J. Org. Chem. **2001,** *66,* 5881−5889 **5881**

Scope and Limitation of Organocuprates, and Copper or Nickel Catalyst-Modified Grignard Reagents for Installation of an Alkyl Group onto *cis*-4-Cyclopentene-1,3-diol Monoacetate

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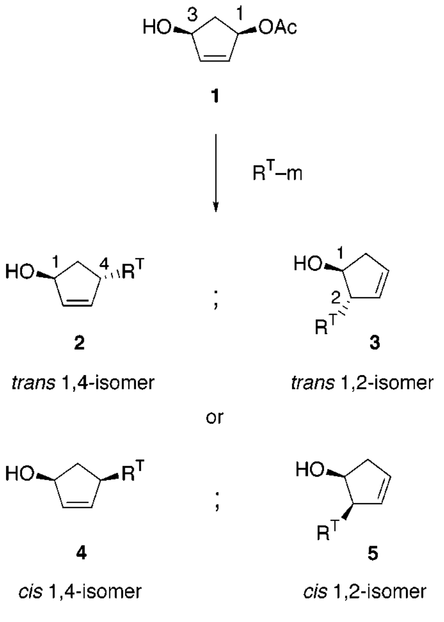
Received May 8, 2001

Alkylation of the title compound **1** was investigated with two types of reagents. One is a copper reagent derived from R^TMgX (X = Cl, Br) and CuX (X = CN, I) and the other is R^TMgX in the presence of a copper or a nickel catalyst. First, butylation was studied with BuCu(CN)(MgX), $Bu_2Cu(CN)(MgX)_2$, BuMgX/CuCN (10 mol %), BuCu (derived from BuMgCl and CuI), and BuMgCl/CuI (10 mol %) in THF or Et_2O. We found that trans 1,4-isomer **2a** and/or trans 1,2-isomer **3a** were produced exclusively with these reagents and that the stoichiometry of BuMgX/CuX and the choice of solvent were critical to attain high regioselectivity and efficient yield. Reaction with $Bu_2Cu(CN)(MgCl)_2$ and BuMgCl/CuX (X = CN, I; 10 mol %) both in THF produced **2a** with 93−94% regioselectivity in 87−92% yields. On the other hand, BuCu(CN)(MgX) in THF, $Bu_2Cu(CN)(MgX)_2$ in Et_2O, and BuMgX/CuCN (10 mol %) in Et_2O furnished **3a** in good yields with >90% selectively, irrespective of X of BuMgX. In the nickel-catalyzed butylation of **1** with BuMgCl, $NiCl_2(dppp)$ among $NiCl_2(tpp)_2$, $NiCl_2(dppf)$, and $NiCl_2(dppp)$ furnished the best result to produce **2a**. The CuCN-based protocol was then applied to other alkyl Grignard reagents, which include Me, Et, $(CH_2)_3Ph$, c-C_6H_{11}, $(CH_2)_6OMOM$, $(CH_2)_9CH{=}CH_2$, and CH_2Ph as the alkyl group (R^T). In addition, the Mitsunobu inversion of **2a** and **3a** afforded the corresponding cis isomers stereoselectively with AcOH as an acid at −78 °C in toluene for **2a** and with $4\text{-}(NO_2)C_6H_4COOH$ in THF at r.t. for **3a**. No racemization during the alkylation was confirmed by the reaction using (1*R*,3*S*)-**1** (>99% ee) to produce (1*S*,4*S*)-**2a** and (1*S*,2*S*)-**3a**, respectively.

Introduction

Preparation of monoacetate of 4-cyclopentene-1,3-diol (**1**)[1] with high enantiomeric excess (ee) of > 95% has been actively studied in the last two decades.[2] With the establishment of the method, acetate **1** has become attractive as a starting compound in organic synthesis, especially in the synthesis of five-membered molecules.[3] As illustrated in Chart 1, a substitution reaction of **1** with conventional nucleophiles or organometallics (R^T-m) is one method to attach a side chain onto the cyclopentene ring. The products **2**−**5** are rich in functional groups on

Chart 1. Reaction of 1 and Organometallics (R^T-m)[a]



[a] Reagents and conditions furnishing trans isomers **2** or **3** with an alkyl group as R^T are described in the text. R^T = Bu for **2a** and **3a**. Other R^T, see Chart 2

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(1) One enantiomer is shown to indicate the relative stereochemistry properly. For convenience, racemic **1** was used for the present investigation unless otherwise specified.

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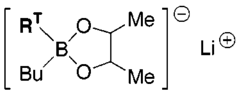
(3) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480−492.

10.1021/jo010474w CCC: $20.00

the ring, thus allowing further carbon−carbon forming reactions and/or chemical decoration of the ring. Consequently, the selectivity to produce one of the four isomers as well as the scope of R^T to be installed on the ring is an important issue of this reaction. Two types of reactions have been reported to date. These are the nickel-catalyzed reaction with alkenyl or aryl borates of the general structure **6** providing trans 1,4-isomers **2**,[4] and the palladium-catalyzed reaction with soft nucleophiles producing cis 1,4-isomers **4**.[5] The former reaction was developed recently by us. With these reactions, efficient syntheses of the primary prostaglandins (PGs),[4b] Δ^7-PGA_1 methyl,[6] aristeromycin,[7,8] and strychnine[9] have been developed by us and other groups.



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R^T: alkenyl and aryl groups

These reactions are, however, not amenable to installation of an alkyl group, though the alkenyl or malonate-type groups introduced by the reactions mentioned above are convertible to any alkyl group by a multistep sequence, though probably with less efficiency. In our attempt, a nickel-catalyzed reaction[10] of **1** with butylborate (**6** of R^T = Bu) aimed to produce **2** of R^1 = Bu was unsuccessful. This situation prompted us to explore a reaction with reagents derived from alkylmagnesium halides (R^TMgX) and CuX. In general, the anti S_N2' reaction is a favorable process with these reagents,[11] as is observed with the copper reagents derived from RLi and other organometallics.[11b,11e,12] However, this mode of the reaction is highly susceptible to steric hindrance around the allylic moiety of the allylic substrates, conjugation of the moiety with a π-electron system, reactivity of a leaving group, and the stereochemistry of the leaving group relative to another substituent. Accordingly, in the case of the monoacetate **1**, influence of the hydroxyl group upon the selectivity as well as the reactivity was not predictable.[13] In addition, coordination of the group to the reagent is likely to result in syn substitution as is observed with the lithium cuprates.[14] Fortunately, the reagents and conditions to afford trans 1,4- or 1,2-products (**2** or **3**) have been elucidated. The stoichiometry of R^T-MgX (X = Cl, Br)/CuX (X = CN, I)[15] and the choice of solvent (Et_2O or THF) are critical to attain high regioselectivity and efficient yield.[16] We also studied a nickel-catalyzed reaction with R^TMgX, in which the ligand of the nickel catalyst was found to control the regiochemistry and the product selectivity. Herein, we report the scope and limitation of these reactions with various alkyl reagents of the primary and secondary classes including methyl, benzyl, and those possessing functional groups.

Results and Discussion

Butylation with the Reagents from BuMgX and CuX. Three types of reagents derived in situ from BuMgX (X = Cl, Br) and CuX (X = CN, I) with different compositions were investigated with racemic **1**.[17] The reactions were carried out at −18 °C for several hours in THF or Et_2O. In the cases the reaction was slow, the reaction temperature was raised to room temperature. The results are presented in Table 1 with "calculated yield" (equal to regioselectivity X combined yield), which is a useful parameter to assess efficiency of the reaction. In all cases, the trans products (**2a** and **3a**) were produced, and the corresponding cis isomers were not detected by ^1H NMR (300 MHz) spectroscopy, thus indicating no coordination of the copper reagents to the alkoxy oxygen at C(3) of **1**. Regarding the regioselectivity, the composition of BuMgX/CuX and the solvent (THF or Et_2O) were found to be the most important factors, as presented in the following paragraphs. Determination of the stereochemistry of the products and synthesis of the authentic samples of the cis isomers are described in the latter section of this paper.

When the lower order cuprate,[15] BuCu(CN)(MgCl), was examined in THF at 0 °C, trans 1,2-product **3a** was obtained with high regioselectivity in 90% calculated yield and in 89% isolated yield (Table 1, entry 1). The

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[12] Selected examples: (a) Goering, H. L.; Singleton, V. D., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854−7855. (b) Kreft, A. *Tetrahedron Lett.* **1977**, 1035−1036. (c) Tanigawa, Y.; Ohta, H.; Sonoda, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1978**, *100*, 4610−4612. (d) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318−2325. (e) Gallina, C. *Tetrahedron Lett.* **1982**, *23*, 3093−3096. (f) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422−426. (g) Goering, H. L.; Kantner, S. S.; Seitz, E. P., Jr. *J. Org. Chem.* **1985**, *50*, 5495−5499.

