Table 1. Cu(I)-Mediated Coupling of Allylic THP Ethers with Aryl Grignard Reagents



(~5:1 ratio of S_N2/S_N2') was observed (compounds **20**, **22**, and **24**). The S_N2 and S_N2' products were readily separable by column chromatography and easily identified by their ^1H NMR spectra.

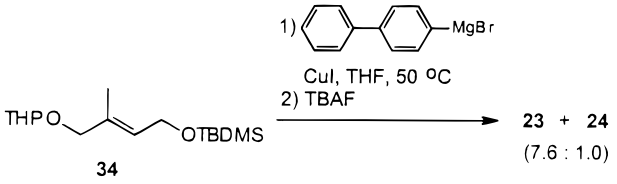
In a similar manner, the reaction of the Grignard reagents derived from aryl bromides **25** and **28** with THP ether **15** was expected to afford the biphenyl derivative **26** and the benzophenone derivative **31.** To prepare the requisite Grignard reagents, commercially available 3-bromobenzaldehyde (**32**) was treated with phenylmagnesium bromide, and the resulting alcohol was treated with PDC to afford the known[23] 3-bromobenzophenone (**33**) in 89% yield. Protection of the carbonyl group with ethylene glycol afforded ketal **28**, while reduction with $NaBH_4$ in trifluoroacetic acid[24] provided the desired bromide **25**.

(18) Dauben, W. G.; Saugier, R. K.; Fleischhauer, I. *J. Org. Chem.* **1985**, *50*, 3767−3774.
(19) For earlier examples of THP ether displacements see: (a) Katzenellenbogen, J. A.; Corey, E. J. *J. Org. Chem.* **1972**, *37*, 1441−1442. (b) Claesson, A.; Tämnefors, I.; Olsson, L.-I. *Tetrahedron Lett.* **1975**, 1509−1512.
(20) Displacements of allylic ethers by Grignard reagents have been observed: (a) Normant, J. F.; Commercon, A.; Gendreau, Y.; Bourgain, M.; Villieras, J. *Bull. Soc. Chim. Fr.* **1979**, 309−314. (b) Normant, J. F.; Commercon, A.; Bourgain, M.; Villieras, J. *Tetrahedron Lett.* **1975**, *44*, 3833−3836. (c) Commercon, A.; Bourgain, M.; Delaumeny, M.; Normant, J. F.; Villieras, J. *Tetrahedron Lett.* **1975**, *44*, 3837−3840.
(21) Marshall, J. A.; Andrews, R. C. *J. Org. Chem.* **1985**, *50*, 1602−1606.
(22) Borcherding, D. R.; Narayanan, S.; Hasobe, M.; McKee, J. G.; Keller, B. T.; Borchardt, R. T. *J. Med. Chem.* **1988**, *31*, 1729−1738.
(23) Wagner, P. J.; Sedon, J. H.; Gudmundsdottir, A. *J. Am. Chem. Soc.* **1996**, *118*, 746−754.
(24) (a) Gribble, G. W.; Leese, R. M. *Synthesis* **1977**, 172−176. (b) Gribble, G. W.; Kelly, W. J.; Emery, S. E. *Synthesis* **1978**, 763−765.



Treatment of THP ether **15** with an excess of the Grignard reagent derived from bromide **25** provided the desired product **26** in moderate yield along with a small amount of the S_N2' product **27**. Reaction of THP ether **15** with the Grignard reagent derived from bromide **28**, followed by deprotection of the resulting ketal **29** by treatment with PPTS, gave ketone **31**. Once again, a small amount of the S_N2' product **30** was observed in the coupling reaction.

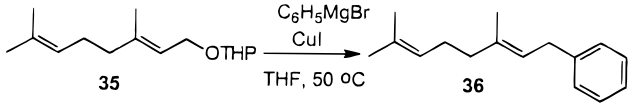
Observation of small amounts of S_N2' products in all five reactions attempted with THP ether **15** might be explained by complexation of the organometallic reagent with the intermediate alkoxide, followed by intramolecular delivery of the aryl group.[25] However, when allylic alcohol **15** was protected with a TBDMS group (**34**), the S_N2' product was still observed albeit in diminished amounts. Thus, it may be that there is still complexation

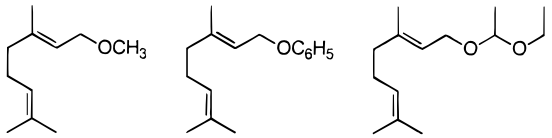


and delivery in the more crowded TBDMS ether or that the longer terpenoid chain of compound **11** provides sufficient steric hindrance to minimize S_N2' coupling in that series, while the smaller prenyl THP ether **15** lacks the steric bulk to completely inhibit S_N2' reaction.

Displacements of ethers have some precedence in reports by Katzenellenbogen and Corey,[19a] Claesson,[19b] and Normant.[20] Even so, the THP displacements summarized above appear to be particularly facile. For example, treatment of the geranyl THP ether **35** with excess phenylmagnesium bromide in the absence of copper(I) salt gave no detectable coupling, demonstrating that allylic THP ethers are stable to Grignard reagents. Parallel reactions also were performed in the presence of catalytic and excess Cu(I)I. In both cases, nearly quantitative yields of the desired coupled product **36** were obtained, although the reaction proceeds more slowly in the presence of catalytic CuI (17 h for 0.1 equiv vs 1.5 h for 1.5 equiv).

While Normant and co-workers observed facile displacement of allylic methyl and ethyl ethers by alkylcopper species, they were unable to obtain comparable results with arylcopper reagents.[20] The facile displacements that we observed with the aryl reagents suggested that allylic THP ethers are more readily displaced than the corresponding methyl and ethyl ethers. Parallel reactions showed that the THP derivative of geraniol (**35**) undergoes copper-mediated Grignard displacement at least 10-fold faster than the corresponding methyl or phenyl ethers (**37** and **38**, respectively). Compound **35** gave the coupled product **36** in 92% yield after 1.5 h, while after 17 h the same product was obtained in 20% and 55% yields from the methyl (**37**) and phenyl ethers (**38**), respectively. The ethoxyethyl ether **39** also was displaced more rapidly than the methyl and phenyl ethers, giving the coupled product in 80% yield after 17 h and demonstrating the importance of the acetal functionality in the coupling reaction. However, a comparison





of the acetal protecting groups suggests that the THP ether is the more proficient leaving group. Finally, reaction of the THP ether **35** proved more facile than reaction of the phenyl ether **38**, despite the difference in stability of the corresponding anions.