[13] Kang reported that $BF_3 \cdot OEt_2$-promoted allylation of acyclic compounds with RMgBr/CuX (R = Bu, Me; X = CN, I) in THF proceeds with the anti S_N2' mode.[11l] On the contrary, we observed the S_N2 reaction with BuMgX (X = Cl, Br)/CuCN in THF (see entries 2, 3, 12, and 13 of Table 1).

[14] (a) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035−1036. (b) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715−721. (c) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1985**, *50*, 1597−1599.

[15] In this paper, "lower order cuprate" and "higher order cuprate" are used to indicate the 1:1 and 2:1 compositions of R^TMgX and CuX, respectively, though the precise structures are still undetermined.

[16] A part of the reaction with R^TMgX and CuX was reported as a communication: Ito, M.; Murugesh, M. G.; Kobayashi, Y. *Tetrahedron Lett.* **2001**, *42*, 423−427.

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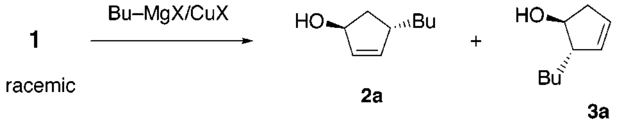
Table 1. Reaction of Acetate 1 with Reagents Derived from BuMgX and CuX



entry	reagent[a]	solvent	temp (°C)	time (h)	ratio of **2a**: **3a**[b]	combined yield (%)[b]	calcd yield (%)[b,c]	
							2a	**3a**
1	BuCu(CN)(MgCl)	THF	0	4	7:93	97	7	90 (89)
2	$Bu_2Cu(CN)(MgCl)_2$	THF	−18	3	93:7	94	87	7
3	BuMgCl, CuCN (10 mol %)	THF	−18	5	94:6	100	94 (85)	6
4	BuCu(CN)(MgCl)	Et_2O	r.t.	5	14:86	37	5	32
5	$Bu_2Cu(CN)(MgCl)_2$	Et_2O	−18	2	7:93	85	6	79
6	BuMgCl, CuCN (10 mol %)	Et_2O	−18	2	8:92	82	7	75
7	BuCu (from CuI + BuMgCl)	THF	0	4	40:60	22[d]	9	13
8	BuMgCl, CuI (10 mol %)	THF	−18	3	92:8	100	92	8
9	BuCu (from CuI + BuMgCl)	Et_2O	0	5	13:87	22[d]	3	19
10	BuMgCl, CuI (10 mol %)	Et_2O	−18	5	19:81	85	16	69
11	BuCu(CN)(MgBr)	THF	0	5	10:90	89[d]	9	80
12	$Bu_2Cu(CN)(MgBr)_2$	THF	−18	3	71:29	98	70	28
13	BuMgBr, CuCN (10 mol %)	THF	−18	3	73:27	96	70	26
14	BuCu(CN)(MgBr)	Et_2O	0	5	4:96	77[d]	3	74
15	$Bu_2Cu(CN)(MgBr)_2$	Et_2O	−18	3	6:94	88	5	83
16	BuMgBr, CuCN (10 mol %)	Et_2O	−18	3	5:95	94	5	89

[a] Three (3) equivalents of the reagents were used. [b] Determined by ^1H NMR spectroscopy. For calculation of the yields, pyridine was used as an internal standard. [c] Isolated yields are given in parentheses. [d] Acetate **1** was recovered in 67% (entry 7), 13% (entry 9), 6% (entry 11), and 7% (entry 14) yields, respectively.

regioselectivity was totally changed with the higher order cuprate[15] ($Bu_2Cu(CN)(MgCl)_2$) in THF to furnish 1,4-isomer **2a** with calculated yield of 87% yield (entry 2). An almost similar efficiency was obtained with BuMgCl/CuCN (10 mol %) in THF (entry 3). Surprisingly, the regioselectivity for $Bu_2Cu(CN)(MgCl)_2$ and BuMgCl/CuCN (cat.) was *reversed in* Et_2O (entries 5 and 6); moreover, the product **3a** was isolated with good efficiency. On the other hand, BuCu(CN)(MgCl) in Et_2O produced a mixture of unidentified compounds, though **3a** was a major product (entry 4). We then examined CuI-based reagents in THF and Et_2O, respectively (entries 7−10). The same tendency of the selectivity as for the CuCN-based reagents was observed with the 1:1 composition and the copper-catalyzed reagent in each of the solvents. However, a high level of efficiency was recorded only with BuMgCl/CuI (cat.) in THF giving 1,4-product **2a** (entry 8). The same reagent in Et_2O furnished moderate selectivity (entry 10). On the other hand, BuCu derived from CuI and BuMgCl showed less reactivity both in THF and in Et_2O (entries 7 and 9).

A similar reactivity and the same tendency for the regioselectivity (**2a**/**3a**) were recorded with three kinds of BuMgBr-based reagents (entries of 11−16 of Table 1). Among them, BuCu(CN)(MgBr) in THF, $Bu_2Cu(CN)(MgBr)_2$ in Et_2O, and BuMgBr/CuCN (cat.) in Et_2O were the reagents of choice to furnish 1,2-isomer **3a** efficiently (entries 11, 15, and 16). Other combinations of the reagent/solvent furnished moderate selectivity for **2a** (entries 12 and 13; cf. entries 2 and 3) or a somewhat low reactivity (entry 14).

In conclusion, entries 2, 3, and 8 are suitable for the production of **2a**, while entries 1, 5, 6, 11, 15, and 16 are recommended for the preparation of **3a**.

Nickel-Catalyzed Butylation with BuMgX. This reaction was investigated in THF and Et_2O at 0 °C for several hours. The nickel catalysts we examined were $NiCl_2(tpp)_2$, $NiCl_2(dppf)$, and $NiCl_2(dppp)$, and the results are summarized in Table 2. The reaction was highly dependent on the ligand (entries 1−4), and the best results were obtained with dppp, producing the trans 1,4-isomer **2a** in high yields (entries 3 and 4). The bromine atom in the Grignard reagent decreased the regio- and/or product-selectivities substantially (entries 5 and 6). Since the conditions to afford 1,2-isomer **3a** were not elucidated with this reagent system, which was always accompanied with the production of a small quantity of **5a** (cis isomer of **3a**), further investigation was dropped.

Table 2. Nickel-catalyzed Reaction of Acetate 1 with BuMgX[a]

entry	reagent	catalyst[c]	solvent	ratio[b] of **2a**:**3a**:**5a**[d]	combined yield (%)[b]
1	BuMgCl	$NiCl_2(tpp)_2$	THF	−	−[e]
2	BuMgCl	$NiCl_2(dppf)$	THF	−	−[e]
3	BuMgCl	$NiCl_2(dppp)$	THF	89:5:6	89
4	BuMgCl	$NiCl_2(dppp)$	Et_2O	93:5:2	80
5	BuMgBr	$NiCl_2(dppp)$	THF	79:5:16	86
6	BuMgBr	$NiCl_2(dppp)$	Et_2O	−	−[e]

[a] Reactions were carried out with BuMgX (3 equiv) and a nickel catalyst (10 mol %) in THF or Et_2O for several hours. [b] Determined by ^1H NMR spectroscopy. For calculation of the yields, pyridine was used as an internal standard. [c] tpp: Triphenylphosphine. dppf: 1,1′-Bis(diphenylphosphino)ferrocene. dppp: 1,4-Bis(diphenylphosphino)butane. [d] R^T = *n*-Bu. [e] A mixture of products was obtained.

Synthesis of Cis 1,4- and 1,2-Isomers. Next, Mitsunobu inversion[18] of **2a** and **3a** was studied in order to produce cis isomers **8** and **10** (Scheme 1), which have the same relative stereochemistry with that of compounds **4** and **5** in Chart 1 with R^T = Bu, respectively. The inversion of 1,2-isomer **3a** was accomplished under the standard conditions using $4\text{-}(NO_2)C_6H_4CO_2H$ in THF at room temperature to produce ester **9**, which upon hydrolysis afforded cis 1,2-isomer **10** in good yield. On the contrary, 1,4-isomer **2a** under these conditions furnished a mixture of products. Fortunately, we found that AcOH in toluene at −78 °C for 6 h produced acetate **7** exclusively, and subsequent hydrolysis afforded cis 1,4-isomer

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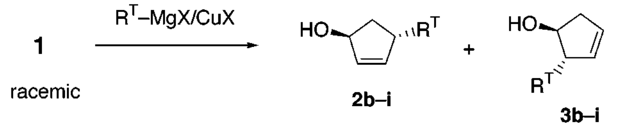
(18) Mitsunobu, O. *Synthesis* **1981**, 1−28.