One explanation for the reactivity of the THP group may involve metal coordination catalysis. It is possible that the acetal oxygens chelate with an organocopper species, delivering the nucleophile directly to the allylic site of S_N2 substitution. Research performed on 2-(allyloxy)benzothiazoles demonstrated that copper(I) π complexes can be used to direct nucleophilic organocopper substitution reactions.[26] Alternatively, bidentate coordination of the acetal oxygens could result in activation of the THP as a leaving group. This hypothesis also has some literature precedence, in that THP ethers have been cleanly deprotected by treatment with magnesium bromide in ether,[27] and a similar process has been shown to facilitate the cleavage of MEM ethers.[28] While it is difficult to distinguish between these possibilities, CuI does accelerate displacement of the THP group significantly relative to reactions attempted in the presence of $MgBr_2$ alone. As noted above, treatment of THP ether **35** with phenylmagnesium bromide gives complete reaction within 90 min at room temperature in the presence of CuI. In the absence of CuI, no coupling was observed at room temperature even in the presence of added $MgBr_2$ (1.5 equiv). Even at elevated temperatures (50 °C), only small amounts of the coupled product were observed in the $MgBr_2$ reactions. Thus, it seems likely that a copper complex is involved in this transformation rather than simple Lewis acid activation of the THP ether. However, in the CuI-mediated reactions of THP ethers **40**, **43**, and

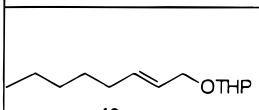
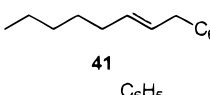
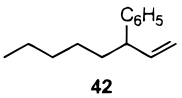
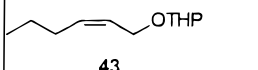
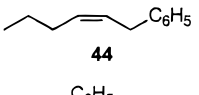
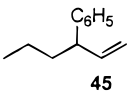
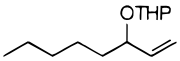
(25) (a) Eisch, J. J.; Merkley, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1148−1155. (b) Eisch, J. J. *J. Organomet. Chem.* **1980**, *200*, 101−117. (c) Eisch, J. J.; Merkley, J. H.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 587−593.

(26) Calo, V.; Lopez, L.; Pesce, G.; Calianno, A. *J. Org. Chem.* **1982**, *47*, 4482−4485.

(27) Kim, S.; Park, J. H. *Tetrahedron Lett.* **1987**, *28*, 439−440.

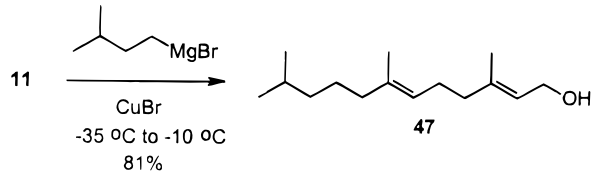
(28) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809−812.

Table 2. Regioselectivity in Cu(I)-Mediated Displacements of Allylic THP Ethers with C_6H_5MgBr

Substrate	Products	Ratio Sn2/Sn2'	Yield
 **40**	 **41** +  **42**	>50:1	85%
 **43**	 **44** +  **45**	7.3:1	89%
 **46**	**42** + *E*/*Z*-**41**	1:11.5	95%

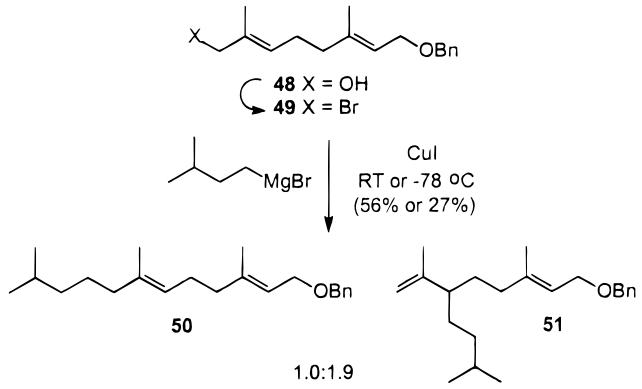
46 with phenylmagnesium bromide, the ether's steric environment appears to dictate the S_N2/S_N2' ratio (Table 2). Because only S_N2 products might be expected if complexation and delivery were involved, observation of the S_N2' products makes it more difficult to determine the precise nature of this CuI-mediated displacement.

In theory, coupling of the allylic THP ether **11** with isoamylmagnesium bromide would allow a regiospecific synthesis of (2*E*,6*E*)-10,11-dihydrofarnesol (**47**),[29] a compound with a saturated terpenoid tail that could serve as a negative control in studies of enzyme binding.[30]



Initial attempts at performing this coupling reaction under the conditions used in the aryl Grignard cases failed to provide any of the coupled product, perhaps because of the lower thermal stability of alkylcopper species and their tendency to undergo β-elimination.[31,32] When this coupling reaction was repeated at lower temperature in the presence of the more soluble Cu(I)-Br,[20a] the desired coupling was obtained. For example, when THP ether **11** was added to a suspension of isoamylmagnesium bromide and CuBr at −35 °C, and the temperature was gradually allowed to warm to −10 °C, the desired product **47** was obtained in 81% yield. None of the S_N2' substitution product was observed in the coupling reaction. Thus, (*E*,*E*)-10,11-dihydrofarnesol (**47**) was prepared in four steps from geranyl acetate (**3**) with an overall yield of 45%.

The regioselectivity of the THP coupling reactions is particularly noteworthy. In contrast to the results described above, when allylic bromide **49** (readily available from alcohol **48**) is treated with isoamylmagnesium bromide in the presence of copper(I) iodide, either at 25 °C or at −78 °C, a 1.9/1.0 ratio of S_N2'(**51**)/S_N2(**50**) products was observed. Because no S_N2' substitution was



observed in the coupling of isoamylmagnesium bromide with the analogous THP ether **11**, these results suggested that allylic THP ethers are displaced with regioselectivity not found in the corresponding allylic bromides. A set of parallel reactions was performed with *n*-butylmagnesium and several pairs of THP ethers and the corresponding bromides (compounds **35** and **54**, **40** and **57**, **43** and **60**, and **46** and **61**), and consistently high regioselectivity was observed with the THP ethers (Table 3). In three of the four cases, the THP ethers provided greater than 50:1 ratios of S_N2/S_N2' products, while the allylic bromides exhibited a much greater proportion of S_N2' substitution. The only exception to this trend was in the case of the secondary THP ether **46**, which gave almost exclusively the S_N2' coupling product **55**. However, even in this case displacement of the THP ether was more selective (>50:1 S_N2' to S_N2) than displacement of the corresponding bromide (1.5:1.0 S_N2' to S_N2). While the basis for this enhanced regioselectivity is not yet clear, this regioselectivity can be very advantageous as shown in the synthesis of (*E*,*E*)-10,11-dihydrofarnesol. Further investigation into the mechanism of Cu(I)-mediated Grignard coupling of THP ethers might lead to a better understanding of this interesting observation.

In conclusion, displacement of THP ethers in Cu(I)-mediated Grignard reactions is an effective strategy for coupling aromatic and alkyl compounds with allylic alcohols. Allylic THP ethers can be synthesized in nearly quantitative yields from the corresponding alcohols and are much more stable than the corresponding allylic halides. This stability allows THP ethers to be viewed as both protecting groups and reactive centers. Both the ease of displacements observed with allylic THP ethers and the enhanced regioselectivity observed for allylic THP ethers versus the corresponding allylic bromides make this coupling reaction a useful and versatile process. Finally, this reaction has allowed preparation of a family of farnesol analogues incorporating aromatic rings as well as (2*E*,6*E*)-10,11-dihydrofarnesol, compounds which should be of use as probes of metabolic processes based on farnesyl pyrophosphate.[33,34]

(29) (a) Eidem, A.; Buchecker, R.; Kjosen, H.; Liaaen-Jensen, S. *Acta Chem. Scand. B* **1975**, *29*, 1015−1023. (b) Washburn, W. N.; Kow, R. *Tetrahedron Lett.* **1977**, 1555−1558. (c) Biller, S. A. U.S. Patent, Patent Number 5,212,164, May 18, 1993. (d) Zhang, H.; Chen, J.; Jiang, J. *Yingyong Huaxue* **1993**, *10*, 104−106. (e) Mechelke, M. F.; Wiemer, D. F. *Tetrahedron Lett.* **1998**, *39*, 9609−9612.

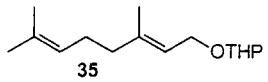
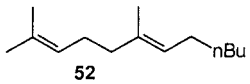
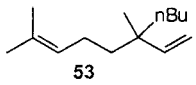
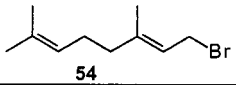
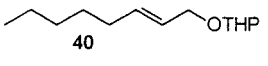
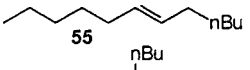
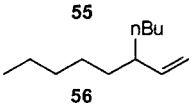
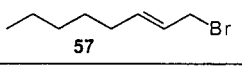
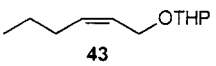
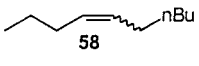
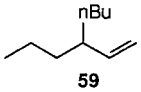
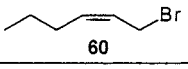
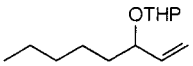
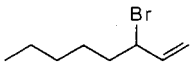
(30) Hohl, R. J.; Lewis, K. A.; Cermak, D. M.; Wiemer, D. F. *Lipids* **1998**, *33*, 39−46.

(31) Costa, G.; Camus, A.; Gatti, L.; Marsich, N. *J. Organomet. Chem.* **1966**, *5*, 568−572.

(32) Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1485−1487.

(33) Westfall, D.; Aboushadi, N.; Shackelford, J. E.; Krisans, S. K. *Biochem. Biophys. Res. Commun.* **1997**, *230*, 562−568.

Table 3. Regioselectivity in Cu(I)-Mediated Displacements of Allylic THP Ethers and Allyl Bromides in Reactions with *n*-BuMgBr

Substrate	Product(s)	Ratio Sn2/Sn2'
 **35**	 **52**  **53**	>50:1
 **54**	**52 + 53**	6.3:1
 **40**	 **55**  **56**	>50:1
 **57**	**55 + 56**	3.3:1
 **43**	 **58**  **59**	>50:1
 **60**	**58 + 59**	2.6:1
 **46**	**56 + *E*/*Z*-55**	1:>50
 **61**	**56 + *E*/*Z*-55**	1:1.5

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use, while dichloromethane, toluene, and pyridine were freshly distilled from calcium hydride. All reactions in these solvents were conducted in oven-dried glassware under a positive pressure of nitrogen. Column chromatography was performed on silica gel (40 μm). NMR spectra (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz) were recorded with $CDCl_3$ as solvent and residual $CHCl_3$ or tetramethylsilane as internal standards. High-resolution mass spectra were obtained on reversed geometry mass spectrometers at the University of Iowa Mass Spectrometry Facility. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

8-Acetoxy-2,6-dimethyl-2*E*,6*E*-octadien-1-ol (4). In a typical procedure,[17] 20.0 mL (146 mmol) of 70% *tert*-butyl hydroperoxide was added to a suspension of SeO_2 (1.84 g, 16.6 mmol) and 4-hydroxybenzoic acid (550 mg, 3.98 mmol) in 50 mL of CH_2Cl_2. The reaction mixture was then treated with a solution of geranyl acetate (8.0 mL, 37.4 mmol) in CH_2Cl_2 (10 mL) via cannula and stirred at room temperature for 18 h. The resulting suspension was washed with saturated $NaHCO_3$, and the aqueous phase was extracted with ether. The combined organic extract were concentrated under vacuum to provide a mixture of the desired alcohol **4** and the corresponding aldehyde. The mixture was dissolved in ice-cold methanol (70 mL), and $NaBH_4$ powder (1.40 g, 37.0 mmol) was added slowly over 0.5 h. After the mixture was stirred for an additional hour, the resulting suspension was quenched by addition of saturated NH_4Cl and extracted with ether and the combined organic extracts were concentrated under vacuum. Purification of the resulting liquid by flash column chromatography (60:40 hexanes/ethyl acetate) afforded alcohol **4**[17,35] as a light yellow oil (4.18 g, 53%): ^{1}H NMR δ 5.37 (tq, 1H, J = 7.0, 1.1 Hz), 5.34 (tq, 1H, J = 7.0, 1.0 Hz), 4.58 (d, 2H, J = 7.0 Hz), 3.97 (s, 2H), 2.31 (br s, 1H), 2.22−2.06 (m, 4H), 2.05 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H).

3,7-Dimethyl-8-[(tetrahydro-2H-pyran-2-yl)oxy]-2*E*,6*E*-octadien-1-ol (11). To a solution of alcohol **4** (1.95 g, 9.2 mmol) in dichloromethane (40 mL) at 0 °C was added dropwise 3,4-dihydro-2H-pyran (DHP) (2.1 mL, 23.0 mmol) followed by *p*-TsOH (28 mg, 0.1 mmol). After the reaction mixture was allowed to stir for 3 h, the resulting suspension was washed with saturated $NaHCO_3$ and extracted with ether and the combined organic extracts were concentrated under vacuum to afford acetate **10**.[21] The residue was dissolved in MeOH (50 mL), and potassium carbonate (5.3 g, 38.4 mmol) was added in one portion. After the mixture was vigorously stirred for 1.5 h, the mixture was treated with saturated NH_4Cl, extracted with ether, and the combined organic extracts were concentrated under vacuum. The resulting liquid was purified by flash column chromatography (60:40 hexanes/ethyl acetate) to provide THP ether **11** (2.34 g, 9.2 mmol) as a clear oil with ^{1}H and ^{13}C NMR spectra comparable to reported data.[21]

4-Acetoxy-2-methyl-2*E*-buten-1-ol (13). Prenyl acetate (5.72 g, 44.7 mmol) in CH_2Cl_2 was treated with 70% *tert*-butyl hydroperoxide (20.0 mL, 140 mmol), SeO_2 (2.14 g, 19.3 mmol), and 4-hydroxybenzoic acid (642 mg, 4.65 mmol) at room temperature for 23 h using the general SeO_2 oxidation procedure described above for alcohol **4**. Standard workup, including treatment with $NaBH_4$ (1.60 g, 42.3 mmol), and purification of the resulting liquid by flash column chromatography (60:40 hexanes/ethyl acetate) afforded alcohol **13**[36] as a light yellow oil (2.22 g, 35%): ^{1}H NMR δ 5.62 (tq, 1H, J = 7.1, 1.4 Hz), 4.64 (d, 2H, J = 7.0 Hz), 4.04 (s, 2H), 3.27 (br s, 1H), 2.05 (s, 3H), 1.72 (s, 3H); ^{13}C NMR δ 171.0, 140.7, 117.9, 66.9, 60.7, 20.6, 13.5.