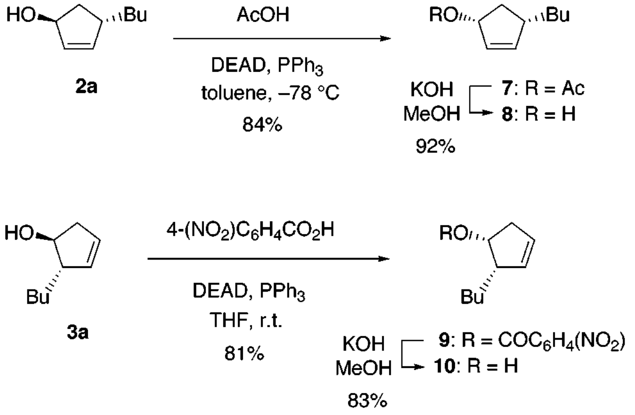
Table 3. Reaction of Acetate 1 with Reagents Derived from R^TMgX and CuCN



entry	suffix for **2** and **3**	reagent[a]	solvent	temp (°C)	time (h)	ratio of **2**: **3**[b]	combined yield (%)[b]	calcd yield (%)[b,c]	
								2	**3**
1	**b**	MeCu(CN)(MgCl)	THF	0	5	9:91	51[d]	5	46
2	**b**	MeCu(CN)(MgCl)[e]	THF	r.t.	8	9:91	94	8	86
3	**b**	$Me_2Cu(CN)(MgCl)_2$	THF	−18	4	93:7	86	80	6
4	**b**	MeMgCl, CuCN (10 mol %)	THF	−18	5	95:5	56[d,f]	53	3
5	**c**	EtCu(CN)(MgCl)	THF	0	5	5:95	87	4	83
6	**c**	EtMgCl, CuCN (10 mol %)	THF	−18	3	94:6	91	86	5
7	**d**	$[Ph(CH_2)_3]_2Cu(CN)(MgBr)_2$	Et_2O	−18	5	3:97	97	3	94 (96)
8	**d**	$Ph(CH_2)_3MgCl$, CuCN (10 mol %)	THF	−18	5	91:9	100	91 (87)	9
9	**e**	$(c\text{-}C_6H_{11})_2Cu(CN)(MgCl)_2$	Et_2O	−18	4	7:93	85	6	79
10	**e**	$(c\text{-}C_6H_{11})MgCl$, CuCN (10 mol %)	Et_2O	−18	4	9:91	91	8	83 (81)
11	**e**	$(c\text{-}C_6H_{11})_2Cu(CN)(MgCl)_2$	THF	−18	4	77:23	79	61	18
12	**e**	$(c\text{-}C_6H_{11})MgCl$, CuCN (10 mol %)	THF	−18	5	89:11	78	69 (66)	9
13	**f**	$MOMO(CH_2)_6Cu(CN)(MgCl)$	THF	0	5	4:96	98	4	94 (91)
14	**f**	$MOMO(CH_2)_6MgCl$, CuCN (10 mol %)	THF	−18	5	94:6	101	95 (92)	6
15	**g**	$[CH_2{=}CH(CH_2)_9]Cu(CN)(MgCl)$	THF	0	5	4:96	100	4	96 (91)
16	**g**	$CH_2{=}CH(CH_2)_9MgCl$, CuCN (10 mol %)	THF	−18	5	95:5	102	97 (90)	5
17	**h**	$PhCH_2Cu(CN)(MgCl)$	THF	0	5	11:89	90	10	80 (75)
18	**h**	$(PhCH_2)_2Cu(CN)(MgCl)_2$	THF	−18	4	90:10	94	85 (82)	9
19	**h**	$PhCH_2MgCl$, CuCN (10 mol %)	THF	−18	4	91:9	91	83 (82)	8
20	**i**	$CH_2{=}CHCH_2Cu(CN)(MgCl)$	THF	0	5	39:61	64[d]	25	39
21	**i**	$(CH_2{=}CHCH_2)_2Cu(CN)(MgCl)_2$	THF	−18	5	–	–[f]		

[a] Three (3) equivalents of the reagents were used unless otherwise noted. [b] Determined by ^1H NMR spectroscopy. For calculation of the yields, pyridine was used as an internal standard. [c] Isolated yields are given in parentheses. [d] Acetate **1** was recovered in 40% (entry 1), 9% (entry 4), and 34% (entry 20) yields. [e] Five (5) equiv of the reagent was used. [f] The corresponding diol was produced in 6% (entry 4) and 33% (entry 21) yields.

Scheme 1. Synthesis of Cis Isomers of 2a and 3a



8 in 77% yield for the two steps. Since the reagents and conditions adopted for the inversion of **2a** and **3a** seem independent of the size of the alkyl group (R^T) on **2** and **3** of Chart 1, a variety of cis isomers with an alkyl group would similarly be synthesized with high efficiency.[19]

Reaction with Other Alkyl Reagents. The best protocols elucidated for the butylation of **1** (Table 1) were applied to other alkyl Grignard reagents, and the results are summarized in Table 3. A variety of alkyl groups, except for the allyl group, were efficiently introduced onto **1** furnishing 1,4-isomers **2b**−**h** or 1,2-isomers **3b**−**h** depending on the conditions (Chart 2). In the following paragraphs, the results are presented in detail.

Methylation with MeCu(CN)(MgCl) (3 equiv) at 0 °C in THF was slower than the butylation, and a mixture of 1,2-isomer **3b** and substrate **1** was obtained in 46% and 40% yields, respectively (Table 3, entry 1 and its footnote d). However, more excess quantity of the reagent (5 equiv) at a higher temperature (r.t.) led to completion of the reaction to afford **3b** in 86% calculated yield with 91% regioselectivity (entry 2). The higher order cuprate ($Me_2Cu(CN)(MgCl)_2$) in THF showed the almost same efficiency as the butylation to afford **2b** in 80% calculated yield with 93% selectivity (entry 3). Reaction with other alkyl reagents (R^T = Et, $(CH_2)_3Ph$, $c\text{-}C_6H_{11}$) proceeded well under the same conditions developed for the butylation (entries 5−12), and 1,4-isomers **2c**, **2d**, **2e** and 1,2-isomers **3c**, **3d**, **3e** were produced, respectively, each with high efficiency.

Chart 2. Alkyl Groups (R^T) in the Reagents Examined in the Present Investigation[a]

R^T:

a, Bu
b, Me
c, Et
d, $(CH_2)_3Ph$
e, $c\text{-}C_6H_{11}$
f, $(CH_2)_6OMOM$
g, $(CH_2)_9CH{=}CH_2$
h, CH_2Ph
i, $CH_2CH{=}CH_2$

[a] The reagents are derived from R^T-MgX. **a**−**i** were used as the suffix to specify the products **2** and **3** by R^T.

Installation of the alkyl groups possessing a functional group at the end of the alkyl chain was also accomplished under the conditions developed for the butylation, thus producing **2f**, **3f**, **2g**, and **3g** depending on the conditions, respectively, with high efficiencies (entries 13−16).

Next, benzylation and allylation of **1** were also examined. The negative charge on the reacting carbon in these reagents is conjugated with the π-electron system, and hence it may not be surprising even if the conjugation

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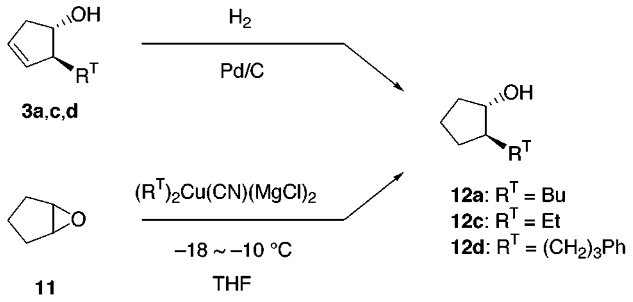
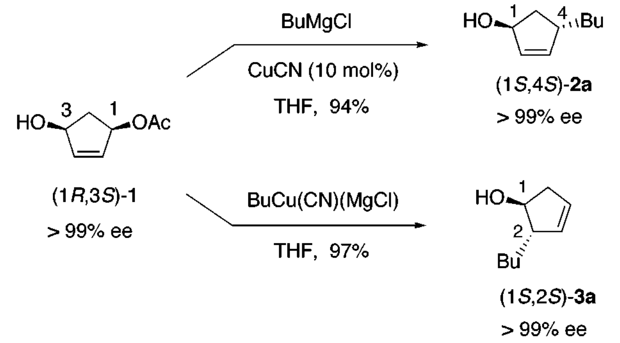
[19] Mitsunobu inversion of **2** ($R^T = (CH_2)_8OTBS$, Ph) and **3** ($R^T = c\text{-}C_6H_{11}$, $(CH_2)_9CH{=}CH_2$) proceeded efficiently (>70% yield) under the conditions mentioned in the text (unpublished results).

Scheme 2



Scheme 3

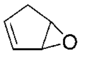


alters the selectivity and the reactivity. Benzylation of **1** fortunately resulted in the efficient production of **2h** and **3h**, respectively, under the conditions for the butylation (entries 17−19). On the contrary, fruitless results were obtained for the attempted allylation with the three types of reagent derived from $CH_2{=}CHCH_2MgCl$ and CuCN in THF (entries 20 and 21) and in Et_2O (data not shown).

Assignment of the Stereochemistry. The trans stereochemistry for the 1,4-isomers **2** is unambiguously determined by ^1H NMR spectroscopy. In general, the differences in the chemical shift between the geminal protons at C(5) for trans and cis isomers ($\Delta\delta_{H(5)}$) are $<$ 0.3 ppm and $>$1 ppm, respectively.[20] Marino assigned the trans stereochemistry for the products **2a** (R^T = Bu) and **2b** (R^T = Me) by this method,[21] and the ^1H NMR spectra of products **2a** and **2b** synthesized by the present method are fully consistent with these data ($\Delta\delta_{H(5)} = 0.15$ and 0.27 ppm, respectively). Likewise, the trans stereochemistry was assigned for other 1,4-isomers **2c**−**h** ($\Delta\delta_{H(5)} = < 0.15$ ppm), and the cis stereochemistry for **8** ($\Delta\delta_{H(5)}$ = ca. 1.2 ppm) which was prepared from **2a** via the Mitsunobu inversion (Scheme 1).

Regarding 1,2-isomers, the ^1H NMR spectrum of **3b** (R^T = Me) was coincident with that reported for the trans isomer which was synthesized by another method.[22a] Compounds **3a**, **3c**, and **3d**, on the other hand, were reduced to the saturated compounds **12a**,**c**,**d** (Scheme 2), which were identical by ^1H NMR spectroscopy and TLC mobility with those of the authentic trans samples prepared from cyclopentene oxide (**11**). We speculate the same (trans) stereochemistry for other 1,2-isomers **3e**−**h** by analogy.

Synthetic Advantages of the Present Reaction. So far, 1,4-isomers **2** and 1,2-isomers **3** with an alkyl group as R^T have been prepared by the several methods. Reactions of cyclopentadiene monoepoxide (**13**) with $R^TCu(CN)Li$,[21] $[R^TZnMe_2]Li/MeCu(CN)Li$ (cat.),[23] and R_2Zn/chiral phosphorus amidite[24] afford 1,4-isomers **2** efficiently. Hydroboration of 5-alkyl-1,3-cyclopentadienes **14** with (+)- or (−)-$(Ipc)_2BH$ furnishes 1,2-isomers **3** with the high ee of a synthetically acceptable level.[22] The carbocyclization of crotylsilanes[25] and the [4 + 1] annulation of dienes[26] also afford **3** in optically active and racemic forms, respectively. From a practical synthetic point of view, however, these methods suffer from serious problems.



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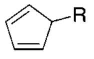

14: R = alkyl
15: R = H

The enantioselective epoxidation of cyclopentadiene (**15**) is reported to afford epoxide **13** in 45% yield with the moderate ee of 64%,[27] which is insufficient for modern organic synthesis. As for the method through the hydroboration, alkylation of the anion of **15** and alkyl halides to produce **14** should be carried out at −78 °C for extremely long periods of time (16−20 h) to prevent the isomerization of **14**. In addition, the isolation of **3** after the hydroboration seems tedious owing to the separation of the coproduced Ipc-OH. The preparation of the crotylsilanes with high ee requires a long sequence of reactions, and hence it is far from practical. Asymmetric version of the [4 + 1] annulation is not yet established at present.

On the other hand, the present reaction can be carried out between −18 °C (an ice/NaCl mixture) and room temperature and completes within several hours to furnish the 1,4-isomers **2** or the 1,2-isomers **3**, depending on the reagent composition and the solvent, with high efficiency as indicated in Tables 1 and 3. In all cases, the major and minor regioisomers were easily separated by chromatography on silica gel since the differences in the ΔR_f value on TLC are large enough to separate the regioisomers (ca. 0.1).

As mentioned in the Introduction, both enantiomers of **1** are easily available,[2] and hence the optically active compounds **2** and **3** are prepared by this method. Scheme 3 demonstrates this advantage with the synthesis of (1*S*,4*S*)-**2a** and (1*S*,2*S*)-**3a** from (1*R*,3*S*)-**1**. Ee of (1*R*,3*S*)-**1**[2d] we used was $>$99% by ^1H NMR spectroscopy of the derived MTPA ester, and those of the products (1*S*,4*S*)-**2a** ($[\alpha]^{28}_D = -204$ (c 0.25, $CHCl_3$)) and (1*S*,2*S*)-**3a** ($[\alpha]^{29}_D = +156$ (c 0.26, $CHCl_3$)) were also $>$99% ee by the same

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[20] (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730−4743. (b) Cocu, F. G.; Wolczunowicz, G.; Bors, L.; Posternak, Th. *Helv. Chim. Acta* **1970**, *53*, 739−749.

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Table 4. Reaction of Acetate 1 with Reagents Derived from BuLi and CuX

entry	reagent[a]	solvent[b]	temp (°C)	time (h)	ratio of **2a**: **3a**[c]	combined yield (%)[c]	calcd yield (%)[c]	
							2a	**3a**
1	BuCu(CN)Li	THF	0	4	3:97	82	2	80
2	$Bu_2Cu(CN)Li_2$	THF	−18	3	47:53	64[d]	30	34
3	BuLi, CuCN (10 mol %)	THF	−18	4	18:82	18[d,e]	3	15
4	BuCu(CN)Li	Et_2O	0	4	2:98	39[d,e]	1	38
5	$Bu_2Cu(CN)Li_2$	Et_2O	−18	4	11:89	92	10	82
6	BuLi, CuCN (10 mol %)	Et_2O	−18	4	23:77	32[d,e]	7	25
7	Bu_2CuLi[f]	THF	−18	4	21:79	98	21	77

[a] Three (3) equivalents of the reagents were used. [b] 4:1 mixtures with hexane. [c] Determined by ^1H NMR spectroscopy. For calculation of the yields, pyridine was used as an internal standard. [d] Unidentified products were also produced. [e] Acetate **1** and the corresponding diol were isolated in 15% and 27% (entry 3), 16% and <5% (entry 4), and 8% and 6% (entry 6) yields, respectively. [f] Prepared from BuLi and CuI.

analysis. This result guarantees the same levels of ee for products **2** and **3** with another R^T (≠ Bu) by the present reaction.

Other advantages of the present reaction are presented herein. The synthesis of **2e** and **3e** (R^T = c-C_6H_{11}) indicates the applicability to other secondary alkyl groups.[28] The olefin moiety and the MOM-oxy group can be converted to other functional groups, and hence compounds possessing an alkyl chain with any functional group would certainly be synthesized via transformations taking advantages of these functionalities.

Consideration of the Reaction Mechanism. Allylation of allylic substrates with the lithium cuprates have extensively been studied.[12,23,24,29] The regioisomeric σ-allylcopper intermediates are proposed to account for the anti S_N2' and S_N2 preferences:[30,31] formation of the σ-allylcopper intermediate leading to the anti S_N2' product is rationalized,[32] while existence of the regioisomeric intermediate furnishing the S_N2 product is proposed only in a rapid equilibrium with the former, producing a mixture of the regioisomers with varying selectivity depending on the structural and electronic factors. Regarding the reagents derived from RMgX and CuX, the anti S_N2' preference is reported in the reaction of cyclohexenyl acetate and RMgX/CuCN (cat.) in Et_2O.[11f−g] On the other hand, the regioselectivity of the acyclic allylic esters is controlled by the solvent and the addition speed of RMgX.[11i]

In our butylation of acetate **1** with the BuMgX/CuCN reagents, the regioselectivity and the reactivity were highly dependent on the stoichiometry of BuMgX/CuCN and the solvent used (THF, Et_2O) as summarized in Table 1. These results strongly suggest that in each of the solvents the real copper species formed from the 2:1 mixture of BuMgX/CuCN is the same as that transiently produced from BuMgX with the CuCN catalyst, and that the species is different from that derived from the 1:1 composition (entries 2 and 3 vs entry 1; entries 5 and 6 vs entry 4; entries 12 and 13 vs entry 11; entries 15 and 16 vs entry 14 (see footnote d)).