4-[(Tetrahydro-2H-pyran-2-yl)oxy]-3-methyl-2*E*-buten-1-ol (15). To a stirred solution of alcohol **13** (1.10 g, 7.63 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added DHP (1.8 mL, 19.8 mmol) and *p*TsOH (14.5 mg, 0.08 mmol). The mixture was stirred for 3 h, and the resulting suspension was washed with saturated $NaHCO_3$ and extracted with ether. After evaporation of solvent, the resulting liquid was dissolved in MeOH (40 mL), and K_2CO_3 (4.21 g, 30.5 mmol) was added in one portion. After being stirred for 2 h, the mixture was neutralized by addition of saturated NH_4Cl and extracted with ether. The combined organic extracts were concentrated in vacuo and purified by column chromatography (60:40 hexanes/ethyl acetate) to afford THP ether **15**[22,37] (1.39 g, 98%) as a clear oil: ^{1}H NMR δ 5.68 (tq, 1H, J = 6.7, 1.4 Hz), 4.63 (dd, 1H, J = 3.2, 3.2 Hz), 4.19 (d, 2H, J = 6.6 Hz), 4.12 (d, 1H, J = 12.3 Hz), 3.91−3.83 (m, 1H), 3.87 (d, 1H, J = 12.3 Hz), 3.56−3.47 (m, 1H), 2.47 (br s, 1H), 1.92−1.71 (m, 2H), 1.70 (s, 3H), 1.69−1.40 (m, 4H); ^{13}C NMR δ 134.9, 125.8, 97.6, 71.9, 61.9, 58.7, 30.4, 25.3, 19.2, 13.9; HRMS calcd for $C_{10}H_{18}O_3$ $(M + Li)^+$ 193.1416, found 193.1414.

3,7-Dimethyl-8-phenyl-2*E*,6*E*-octadien-1-ol (16). Commercially available phenylmagnesium bromide (3.8 mL of a 3

(34) Crick, D. C.; Andres, D. A.; Waechter, C. J. *Biochem. Biophys. Res. Commun.* **1995**, *211*, 590−599.

(35) Sato, K.; Inoue, S.; Onishi, A.; Uchida, N.; Minowa, N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 761−769.

(36) Masaki, Y.; Hashimoto, K.; Kaji, K. *Tetrahedron Lett.* **1978**, 4539−4542.

(37) Watanabe, H.; Hatakeyama, S.; Tazumi, K.; Takano, S.; Masuda, S.; Okano, T.; Kobayashi, T.; Kubodera, N. *Chem. Pharm. Bull.* **1996**, *44*, 2280−2286.

M solution, 11.4 mmol) was added dropwise to a mixture of THP ether **11** (269 mg, 1.06 mmol) and copper(I) iodide (988 mg, 5.19 mmol) stirring at room temperature in THF (20 mL). The resulting mixture was heated to 50 °C and allowed to stir for 4 h. The reaction was then quenched by addition of saturated NH_4Cl and extracted with ether. Concentration of the combined extracts in vacuo provided a yellow oil, which upon purification by flash column chromatography (60:40 hexanes/ethyl acetate) afforded compound **16** as a pale yellow oil (197 mg, 81%): ^{1}H NMR δ 7.28−7.12 (m, 5H), 5.39 (tq, 1H, J = 6.9, 1.1 Hz), 5.22 (tq, 1H, J = 7.0, 1.2 Hz), 4.10 (d, 2H, J = 6.9 Hz), 3.26 (s, 2H), 2.19−2.03 (m, 4H), 1.65 (s, 3H), 1.52 (s, 3H); ^{13}C NMR δ 140.2, 138.8, 134.5, 128.6 (2C), 128.0 (2C), 127.7, 125.7, 123.6, 59.0, 46.0, 39.3, 26.1, 16.0, 15.6. Anal. Calcd for $C_{16}H_{22}O$: C, 83.42; H, 9.63. Found: C, 83.40; H, 9.59.

1-[8′-Hydroxy-2′,6′-dimethyl-2′*E*,6′*E*-octadienyl]-3-methylbenzene (17). Ground Mg^0 turnings (2.0 g, 82.3 mmol) were placed in a flame-dried, 100 mL, three-necked flask followed by the addition of THF (30 mL) and a crystal of iodine. The mixture was gradually heated to reflux as 3-bromotoluene (6.0 mL, 49.5 mmol) was added dropwise via cannula. When Grignard reagent formation was evident (0.5 h), the reaction mixture was allowed to cool to ∼40 °C. Copper(I) iodide (4.13 g, 21.7 mmol) was subsequently added in one portion followed by the addition of THP ether **11** (1.09 g, 42.8 mmol) in THF (10 mL). The resulting suspension was heated at 50 °C until the reaction was complete by TLC analysis (1 h). The mixture was quenched by addition of saturated NH $_4$Cl and extracted with ether to afford, after purification by column chromatography (60:40 hexanes/ethyl acetate), the product **17** as a yellow oil (951 mg, 91%).

3-(8′-Hydroxy-2′,6′-dimethyl-2′*E*,6′*E*-octadienyl)phenol (18). In the same manner described above for compound **17**, THP ether **11** (1.20 g, 4.74 mmol) was treated with the Grignard reagent prepared from the known[38] TBDMS-protected derivative of 3-bromophenol (8.17 g, 28.5 mmol). After the mixture was stirred for 3 h at 50 °C and standard workup, the resulting yellow oil was dissolved in THF (20 mL), treated with tetrabutylammonium fluoride (15.0 mL of a 1 M solution in THF, 15.0 mmol), and allowed to stir at room temperature for 2 h. The solution was then washed with saturated NH_4Cl and extracted with ether. The combined extracts were concentrated in vacuo and purified by flash column chromatography (60:40 hexanes/ethyl acetate) to afford phenol **18** (1.07 g, 92%).

1-(4′-Hydroxy-2′-methyl-2′*E*-butenyl)naphthalene (19). Ground Mg^0 turnings (2.58 g, 106 mmol) were placed in a flame-dried, 250 mL, three-necked round-bottom flask followed by addition of THF (100 mL) and a crystal of iodine. The mixture was gradually heated to reflux as commercially available 1-bromonaphthalene (9.8 mL, 70.8 mmol) was added dropwise via cannula. When Grignard reagent formation was evident (1 h), the reaction mixture was allowed to cool to ∼40 °C. CuI (6.0 g, 31.5 mmol) was subsequently added in one portion followed by the addition of THP ether **15** (1.32 g, 7.08 mmol) in THF (10 mL). The resulting suspension was heated to 50 °C and allowed to stir for 3 h. After the reaction was cooled to room temperature, the reaction was quenched by addition of saturated NH_4Cl and extracted with ether and the combined organic extracts were concentrated in vacuo. Purification by column chromatography on silica gel (60:40 hexanes/ethyl acetate) afforded both the S_N2 product **19** (1.03 g, 69%) and the S_N2' product **20** (181 mg, 12%) as yellow oils.