Recently, the structure of the reagents derived from RLi and CuCN has been elucidated and the mechanism of the reactions with these reagents has been debated.[31a,32] To obtain information about the structure(s) of the reagents derived from BuMgX and CuCN, the BuLi-based reagents were subjected to the reaction with acetate **1**. As delineated in Table 4, a variety of the results was obtained, and this outcome was unpredictable from the results shown in Table 1. Entirely different regioselectivity to that observed with the BuMgX/CuCN reagents was obtained with $Bu_2Cu(CN)Li_2$ in THF[33] and BuLi/CuCN (cat.) in both THF and Et_2O (entries 2, 3, and 6 vs entries 2, 3, and 6 of Table 1), while other combination of the reagents and the solvent showed a similar efficiency (regioselectivity and yield): BuCu(CN)Li both in THF and Et_2O, and $Bu_2Cu(CN)Li_2$ in Et_2O (entries 1, 4, and 5). In addition, $Bu_2Cu(CN)Li_2$ and Bu_2CuLi derived from BuLi and CuI, both in THF, furnished different efficiency each other (entries 2 and 7), though these efficiencies are lower than that obtained with the BuMgCl-based reagent (entry 2 of Table 1). These results strongly suggest a different type of mechanism to be involved in the reaction of **1** and the BuMgX/CuCN reagents.

We propose the following reaction mechanism (Scheme 4)[34] in which the reagents derived from BuMgX and CuCN afford kinetically the σ-allylcopper intermediates **16** or **17**, depending on the composition and the solvent used, thus producing 1,4-isomer **2a** or 1,2-isomer **3a**, respectively.[35] The former intermediate **16** would be produced by coordination of the copper reagent to the

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[28] Synthesis of **3e** through hydroboration of **14** (R^T = c-C_6H_{11}) with $(Ipc)_2BH$[22] would be hard since the alkylation of the anion derived from **15** with c-$C_6H_{11}X$ at −78 °C is expected not to proceed efficiently.

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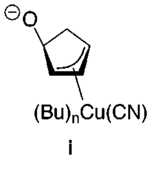
[33] Addition of $MgCl_2$ (3.5 equiv) into the reagent of entry 2 in Table 4 ($Bu_2Cu(CN)Li_2$ in THF) marginally changed the regioselectivity.

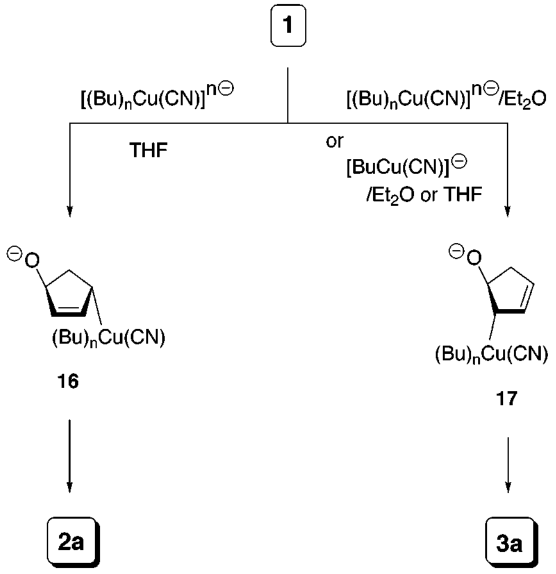
[34] The countercation, MgX, is omitted for convenience.

[35] The π-allylcopper **i** is unlikely since the alkoxy group at C(3) of **i** is placed on the other side of the ring and hence both the sides of the π-allyl moieties are equally accessible so as to produce the regioisomers **2a** and **3a**. Equilibrium between **16** and **17** is not likely for the same reason.



i

Scheme 4



olefin moiety of **1** followed by the oxidative, nucleophilic substitution of the reagent at the C(1) position with inversion of the stereochemistry. This speculation is consistent with that **2a** is produced only with the reagent(s) of the higher composition of BuMgX/CuCN in the polar solvent (THF) (Table 1, entries 2, 3, 12, and 13). On the other hand, the less nucleophilic species (entries 1 and 11) or the species in the less polar solvent (Et_2O) (entries 4−6, 14−16) probably furnish the σ-allylcopper **17** by a similar mechanism to R_2CuLi,[30,31] thus producing **3a** selectively.

Conclusion

In summary, the reaction of acetate **1** and the reagents derived from R^TMgX (X = Cl, Br) and CuCN produced trans isomers **2** and **3** exclusively, and the regioselectivity as well as the reactivity was found to be highly controlled by the composition of the reagents and the solvent used. These results are definitely useful in organic synthesis, and new strategies for synthesis of the cyclopentanoids will be designed with the present reaction. In addition, the results of the butylation, studied especially under various conditions, are no doubt useful for the investigation to determine the copper species and the intermediates for the allylation.

Experimental Section

General Methods. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}). ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ = 0 ppm) and the center line of $CDCl_3$ triplet (δ = 77.1 ppm) as internal standards, respectively. THF and Et_2O were distilled from Na/benzophenone before use. MeMgCl in THF and CuCN were purchased from Aldrich. EtMgCl in THF and $PhCH_2MgCl$ in THF were from Kanto Chemical, Jpn. Other Grignard reagents were prepared from the corresponding alkyl halides. An ice/NaCl/water bath was used for the reaction at −18 °C. The regioisomeric ratios of the products **2** and **3** were determined by ^1H NMR spectroscopy and the NMR-yields were calculated by using pyridine (1 equiv) as an internal standard.

The General Procedure for the Reaction of Acetate 1 and $R^TCu(CN)(MgX)$. Representative experiment (Table 1, entry 1): To a slurry of CuCN (224 mg, 2.50 mmol) in THF (4.5 mL) was added BuMgCl (1.4 mL, 1.49 M in THF, 2.09 mmol) slowly at −18 °C. After 20 min of stirring at −18 °C, acetate **1** (100 mg, 0.70 mmol) dissolved in THF (0.5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 4 h, and the reaction was quenched by addition of saturated NH_4Cl and 28% NH_4OH. The resulting mixture was extracted with Et_2O several times. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford a 7:93 mixture of **2a** and **3a** in 97% NMR-yield. The crude product was purified by chromatography on silica gel with hexane/EtOAc (100/0 to 75/25) to give **3a** (87 mg) in 89% yield.

The General Procedure for the Reaction of Acetate 1 and $(R^T)_2Cu(CN)(MgX)_2$. Representative experiment (Table 1, entry 2): To a slurry of CuCN (187 mg, 2.09 mmol) in THF (4.5 mL) was added BuMgCl (2.8 mL, 1.49 M in THF, 4.17 mmol) slowly at −18 °C. After 20 min of stirring at −18 °C, acetate **1** (100 mg, 0.70 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 3 h. Isolation as described above furnished a 93:7 mixture of **2a** and **3a** in 94% NMR-yield, and purification of the crude product by chromatography on silica gel with hexane/EtOAc (100/0 to 75/25) afforded **2a**.

The General Procedure for the CuCN-Catalyzed Reaction of Acetate 1 with R^TMgX. Representative experiment (Table 1, entry 3): To a slurry of CuCN (63 mg, 0.70 mmol) in THF (14 mL) was added BuMgCl (14 mL, 1.49 M in THF, 20.7 mmol) slowly at −18 °C. After 20 min of stirring at −18 °C, acetate **1** (997 mg, 7.01 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 5 h to afford a 94:6 mixture of **2a** and **3a** in 94% NMR-yield after the isolation as described above. Chromatography of the crude product on silica gel with hexane/EtOAc (100/0 to 75/25) furnished **2a** (832 mg) in 85% yield.

The General Procedure for the Ni-Catalyzed Reaction of Acetate 1 with R^TMgX. Representative experiment (Table 2, entry 3): To an ice-cold mixture of $NiCl_2(dppp)$ (38 mg, 0.07 mmol) in THF (1.5 mL) was added BuMgCl (1.3 mL, 1.61 M in THF, 2.09 mmol) slowly. The mixture was stirred at 0 °C for 5 min and then at room temperature further for 15 min. Acetate **1** (103 mg, 0.73 mmol) dissolved in THF (0.5 mL) was added dropwise to the mixture at 0 °C. After 3 h at 0 °C, the reaction was quenched by addition of saturated NH_4Cl. The mixture was extracted with Et_2O three times. The combined extracts were dried over $MgSO_4$ and concentrated by evaporation to afford **2a** in 89% NMR-yield.

***trans*-4-Butyl-2-cyclopenten-1-ol (2a).** The IR, ^1H NMR, and ^{13}C NMR spectra of **2a** prepared by the method described above were identical with those reported.[21]

***trans*-2-Butyl-3-cyclopenten-1-ol (3a).** IR (neat) 3341, 3055, 709 cm^{-1}; ^1H NMR δ 0.90 (t, J = 7 Hz, 3 H), 1.22−1.42 (m, 6 H), 1.68 (br s, 1 H), 2.24 (dm, J = 17 Hz, 1 H), 2.45−2.54 (m, 1 H), 2.70 (ddq, J = 17, 7, 2 Hz, 1 H), 4.05−4.13 (m, 1 H), 5.63−5.73 (m, 2 H); ^{13}C NMR δ 133.5, 127.7, 77.7, 55.2, 41.7, 32.9, 29.9, 22.9, 14.0. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.80; H, 11.17.