For compound **19**: ^{1}H NMR δ 8.08−7.22 (m, 7H), 5.33 (tq, 1H, J = 6.8, 1.4 Hz), 4.08 (d, 2H, J = 6.8 Hz), 3.74 (s, 2H), 1.66 (s, 3H); ^{13}C NMR δ 138.1, 135.2, 133.8, 132.3, 128.6, 127.2, 127.0, 125.7, 125.5, 125.4, 125.4, 124.1, 59.2, 42.6, 16.6. Anal. Calcd for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.60; H, 7.56.

For compound **20**: ^{1}H NMR δ 8.14 (d, 1H, J = 8.0 Hz), 7.83 (dd, 1H, J = 7.4, 2.0 Hz), 7.72 (dd, 1H, J = 7.5, 1.9 Hz), 7.52−7.34 (m, 4H), 5.09 (s, 1H), 5.02 (s, 1H), 4.30 (dd, 1H, J = 6.8, 6.8 Hz), 4.12−3.93 (m, 2H), 1.92 (br s, 1H), 1.63 (s, 3H); ^{13}C NMR δ 144.9, 135.8, 134.0, 132.3, 128.8, 127.4, 126.0, 125.5, 125.3, 124.3, 123.2, 112.7, 64.0, 49.9, 21.9; HRMS calcd for $C_{15}H_{16}O$ $(M + Na)^+$ 235.1099, found 235.1084.

2-(4′-Hydroxy-2′-methyl-2′*E*-butenyl)naphthalene (21). THP ether **15** (655 mg, 3.52 mmol) was treated with CuI (2.66 g, 14.0 mmol) and the Grignard reagent prepared from commercially available 2-bromonaphthalene (4.70 g, 22.7 mmol), using the procedure described above for compound **19**. After the mixture was stirred for 1 h at 50 °C, the reaction mixture was quenched by addition of saturated NH_4Cl and extracted with ether and the combined organic extracts were concentrated under vacuum. The resulting yellow oil was purified by flash column chromatography (60:40 hexanes/ethyl acetate) to afford both the S_N2 product **21** (562 mg, 75%) and the S_N2' product **22** (116 mg, 16%).

4-(4′-Biphenyl)-3-methyl-2*E*-buten-1-ol (23). THP ether **15** (1.14 g, 6.12 mmol) was treated with CuI (1.30 g, 6.83 mmol) and the Grignard reagent prepared from commercially available 4-bromobiphenyl (9.10 g, 39.0 mmol) using the procedure described above for compound **19**. After the mixture was stirred for 4 h at 50 °C, the reaction mixture was quenched by addition of saturated NH_4Cl and extracted with ether and the combined organic extracts were concentrated under vacuum. Purification by flash column chromatography (60:40 hexanes/ethyl acetate) afforded both the S_N2 product **23** (1.12 g, 77%) and the S_N2' product **24** (220 mg, 15%) as white solids.

3-Bromobenzophenone (33). 3-Bromobenzaldehyde (5.50 g, 29.7 mmol) was dissolved in THF (30 mL) and treated with phenylmagnesium bromide (15.0 mL of a 2 M solution in THF, 30.0 mmol). After the mixture was stirred for 1 h, the reaction mixture was quenched by addition of saturated NH_4Cl and extracted with ether. Concentration of the ethereal extracts under vacuum afforded an oil, which was dissolved immediately in CH_2Cl_2 (60 mL). PDC (15.5 g, 41.2 mmol) and molecular sieve powder (2 g) were subsequently added to the solution, and the resulting dark brown mixture was allowed to stir for 3 h at room temperature. Filtration of the reaction mixture through a thin layer of silica gel, concentration of the filtrate under vacuum, and purification by flash column chromatography (90:10 toluene/hexanes) afforded 3-bromobenzophenone[23] (**33**) as a white solid (6.87 g, 89%). Both ^{1}H and ^{13}C NMR spectra agreed with literature data.

1-Bromo-3-benzylbenzene (25). Excess $NaBH_4$ pellets (∼2.4 g, 63.5 mmol) were added slowly (1 pellet/ 5 min) to trifluoroacetic acid (30 mL) stirring at 0 °C. After the $NaBH_4$ addition was complete (∼30 min), a solution of 3-bromobenzophenone (2.04 g, 7.83 mmol) in CH_2Cl_2 (15 mL) was added dropwise via cannula, and the solution turned from clear to yellow to cloudy white upon ketone addition. After the mixture was stirred for 21 h, the reaction mixture was diluted with distilled water (20 mL) and adjusted to pH ∼10 by addition of solid NaOH. Extraction with ether, concentration under vacuum, and purification by column chromatography (80:20 toluene/hexanes) afforded the desired aryl bromide **25** (1.51 g, 78%): ^{1}H NMR δ 7.31−7.03 (m, 9H), 3.86 (s, 2H); ^{13}C NMR δ 143.3, 140.0, 131.8, 129.9, 129.1, 128.8 (2C), 128.5 (2C), 127.5, 126.3, 122.5, 41.4. Anal. Calcd for $C_{13}H_9Br$: C, 63.41; H, 4.51. Found: C, 63.35; H, 4.55.

1-Benzyl-3-(4′-hydroxy-2′-methyl-2′*E*-butenyl)benzene (26). According to the procedure described above for compound **19**, THP ether **15** (190 mg, 1.02 mmol) was treated with CuI (305 mg, 1.61 mmol) and the Grignard reagent prepared from aryl bromide **25** (1.32 g, 5.35 mmol). After the mixture was stirred for 2 h at 50 °C, standard workup and purification of the resulting oil by flash column chromatography (60:40 hexanes/ethyl acetate) afforded both the S_N2 coupled product **26** (158 mg, 61%) and the S_N2' product **27** (31 mg, 12%).

3-Bromobenzophenone acetal (28). Benzophenone **33** (2.22 g, 8.51 mmol) was added to a mixture of toluene (20 mL), ethylene glycol (3.1 mL, 55.6 mmol), and *p*TsOH (245 mg, 1.29 mmol) stirring in a 100 mL round-bottom flask. The flask was fitted with a Dean−Stark trap, and the reaction mixture was heated to reflux. After 16 h, the reaction was diluted with

(38) Bosse, F.; Tunoori, A. R.; Maier, M. E. *Tetrahedron* **1997**, *53*, 9159−9168.

water and extracted with ether. TLC analysis (90:10 toluene/hexanes) of the concentrated organic fractions showed a mixture of desired ketal **28** ($R_f = 0.53$, stains pink with iodine) and starting material **33** ($R_f = 0.45$, stains yellow with iodine). These two compounds were not readily separated by column chromatography (90:10 toluene/hexanes), but some fractions of the pure ketal **28** could be isolated (1.31 g, 51%): ^{1}H NMR δ 7.70 (dd, 1H, J = 1.9, 1.9 Hz), 7.52−7.25 (m, 7H), 7.16 (dd, 1H, J = 7.9, 7.9 Hz), 4.03 (s, 4H); ^{13}C NMR δ 144.6, 141.5, 131.1, 129.7, 129.1, 128.2 (2C), 128.2, 125.9 (2C), 124.8, 122.3, 108.6, 64.9 (2C). Anal. Calcd for $C_{15}H_{13}BrO_2$: C, 59.21; H, 4.31. Found: C, 59.10; H, 4.24.

Ketal 29. According to the procedure described above for compound **19**, THP ether **15** (166 mg, 0.89 mmol) was treated with CuI (255 mg, 1.34 mmol) and the Grignard reagent prepared from aryl bromide **28** (1.51 g, 4.97 mmol). After the mixture was stirred for 4 h at 50 °C, standard workup and purification of the resulting oil by column chromatography on silica gel (60:40 hexanes/ethyl acetate) afforded both the S_N2 coupled product **29** (148 mg, 54%) and the S_N2' product **30** (29 mg, 10%).

3-(4′-Hydroxy-2′-methyl-2′*E*-butenyl) benzophenone (31). Alcohol **29** (93 mg, 0.30 mmol) was dissolved in acetone (10 mL) and treated with PPTS (26 mg, 0.10 mmol). The resulting suspension was heated to reflux and stirred for 23 h. The reaction mixture was then diluted with $NaHCO_3$ and extracted with ether and the combined organic extracts were concentrated in vacuo. Final purification by flash column chromatography (60:40 hexanes/ethyl acetate) afforded the desired benzophenone **31** as a clear oil (70 mg, 88%): ^{1}H NMR δ 7.82−7.75 (m, 2H), 7.66−7.34 (m, 7H), 5.49 (tq, 1H, J = 6.8, 1.2 Hz), 4.16 (d, 2H, J = 6.7 Hz), 3.37 (s, 2H), 2.05 (br s, 1H), 1.61 (s, 3H); ^{13}C NMR δ 196.8, 139.7, 137.5, 137.4 (2C), 133.0, 132.3, 130.3, 129.9 (2C), 128.1 (3C), 128.1, 126.0, 59.0, 45.6, 16.0; HRMS calcd for $C_{18}H_{18}O_2$ $(M + Na)^+$ 289.1188, found 289.1194.

Effects of CuI on THP Ether Substitution 3,7-Dimethyl-1-phenyl-2*E*,6*E*-octadiene (36). *Absence of CuI*: To a solution of THP ether **35**[14] (272 mg, 1.14 mmol) in THF (10 mL) was added phenylmagnesium bromide (1.8 mL of a 3 M solution, 5.40 mmol). No coupled product was observed after 17 h at 50 °C.

Catalytic CuI: To a solution of THP ether **35** (252 mg, 1.06 mmol) in THF (10 mL) was added CuI (20.1 mg, 0.106 mmol) and phenylmagnesium bromide (1.8 mL of a 3 M solution, 5.40 mmol). The reaction mixture was stirred at 50 °C and product formation was monitored by TLC analysis. After the mixture was stirred for 17 h, the reaction appeared to be complete. The resulting mixture was quenched by addition of saturated NH_4Cl and extracted with ether and combined organic extracts were concentrated under vacuum. Purification of the residue by flash column chromatography (95:5 hexanes/toluene) afforded the product **36**[39] (211 mg, 93%) as a clear oil. Both ^{1}H and ^{13}C NMR were identical to literature values.[39]

Excess CuI: To a solution of THP ether **35** (247 mg, 1.04 mmol) in THF (10 mL) was added CuI (300 mg, 1.58 mmol) and phenylmagnesium bromide (1.8 mL of a 3 M solution, 5.40 mmol). After the mixture was stirred for 1.5 h, the reaction was observed to be complete by TLC analysis. The mixture was then quenched by addition of saturated NH_4Cl and extracted with ether and the combined organic extracts were concentrated in vacuo. The resulting oil was purified by column chromatography to afford the coupled product **36** (204 mg, 92%).

Comparison of Ether Displacement: 3,7-Dimethyl-1-phenyl-2*E*,6*E*-octadiene (36). In a parallel set of reactions, the methyl (**37**,[40] 247 mg, 1.47 mmol), phenyl (**38**,[41] 254 mg, 1.10 mmol), ethoxyethyl (**39**,[42] 264 mg, 1.17 mmol), and THP (**35**,[14] 247 mg, 1.04 mmol) ether derivatives of geraniol were dissolved in THF (10 mL) and treated with excess CuI (1.5 equiv) and phenylmagnesium bromide (5.0 equiv). All four flasks were heated to 50 °C, and the reaction mixtures were monitored by TLC analysis. After 1.5 h, THP ether **35** appeared to be completely converted to the coupled product **36**. This reaction was quenched by addition of saturated NH_4Cl and extracted with ether and the combined extracts were concentrated in vacuo to afford after purification by column chromatography (95:5 hexanes/toluene) the coupled product **36** (204 mg, 92%). The other three ethers were allowed to stir for 17 h at 50 °C. Upon standard workup and purification by column chromatography, methyl ether **37** afforded a 20% yield of coupled product (64 mg), phenyl ether **38** gave a 55% yield of product (131 mg), and ethoxyethyl ether **39** provided an 80% yield of the coupled product **36** (199 mg).

1-Phenyl-2*E*-octene (41) and 3-phenyl-1-octene (42). A solution of known[43] THP ether **40** (414 mg, 1.95 mmol) in THF (10 mL) was treated with phenylmagnesium chloride (5 mL of a 2 M solution, 10 mmol) in the presence of CuI (581 mg, 3.05 mmol). The reaction mixture was heated to 50 °C and monitored by TLC analysis. After 3 h, the reaction was quenched by addition of saturated NH_4Cl and extracted with hexanes and the combined organic extracts were concentrated under vacuum. Purification by column chromatography (hexanes) afforded a mixture of the S_N2 coupled product **41**[44] and trace amounts of the S_N2' product **42**[44] (314 mg, 85%, >50:1 ratio of S_N2/S_N2' as observed by ^{1}H NMR).

1-Phenyl-2*Z*-hexene (44) and 3-Phenyl-1-hexene (45). A solution of THP ether **43**[45] (538 mg, 2.93 mmol) in THF (10 mL) was treated with phenylmagnesium chloride (7.5 mL of a 2 M solution, 15 mmol) in the presence of CuI (841 mg, 4.42 mmol). The reaction mixture was heated to 50 °C and monitored by TLC analysis. After 3 h, standard workup and purification by column chromatography (hexanes) afforded a mixture of the S_N2 product **44**[46] and the S_N2' product **45**[47] (418 mg, 89%, 7.3:1.0 ratio of S_N2/S_N2' as observed by ^{1}H NMR).