***trans*-4-Methyl-2-cyclopenten-1-ol (2b).** Reaction of **1** (101 mg, 0.71 mmol) and the reagent prepared from MeMgCl (1.50 mL, 2.80 M in THF, 4.20 mmol) and CuCN (188 mg, 2.10 mmol) in THF (3 mL) was carried out at −18 °C for 4 h according to the general procedure with $(R^T)_2Cu(CN)(MgX)_2$ to produce **2b** (80% calculated yield) and **3b** in a ratio of 93:7. The ^1H NMR spectrum of **2b** was identical with that reported.[21]

***trans*-2-Methyl-3-cyclopenten-1-ol (3b).** The general procedure with $R^TCu(CN)(MgX)$ was used with modification in this particular case: **1** (101 mg, 0.71 mmol) in THF (0.5 mL) was added to a mixture of MeMgCl (1.20 mL, 2.80 M in THF, 3.36 mmol) and CuCN (361 mg, 4.03 mmol) in THF (3 mL), and the reaction was carried out at room temperature for 8 h to produce **2b** and **3b** (86% calculated yield) in a ratio of 9:91. The ^1H NMR spectrum of **3b** was identical with that reported.[22a]

***trans*-4-Ethyl-2-cyclopenten-1-ol (2c).** Reaction of **1** (102 mg, 0.72 mmol) and EtMgCl (2.60 mL, 0.82 M in THF, 2.13 mmol) in the presence of CuCN (6 mg, 0.07 mmol) in THF (1.5 mL) was carried out at −18 °C for 3 h according to the general procedure with R^TMgX/ CuCN (cat.) to produce **2c** (86%

calculated yield) and **3b** in a ratio of 94:6. **2c**: IR (neat) 3327, 3054, 1033 cm^{-1}; ^{1}H NMR δ 0.91 (t, *J* = 7 Hz, 3 H), 1.22−1.57 (m, 3 H), 1.78 (ddd, *J* = 14, 7, 5 Hz, 1 H), 1.91 (ddd, *J* = 14, 7.5, 3 Hz, 1 H), 2.75−2.87 (m, 1 H), 4.81−4.90 (m, 1 H), 5.83 (dt, *J* = 5.5, 2 Hz, 1 H), 5.96 (dd, *J* = 5.5, 2 Hz, 1 H); ^{13}C NMR δ 140.2, 132.7, 77.3, 45.7, 40.2, 28.5, 12.0.

***trans*-2-Ethyl-3-cyclopenten-1-ol (3c).** Reaction of **1** (101 mg, 0.71 mmol) and the reagent prepared from EtMgCl (2.60 mL, 0.82 M in THF, 2.13 mmol) and CuCN (228 mg, 2.55 mmol) in THF (2.5 mL) was carried out at 0 °C for 5 h according to the general procedure with R^{T}Cu(CN)(MgX) to produce **2c** and **3c** (83% calculated yield) in a ratio of 5:95. **3c**: IR (neat) 3354, 3052 cm^{-1}; ^{1}H NMR δ 0.96 (t, *J* = 7.5 Hz, 3 H), 1.26−1.50 (m, 2 H), 1.66−1.78 (m, 1 H), 2.25 (dm, *J* = 17 Hz, 1 H), 2.41−2.49 (m, 1 H), 2.70 (ddq, *J* = 17, 7, 2 Hz, 1 H), 4.11 (dt, *J* = 6, 3 Hz, 1 H), 5.65−5.73 (m, 2 H); ^{13}C NMR δ 133.1, 127.9, 77.3, 56.8, 41.8, 25.9, 11.9.

***trans*-4-(3-Phenylpropyl)-2-cyclopenten-1-ol (2d).** Reaction of **1** (101 mg, 0.71 mmol) and Ph(CH$_2$)$_3$MgCl (1.70 mL, 1.24 M in THF, 2.11 mmol) in the presence of CuCN (6 mg, 0.07 mmol) in THF (1.5 mL) was carried out at −18 °C for 5 h according to the general procedure with R^{T}MgX/ CuCN (cat.) to produce **2d** (123 mg, 87% isolated yield) and **3d** in a ratio of 91:9. **2d**: IR (neat) 3344, 3058, 3025 cm^{-1}; ^{1}H NMR δ 1.23−1.55 (m, 3 H), 1.58−1.71 (m, 2 H), 1.76 (ddd, *J* = 14, 7, 5 Hz, 1 H), 1.91 (ddd, *J* = 14, 8, 3 Hz, 1 H), 2.61 (t, *J* = 8 Hz, 2 H), 2.82−2.94 (m, 1 H), 4.80−4.87 (m, 1 H), 5.81 (dt, *J* = 5.5, 2 Hz, 1 H), 5.94 (ddd, *J* = 5.5, 2, 0.5 Hz, 1 H), 7.14−7.21 (m, 3 H), 7.24−7.32 (m, 2 H); ^{13}C NMR δ 142.6, 140.2, 132.7, 128.5, 128.4, 125.9, 77.2, 43.9, 40.5, 36.0, 35.4, 29.8. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.98; H, 8.66.

***trans*-2-(3-Phenylpropyl)-3-cyclopenten-1-ol (3d).** Reaction of **1** (100 mg, 0.70 mmol) and the reagent prepared from Ph(CH$_2$)$_3$MgCl (3.40 mL, 1.25 M in Et$_2$O, 4.25 mmol) and CuCN (188 mg, 2.10 mmol) in Et$_2$O (2 mL) was carried out at −18 °C for 5 h according to the general procedure with (R^{T})$_2$Cu(CN)(MgX)$_2$ to produce **2d** and **3d** (141 mg, 96% isolated yield) in a ratio of 3:97. **3d**: IR (neat) 3356, 3059, 3024 cm^{-1}; ^{1}H NMR δ 1.26−1.49 (m, 2 H), 1.63−1.75 (m, 3 H), 2.22 (dm, *J* = 17 Hz, 1 H), 2.47−2.56 (m, 1 H), 2.62 (t, *J* = 8 Hz, 2 H), 2.68 (ddq, *J* = 17, 6, 2 Hz, 1 H), 4.07 (dt, *J* = 7, 3 Hz, 1 H), 5.62−5.71 (m, 2 H), 7.14−7.31 (m, 5 H); ^{13}C NMR δ 142.6, 133.2, 128.5, 128.4, 127.9, 125.9, 77.6, 55.0, 41.7, 36.1, 32.8, 29.5. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.02; H, 8.76.

***trans*-4-Cyclohexyl-2-cyclopenten-1-ol (2e).** Reaction of **1** (101 mg, 0.71 mmol) and (*c*-C$_6$H$_{11}$)MgCl (1.50 mL, 1.38 M in THF, 2.07 mmol) in the presence of CuCN (6 mg, 0.07 mmol) in THF (2 mL) was carried out at −18 °C for 5 h according to the general procedure with R^{T}MgX/ CuCN (cat.) to produce **2e** (79 mg, 66% isolated yield) and **3e** in a ratio of 89:11. **2e**: IR (neat) 3327, 3054, 1448, 1021 cm^{-1}; ^{1}H NMR δ 0.84−1.30 (m, 6 H), 1.59−1.77 (m, 6 H), 1.80 (ddd, *J* = 14, 8, 3 Hz, 1 H), 1.89 (ddd, *J* = 14, 7, 5 Hz, 1 H), 2.65−2.75 (m, 1 H), 4.77−4.86 (m, 1 H), 5.83 (dt, *J* = 5.5, 2 Hz, 1 H), 5.99 (ddd, *J* = 5.5, 2, 0.5 Hz, 1 H); ^{13}C NMR δ 138.5, 133.1, 77.15, 50.2, 42.7, 38.2, 31.1, 31.0, 26.5, 26.4 (two carbons).

***trans*-2-Cyclohexyl-3-cyclopenten-1-ol (3e).** Reaction of **1** (101 mg, 0.71 mmol) and (*c*-C$_6$H$_{11}$)MgCl (1.10 mL, 1.95 M in Et$_2$O, 2.15 mmol) in the presence of CuCN (6 mg, 0.07 mmol) in Et$_2$O (2.5 mL) was carried out at −18 °C for 4 h according to the general procedure with R^{T}MgX/ CuCN (cat.) to produce **2e** and **3e** (96 mg, 81% isolated yield) in a ratio of 9:91. **3e**: IR (neat) 3340, 3054, 1448, 1035 cm^{-1}; ^{1}H NMR δ 0.92−1.35 (m, 6 H), 1.59−1.82 (m, 6 H), 2.23 (dm, *J* = 17 Hz, 1 H), 2.32−2.38 (m, 1 H), 2.67 (ddm, *J* = 17, 7 Hz, 1 H), 4.20−4.28 (m, 1 H), 5.68 (s, 2 H); ^{13}C NMR δ 131.6, 128.2, 75.4, 61.6, 42.4, 40.7, 31.3, 30.6, 26.52, 26.47, 26.38. Anal. Calcd for Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.46; H, 10.62.