3-Phenyl-1-octene (42) and *E*/*Z*-1-Phenyl-2-octene (41). A solution of THP ether **46**[48] (505 mg, 2.38 mmol) in THF (10 mL) was treated with phenylmagnesium chloride (6 mL of a 2 M solution, 12 mmol) in the presence of CuI (692 mg, 3.64 mmol). The reaction mixture was heated to 50 °C and monitored by TLC analysis. After 3 h, standard workup and purification by column chromatography (hexanes) afforded a mixture of the S_N2 product **42**[44] and the cis/trans isomers of the S_N2' product **41**[44] (425 mg, 95%, 11.5:1.0 ratio of S_N2'/S_N2 products; the S_N2' product **41** is in a 1.2:1.0 ratio of cis/trans isomers as observed by ^{1}H NMR). Data for olefins *E*-**41** and **42** agreed with that reported above.

3,7,11-Trimethyl-2*E*,6*E*-dodecadien-1-ol (47). Ground Mg^0 turnings (702 mg, 28.9 mmol) were placed in a flame-dried, 100 mL three-necked flask followed by addition of THF (20 mL) and a crystal of iodine. Commercially available 3-methyl-1-bromobutane (2.40 mL, 20.0 mmol) in 10 mL of THF was added dropwise via cannula, and formation of the Grignard reagent was observed by the disappearance of Mg^0. THP ether **11** (499 mg, 1.96 mmol) was dissolved in THF (10 mL) in a second 100 mL flask and cooled to −35 °C. Addition of CuBr (501 mg, 3.49 mmol) in one portion to the THP ether solution was followed by dropwise addition of the freshly prepared Grignard reagent via cannula. The resulting mixture

(39) Bäckvall, J.-E.; Persson, E. S. M.; Bombrun, A. *J. Org. Chem.* **1994**, *59*, 4126−4130.
(40) Burk, R. M.; Gac, T. S.; Roof, M. B. *Tetrahedron Lett.* **1994**, *35*, 8111−8112.
(41) Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585−4593.
(42) Still, W. C.; McDonald, J. H.; Collum, D. B.; Mitra, A. *Tetrahedron Lett.* **1979**, 593−594.
(43) Porter, N. A.; Ziegler, C. B., Jr.; Khouri, F. F.; Roberts, D. H. *J. Org. Chem.* **1985**, *50*, 2252−2258.
(44) Mizojiri, R.; Kobayashi, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2073−2075.
(45) Kantam, M. L.; Santhi, P. L. *Synth. Commun.* **1993**, *23*, 2225−2228.
(46) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-I. *J. Org. Chem.* **1997**, *62*, 6997−7005.
(47) Flemming, S.; Kabbara, J.; Nickisch, K.; Westermann, J.; Mohr, J. *Synlett* **1995**, 183−185.
(48) Maiti, G.; Roy, S. C. *J. Org. Chem.* **1996**, *61*, 6038−6039.

was stirred at −35 °C for 1 h and then allowed to warm gradually to −10 °C. After the mixture was stirred for 48 h, the resulting dark brown suspension was quenched by addition of NH_4Cl and extracted with ether and the combined organic extracts were concentrated in vacuo. Final purification by column chromatography (70:30 hexanes/ethyl acetate) afforded (2*E*,6*E*)-10,11-dihydrofarnesol **47**[29c] as a clear oil (355 mg, 81%): ^{1}H NMR δ 5.40 (tq, 1H, J = 6.9, 1.3 Hz), 5.10 (tq, 1H, J = 6.8, 1.3 Hz), 4.12 (d, 2H, J = 6.8 Hz), 2.37 (br s, 1H), 2.16−1.99 (m, 4H), 1.94 (t, 2H, J = 7.3 Hz), 1.67 (s, 3H), 1.58 (s, 3H), 1.57−1.11 (m, 5H), 0.87 (d, 6H, J = 6.5 Hz); ^{13}C NMR δ 139.1, 135.5, 123.5, 123.4, 59.0, 39.8, 39.5, 38.5, 27.7, 26.2, 25.6, 22.5 (2C), 16.1, 15.7.

3,7,11-Trimethyl-2*E*,6*E*-dodecadienyl Benzyl Ether (50) and 6-Isoamyl-3,7-dimethyl-2*E*,7-octadienyl Benzyl Ether (51). Alcohol **48**[49] (510 mg, 1.96 mmol) in THF (20 mL) at 0 °C was treated with pyridine (0.05 mL, 0.62 mmol) and PBr_3 (0.10 mL, 1.05 mmol). The resulting suspension was stirred for 1 h and then washed with $NaHCO_3$. Extraction with ether, treatment with $MgSO_4$, and filtration through Celite afforded bromide **49**[50] as a yellow oil. The Grignard reagent derived from 3-methyl-1-bromobutane (1.0 mL, 8.35 mmol) was then prepared in the typical manner, using Mg^0 turnings (206 mg, 8.47 mmol) and a crystal of iodine. CuI (50.2 mg, 0.26 mmol) was added in one portion to bromide **49**, stirring at room temperature in THF (10 mL) followed by immediate addition of the freshly prepared Grignard reagent. After the mixture was stirred for 5 h, the resulting mixture was quenched by addition of NH_4Cl and extracted with ether and the organic extracts were concentrated in vacuo. Purification by column chromatography (90:10 hexanes/ethyl acetate) afforded a mixture of the S_N2 (**50**)[51] and S_N2' (**51**) substitution products in a 1.0:1.9 ratio as determined by ^{1}H NMR (346 mg, 56%).

For the S_N2 product **50**: ^{1}H NMR δ 7.35−7.21 (m, 5H), 5.39 (tq, 1H, J = 6.8, 1.3 Hz), 5.10 (tq, 1H, J = 6.7, 1.1 Hz), 4.48 (s, 2H), 4.01 (d, 2H, J = 6.6 Hz), 2.15−1.89 (m, 6H), 1.63 (s, 3H), 1.58 (s, 3H), 1.57−1.10 (m, 5H), 0.85 (d, 6H, J = 6.6 Hz).

For S_N2' product **51**: ^{1}H NMR (selected) δ 4.75−4.73 (m, 1H), 4.67−4.65 (m, 1H), 1.62 (s, 3H), 0.86 (d, 6H, J = 6.5 Hz).

The same reaction was also performed at −78 °C, and similar results were obtained (1.0:2.0 of **50**:**51**, 205 mg, 27%).

General Procedure for *n*-Butylmagnesium Bromide Addition to Allylic Bromides and THP Ethers. 2,6-dimethyl-2*E*,6*E*-dodecadiene (52) and 3-*n*-Butyl-3,7-dimethyl-1,6*E*-octadiene (53). THP ether **35** (288 mg, 1.21 mmol) was dissolved in THF (10 mL), the solution was cooled to −30 °C and treated with CuBr (261 mg, 1.82 mmol) and *n*-butylmagnesium chloride (3.3 mL of a 2 M solution in THF, 6.6 mmol). After the mixture was stirred for 1 h, the reaction mixture was allowed to gradually warm to −10 °C and then stirred for an additional 42 h. The resulting suspension was quenched by addition of NH_4Cl and extracted with ether and the combined extracts were concentrated in vacuo and then purified by column chromatography (hexanes) to afford a >50:1 mixture of S_N2(**52**)/S_N2'(**53**) coupled products as determined by ^{1}H NMR analysis (130 mg, 56%).

For the S_N2 product **52**: ^{1}H NMR spectrum agreed with literature data;[20a,57] ^{13}C NMR δ 134.7, 131.1, 124.9, 124.5, 39.8, 31.6, 29.6, 27.9, 26.8, 25.7, 22.7, 17.6, 15.9, 14.1.

For the S_N2' product **53**: ^{1}H NMR spectrum agreed with literature data;[52,57] ^{13}C NMR (selected) δ 147.5, 125.2, 111.3, 40.8, 40.6, 39.4, 26.3, 23.6, 22.9, 22.6, 17.5, 14.1.

In a parallel reaction, a solution of geranyl bromide **54** (0.22 mL, 1.11 mmol) in THF (10 mL) was cooled to −30 °C and treated with CuBr (260 mg, 1.81 mmol) and *n*-butylmagnesium chloride (3.3 mL of a 2 M solution in THF, 6.6 mmol) under the same reaction conditions described above. After 1 h, the reaction mixture was allowed to warm to −10 °C and left to stir overnight (17 h). The resulting suspension was quenched by addition of NH_4Cl and extracted with ether the combined organic extracts were and then purified by column concentrated in vacuo chromatography (hexanes) to afford a 6.3:1.0 mixture of S_N2(**52**)/S_N2'(**53**) products as measured by ^{1}H NMR (223 mg, 100%).

6*E*-Dodecene (55) and 3-*n*-Butyl-1-octene (56). In a set of reactions similar to those described in the general procedure above, THP ether **40**[43] (521 mg, 2.46 mmol) in THF (10 mL) at −30 °C was treated with CuBr (582 mg, 4.05 mmol) and *n*-butylmagnesium chloride (7.6 mL of a 2 M solution in THF, 15.2 mmol). After the mixture was stirred for 2 h, the reaction mixture was quenched and the products were purified under standard conditions to afford a >50:1 mixture of S_N2(**55**)/S_N2'-(**56**) substitution products as determined by ^{1}H NMR analysis[53,54] (366 mg, 89%).

Bromide **57**[55] (527 mg, 2.76 mmol) was treated with *n*-BuMgCl reaction conditions as described above for THP ether **40**. After the mixture was stirred for 2 h at −30 °C, standard workup and purification provided a 3.3:1.0 mixture of S_N2-(**55**)/S_N2'(**56**) products (385 mg, 83%).

4-Decene (58) and 3-*n*-Propyl-1-heptene (59). Following the general procedure described above, THP ether **43**[45] (626 mg, 3.40 mmol) in 10 mL THF at −30 °C was treated with CuBr (723 mg, 5.04 mmol) and *n*-BuMgCl (9.0 mL of a 2 M solution in THF, 18.0 mmol). After 1 h, the reaction mixture was allowed to warm to −10 °C and then stirred for an additional 24 h. Standard workup and purification provided a >50:1 ratio of S_N2 (**58**)/S_N2' (**59**) products as measured by ^{1}H NMR analysis[56] (302 mg, 64%). On the basis of ^{1}H and ^{13}C NMR data, alkene **58** was a 1:1 mixture of cis/trans isomers.

Bromide **60**[58] (518 mg, 3.18 mmol) was subjected to reaction conditions as described above for THP ether **43**. The reaction mixture was stirred for 7 h and then purified using standard procedures. A 2.6:1 ratio of S_N2/S_N2' products (**58**:**59**) was observed by ^{1}H NMR (210 mg, 47%), and only trace amounts of isomerized trans S_N2 product could be detected.

6-Dodecene (55) and 3-*n*-Butyl-1-octene (56) from Ether 46 and Bromide 61. THP ether **46**[48] (631 mg, 2.98 mmol) was treated with CuBr (660 mg, 4.60 mmol) and *n*-BuMgCl (7.5 mL of a 2 M solution in THF, 15 mmol) at −30 °C in THF (10 mL). After 1 h, the reaction mixture was allowed to warm gradually to −10 °C and then stirred for an additional 24 h. Standard workup and purification provided a >50:1 ratio of S_N2'/S_N2 products (**55**:**56**) as determined by ^{1}H NMR analysis (333 mg, 67%). Data for olefins *E*-**55** and **56** agreed with that reported above.

The bromide **61**[59] (620 mg, 3.25 mmol) was subjected to similar conditions as THP ether **46**, and workup of the resulting suspension afforded a 1.5:1.0 mixture of S_N2'/S_N2 (**55**:**56**) products (375 mg, 69%). In the S_N2' products from both the THP ether and bromide, small amounts of the cis isomer could be observed in the ^{13}C NMR spectra, but it was not possible to determine this ratio by ^{1}H NMR.

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(49) (a) Altman, L. J.; Ash, L.; Marson, S. *Synthesis* **1974**, 129−131. (b) Masaki, Y.; Iwata, I.; Mukai, I.; Oda, H.; Nagashima, H. *Chem. Lett.* **1989**, 659−662.

(50) Masaki, Y.; Hashimoto, K.; Iwai, H.; Kaji, K. *Chem. Lett.* **1978**, 1203−1204.

(51) Miyakoshi, T.; Takazawa, H.; Hagimoto, M. *Yukagaku* **1990**, *39*, 83−86.

(52) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017−6028.

(53) Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1996**, *61*, 6770−6771.

(54) Mesnard, D.; Miginiac, L. *C. R. Acad. Sci., Ser. C* **1973**, *277*, 567−570.

(55) Nakanishi, S.; Yamamoto, T.; Furukawa, N.; Otsuji, Y. *Synthesis* **1994**, 609−612.

(56) Suzuki, N.; Kondakov, D. Y.; Takahashi, T. *J. Am. Chem. Soc.* **1993**, *115*, 8485−8486.

(57) Bäckvall, J. E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615−6621.

(58) Doyle, M. P.; Kalinin, A. V. *J. Org. Chem.* **1996**, *61*, 2179−2184.

(59) Haley, N. F.; Fichtner, M. W. *J. Org. Chem.* **1980**, *45*, 2959−2962.

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Supporting Information Available: The product characterization data for 20 compounds (**17**, **18**, **21**, **22**, **23**, **24**, **26**, **27**, **29**, **30**, *E*- and *Z*-**41**, **42**, **44**, **45**, *E*- and *Z*-**55**, **56**, *E*- and *Z*-**58**). This material is available free of charge via the Internet at http://pubs.acs.org.

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