***trans*-4-(6-Methoxymethoxyhexyl)-2-cyclopenten-1-ol (2f).** Reaction of **1** (100 mg, 0.70 mmol) and MOMO(CH$_2$)$_6$MgCl (1.50 mL, 1.40 M in THF, 2.10 mmol) in the presence of CuCN (6 mg, 0.07 mmol) in THF (1.5 mL) was carried out at −18 °C for 5 h according to the general procedure with R^{T}MgX/ CuCN (cat.) to produce **2f** (147 mg, 92% isolated yield) and **3f** in a ratio of 94:6. **2f**: IR (neat) 3384, 1112, 1042 cm^{-1}; ^{1}H NMR δ 1.20−1.45 (m, 8 H), 1.52−1.67 (m, 3 H), 1.76 (ddd, *J* = 14, 7, 5 Hz, 1 H), 1.91 (ddd, *J* = 14, 7.5, 2.5 Hz, 1 H), 2.79−2.91 (m, 1 H), 3.36 (s, 3 H), 3.52 (t, *J* = 7 Hz, 2 H), 4.62 (s, 2 H), 4.81−4.89 (m, 1 H), 5.81 (dt, *J* = 5.5, 2 Hz, 1 H), 5.95 (ddd, *J* = 5.5, 2, 0.5 Hz, 1 H); ^{13}C NMR δ 140.4, 132.6, 96.5, 77.2, 67.9, 55.1, 44.0, 40.6, 35.8, 29.7, 29.5, 27.8, 26.1. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.06; H, 10.65.

***trans*-2-(6-Methoxymethoxyhexyl)-3-cyclopenten-1-ol (3f).** Reaction of **1** (100 mg, 0.70 mmol) and the reagent prepared from MOMO(CH$_2$)$_6$MgCl (1.50 mL, 1.40 M in THF, 2.10 mmol) and CuCN (228 mg, 2.55 mmol) in THF (2.5 mL) was carried out at 0 °C for 5 h according to the general procedure with R^{T}Cu(CN)(MgX) to produce **2f** and **3f** (145 mg, 91% isolated yield) in a ratio of 4:96. **3f**: IR (neat) 3406, 1113, 1043 cm^{-1}; ^{1}H NMR δ 1.22−1.45 (m, 8 H), 1.53−1.74 (m, 3 H), 2.24 (dm, *J* = 17 Hz, 1 H), 2.45−2.54 (m, 1 H), 2.70 (ddq, *J* = 17, 6.5, 2 Hz, 1 H), 3.36 (s, 3 H), 3.52 (t, *J* = 7 Hz, 2 H), 4.05−4.13 (m, 1 H), 4.62 (s, 2 H), 5.63−5.72 (m, 2 H); ^{13}C NMR δ 133.4, 127.7, 96.5, 77.6, 67.9, 55.1, 41.7, 33.1, 29.7, 29.6, 27.6, 26.1. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.13; H, 10.62.

***trans*-4-(10-Undecenyl)-2-cyclopenten-1-ol (2 g).** Reaction of **1** (100 mg, 0.70 mmol) and CH$_2$═CH(CH$_2$)$_9$MgCl (1.70 mL, 1.27 M in THF, 2.16 mmol) in the presence of CuCN (6 mg, 0.07 mmol) in THF (1.5 mL) was carried out at −18 °C for 5 h according to the general procedure with R^{T}MgX/ CuCN (cat.) to produce **2g** (149 mg, 90% isolated yield) and **3g** in a ratio of 95:5. **2g**: IR (neat) 3232, 1469 cm^{-1}; ^{1}H NMR δ 1.20−1.43 (m, 16 H), 1.46−1.54 (br s, 1 H), 1.76 (ddd, *J* = 14, 7, 5 Hz, 1 H), 1.91 (ddd, *J* = 14, 7, 3 Hz, 1 H), 2.04 (q, *J* = 7 Hz, 2 H), 2.78−2.92 (m, 1 H), 4.81−4.89 (m, 1 H), 4.93 (dm, *J* = 10 Hz, 1 H), 4.99 (dq, *J* = 17, 2 Hz, 1 H), 5.74−5.89 (m, 2 H), 5.95 (ddd, *J* = 6, 2, 0.5 Hz, 1 H); ^{13}C NMR δ 140.5, 139.4, 132.5, 114.2, 77.2, 44.1, 40.7, 35.9, 33.8, 29.7, 29.58, 29.55, 29.47, 29.1, 28.9, 27.9. Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.04; H, 11.78.

***trans*-2-(10-Undecenyl)-3-cyclopenten-1-ol (3g).** Reaction of **1** (100 mg, 0.70 mmol) and the reagent prepared from CH$_2$═CH(CH$_2$)$_9$MgCl (1.70 mL, 1.27 M in THF, 2.16 mmol) and CuCN (228 mg, 2.55 mmol) in THF (2.5 mL) was carried out at 0 °C for 5 h according to the general procedure with R^{T}Cu(CN)(MgX) to produce **2g** and **3g** (151 mg, 91% isolated yield) in a ratio of 4:96. **3g**: IR (neat) 3341, 3058 cm^{-1}; ^{1}H NMR δ 1.20−1.44 (m, 16 H), 1.59−1.76 (m, 1 H), 2.04 (q, *J* = 7 Hz, 2 H), 2.24 (dm, *J* = 17 Hz, 1 H), 2.44−2.54 (m, 1 H), 2.70 (ddq, *J* = 17, 6, 2 Hz, 1 H), 4.04−4.13 (m, 1 H), 4.93 (ddt, *J* = 10, 2, 1 Hz, 1 H), 4.99 (dq, *J* = 17, 2 Hz, 1 H), 5.63−5.73 (m, 2 H), 5.82 (ddt, *J* = 17, 10, 7 Hz, 1 H); ^{13}C NMR δ 139.4, 133.5, 127.7, 114.2, 77.7, 55.2, 41.7, 33.8, 33.2, 29.8, 29.6 (two carbons), 29.5, 29.1, 28.9, 27.7. Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.02; H, 11.95.

***trans*-4-Benzyl-2-cyclopenten-1-ol (2h).** Reaction of **1** (100 mg, 0.70 mmol) and PhCH$_2$MgCl (2.80 mL, 2.13 M in THF, 0.76 mmol) in the presence of CuCN (6 mg, 0.07 mmol) in THF (1.5 mL) was carried out at −18 °C for 4 h according to the general procedure with R^{T}MgX/ CuCN (cat.) to produce **2h** (100 mg, 82% isolated yield) and **3h** in a ratio of 91:9. **2h**: IR (neat) 3345, 3058, 3026, 1029, 700 cm^{-1}; ^{1}H NMR δ 1.55−1.68 (m, 1 H), 1.85−1.90 (m, 2 H), 2.62 (d, *J* = 8 Hz, 2 H), 3.12−3.25 (m, 1 H), 4.78−4.86 (m, 1 H), 5.83 (dt, *J* = 6, 2 Hz, 1 H), 5.91 (dd, *J* = 6, 2 Hz, 1 H), 7.13−7.32 (m, 5 H); ^{13}C NMR δ 140.8, 139.5, 133.3, 129.0, 128.4, 126.1, 77.0, 45.8, 42.0, 40.2. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.64; H, 7.89.

***trans*-2-Benzyl-3-cyclopenten-1-ol (3h).** Reaction of **1** (100 mg, 0.70 mmol) and the reagent prepared from PhCH$_2$MgCl (2.00 mL, 1.09 M in THF, 2.18 mmol) and CuCN (228 mg, 2.55 mmol) in THF (2 mL) was carried out at 0 °C for 5 h according to the general procedure with R^{T}Cu(CN)(MgX) to produce **2h** and **3h** (91 mg, 75% isolated yield) in a ratio of 11:89. **3h**: IR (neat) 3355, 3058, 3025 cm^{-1}; ^{1}H NMR δ 1.54 (br s, 1 H), 2.25 (dm, *J* = 17 Hz, 1 H), 2.61−2.73 (m, 3 H), 2.79−2.89 (m, 1 H), 4.13−4.21 (m, 1 H), 5.63 (dq, *J* = 6, 2 Hz, 1 H), 5.69 (dq, $J = 6$, 2 Hz, 1 H), 7.17−7.33 (m, 5 H); ^{13}C NMR δ 140.4, 132.9, 129.1, 128.6, 128.4, 126.2, 77.0, 56.5, 41.3, 39.4. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.86; H, 8.39.

***cis*-4-Butyl-2-cyclopenten-1-ol (8).** To a mixture of alcohol **2a** (200 mg, 1.43 mmol), Ph_3P (750 mg, 2.86 mmol), AcOH (0.164 mL, 2.86 mmol) in toluene (10 mL) was added diethyl azodicarboxylate (0.45 mL, 2.86 mmol) at −78 °C. The mixture was stirred at the same temperature for 6 h. Saturated $NaHCO_3$ was added, and the resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated by using a rotary evaporator to give a residue, which was purified by chromatography on silica gel with hexane/EtOAc (100/0 to 90/10) to furnish the corresponding ester **7** (217 mg, 84%): ^{1}H NMR δ 0.92 (t, $J = 7$ Hz, 3 H), 1.2−1.6 (m, 7 H), 2.02 (s, 3 H), 2.44−2.63 (m, 2 H), 5.59−5.63 (m, 1 H), 5.78 (dm, $J = 6$ Hz, 1 H), 6.00 (dm, $J = 6$ Hz, 1 H).

A mixture of ester **7** (72 mg, 0.38 mmol) and 5% KOH in MeOH (1 mL) was stirred at room temperature for 1 h. Brine was added to the mixture, and the product was extracted with Et_2O repeatedly. As described above, the combined extracts were dried and concentrated to give a residue, which was purified by chromatography on silica gel with hexane/EtOAc (100/0 to 75/25) to furnish alcohol **8** (51 mg, 92%): IR (neat) 3331, 3054, 1053 cm^{-1}; ^{1}H NMR δ 0.90 (t, $J = 7$ Hz, 3 H), 1.09−1.40 (m, 6 H), 1.40−1.54 (m, 2 H), 2.45−2.60 (m, 2 H), 4.76−4.86 (m, 1 H), 5.77 (dt, $J = 6$, 2 Hz, 1 H), 5.90 (dt, $J = 6$, 2 Hz, 1 H); ^{13}C NMR δ 139.2, 133.0, 77.5, 44.5, 40.5, 36.6, 30.1, 22.8, 14.0. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.70; H, 11.37.

***cis*-2-Butyl-3-cyclopenten-1-ol (10).** To an ice-cold mixture of alcohol **3a** (81 mg, 0.58 mmol), Ph_3P (304 mg, 1.16 mmol), and 4-nitrobenzoic acid (194 mg, 1.16 mmol) in THF (2 mL) was added diethyl azodicarboxylate (0.18 mL, 1.14 mmol). The mixture was stirred at room temperature overnight. Brine was added, and the resulting mixture was extracted with EtOAc three times. As described above, the combined extracts were dried and concentrated to give a residue, which was purified by chromatography on silica gel with hexane/EtOAc (100/0 to 85/15) to furnish the corresponding ester **9** (135 mg, 81%): ^{1}H NMR δ 0.86 (t, $J = 7$ Hz, 3 H), 1.24−1.66 (m, 6 H), 2.54 (dm, $J = 17$ Hz, 1 H), 2.82 (ddm, $J = 17$, 7 Hz, 1 H), 2.92 (qq, $J = 6$, 1.5 Hz, 1 H), 5.67 (dt, $J = 3$, 6 Hz, 1 H), 5.75−5.84 (m, 2 H), 8.19 (dm, $J = 9$ Hz, 2 H), 8.29 (dm, $J = 9$ Hz, 2 H).

A mixture of ester **9** (102 mg, 0.35 mmol) and 5% KOH in MeOH (2 mL) was stirred at room temperature for 30 min. Brine was added to the mixture, and the product was extracted with Et_2O repeatedly. As described above, the combined extracts were dried and concentrated to give a residue, which was purified by chromatography on silica gel with hexane/EtOAc (100/0 to 75/25) to furnish the alcohol **10** (41 mg, 83%). IR (neat) 3366, 3056 cm^{-1}; ^{1}H NMR δ 0.92 (t, $J = 7$ Hz, 3 H), 1.29−1.64 (m, 7 H), 2.32 (dm, $J = 17$ Hz, 1 H), 2.51−2.66 (m, 2 H), 4.32−4.41 (m, 1 H), 5.64−5.70 (m, 1 H), 5.71−5.76 (m, 1 H); ^{13}C NMR δ 133.7, 127.9, 73.4, 50.1, 42.2, 30.6, 27.5, 23.0, 14.0. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.12; H, 11.37.

***trans*-2-Butylcyclopentan-1-ol (12a). From 3a:** A mixture of alcohol **3a** (50 mg, 0.58 mmol) and 10% Pd/C (15 mg) in MeOH (1 mL) was stirred at room temperature for 1.5 h under hydrogen and filtered through a pad of Celite with Et_2O. The filtrate was concentrated to give an oil, which was purified by chromatography on silica gel with hexane/EtOAc (100/0 to 90/10) to furnish **12a** (29 mg, 57%). The spectral data of **12a** were identical with those obtained from **11** as described below.

From epoxide 11: To a slurry of CuCN (181 mg, 2.02 mmol) in THF (2 mL) was added *n*-BuMgCl (2.7 mL, 1.47 M in THF, 3.97 mmol) slowly at −18 °C. After 20 min of stirring at −18 °C, **11** (0.088 mL, 1.01 mmol) was added to the slurry. The reaction mixture was stirred for 2 h and quenched by addition of saturated NH_4Cl and 28% NH_4OH. The resulting mixture was extracted with Et_2O several times. The combined extracts were dried over $MgSO_4$ and concentrated by using a rotary evaporator to afford a crude oil, which was purified by chromatography on silica gel with hexane/EtOAc (100/0 to 90/10) to furnish **12a** (98 mg, 69%): IR (neat) 3338, 1073 cm^{-1}; ^{1}H NMR δ 0.90 (t, $J = 7$ Hz, 3 H), 1.06−1.39 (m, 6 H), 1.41−1.98 (m, 8 H) 3.80 (q, $J = 5{-}6$ Hz, 1 H); ^{13}C NMR δ 79.3, 48.3, 34.6, 33.5, 30.5, 29.9, 22.9, 21.8, 14.0. Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.75. Found: C, 75.72; H, 12.78.

***trans*-2-Ethylcyclopentan-1-ol (12c).** In a similar manner as described above, the title compound was prepared from **3c** and **11**, respectively: IR (neat) 3339 cm^{-1}; ^{1}H NMR δ 0.93 (t, $J = 7$ Hz, 3 H), 1.10−1.24 (m, 2 H), 1.45−1.78 (m, 6 H), 1.82−1.98 (m, 2 H), 3.83 (dt, $J = 6$, 3 Hz, 1 H); ^{13}C NMR δ 79.1, 50.2, 34.7, 29.6, 26.5, 21.8, 12.6.

***trans*-2-(3-Phenylpropyl)cyclopentan-1-ol (12d).** In a similar manner as described above, the title compound was prepared from **3d** and **11**, respectively: IR (neat) 3352, 3026, 1496, 1453, 698 cm^{-1}; ^{1}H NMR δ 1.08−1.28 (m, 2 H), 1.45−1.97 (m, 10 H), 2.61 (t, $J = 8$ Hz, 2 H), 3.79 (q, $J = 6$ Hz, 1 H), 7.13−7.31 (m, 5 H); ^{13}C NMR δ 142.8, 128.5, 128.4, 125.8, 79.3, 48.2, 36.2, 34.6, 33.5, 30.1, 29.9, 21.8.

(1*S*,4*S*)-4-Butyl-2-cyclopenten-1-ol ((1*S*,4*S*)-2a). According to the method described in the general procedure using BuMgCl (3.1 equiv) and CuCN (0.1 equiv) in THF, (1*R*,3*S*)-**1**[2d] ($[\alpha]^{28}_D = +71$ (c 0.24, $CHCl_3$)) of >99% ee, determined by ^{1}H NMR spectroscopy of the derived MTPA ester, was converted into the title compound, which was >99% ee by ^{1}H NMR spectroscopy of the derived MTPA ester: $[\alpha]^{28}_D = -204$ (c 0.25, $CHCl_3$).

(1*S*,2*S*)-2-Butyl-3-cyclopenten-1-ol ((1*S*,2*S*)-3a). According to the method described in the general procedure using BuMgCl (3.1 equiv) and CuCN (3.6 equiv) in THF, (1*R*,3*S*)-**1**[2d] of >99% ee was converted into the title compound, which was >99% ee by ^{1}H NMR spectroscopy of the derived MTPA ester: $[\alpha]^{29}_D = +156$ (c 0.26, $CHCl_3$).

Acknowledgment. We are grateful to Professor Masaharu Nakamura of University of Tokyo for his helpful discussions and valuable comments on the structure of the cuprates. This work was supported by a Grand-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Government of Japan and General Sekiyu Research and Development Encouragement and Assistance Foundation.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds lacking elemental analyses (**2c**, **2e**, **3c**, **12c**, and **12d**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO010474W