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Alkylation of 4-substituted 1-acetoxy-2-cyclopentenes by using copper reagents derived from alkylmagnesium halides and copper(I) cyanide

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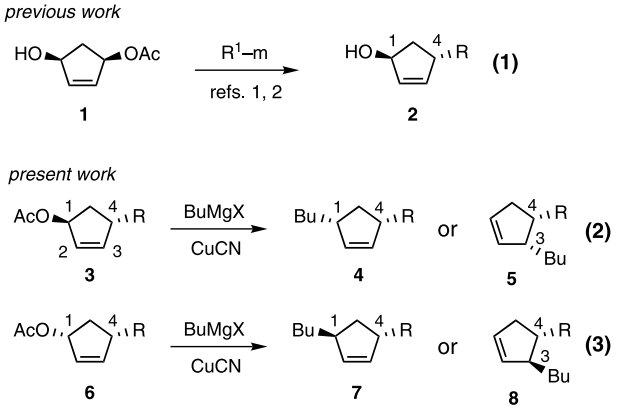
Abstract—Alkylation of the acetates derived from 4-phenyl- and 4-butyl-2-cyclopenten-1-ols **2** was investigated with copper reagents derived from *n*-BuMgX (X = Cl, Br) and CuCN in 2:1 and 1:1 ratios in THF and in Et_2O. *cis* 1,4-Isomers **4a**,**b** (R = Ph, *n*-Bu) were produced regioselectively from the corresponding *trans* acetates **3a**,**b** with the reagent in a 2:1 ratio of BuMgCl and CuCN in THF, while the BuMgBr-based reagents of 2:1 and 1:1 ratios in Et_2O furnished *cis* 3,4-isomers **5a**,**b**. A similar tendency was obtained with *cis* acetates **6a**,**b** (R = Ph, *n*-Bu).

Installation of carbon nucleophiles on the cyclopentane (or -ene) ring is an important step for synthesis of cyclopentanoids. Recently, we have published arylation[1a] and alkenylation[1b] of monoacetate **1** using borates and nickel catalysis, and later, alkylation[2] of **1** using copper reagents derived from alkylmagnesium halides and copper(I) salts (Scheme 1, Eq. (1)). The allylic alcohol moiety on the ring of these reaction products **2** is the reaction site for installation of a second carbon nucleophile by allylation, and thence it is practically worthwhile to find reagents which furnish high regio- and stereoselectivities as well as efficient reactivity in the allylation of easily preparable **2**. However, to the best of our knowledge, this sort of reaction was little studied even with related compounds. We investigated alkylation of *trans* and *cis* acetates **3** and **6** derived from alcohols **2** with the reagents prepared from butylmagnesium halides and CuCN, the result of which is presented in this letter. In addition, we applied the reaction to synthesis of dihydromultifidene.[3]



Scheme 1. Previous and present works. note: R for **2**–**8**: **a**, Ph; **b**, *n*-Bu.

Standard acetylation of alcohols **2a** (R = Ph) and **2b** (R = *n*-Bu) with Ac_2O and pyridine afforded *trans* acetates **3a** and **3b** in 91 and 99% yields, respectively, while the Mitsunobu reaction[4] (AcOH, DEAD, PPh_3) at −78°C in toluene furnished *cis* acetates **6a** and **6b** with >99% diastereoselectivity in 90 and 84% yields, respectively.

On the basis of the previous results that the reactivity and regioselectivity in reaction of **1** are highly controlled by the ratio of RMgX/CuCN and the solvent (THF, Et_2O),[5] three reagents (each 3 equiv.) consisting of different compositions of BuMgCl and CuCN in THF were submitted to the reaction with *trans* acetate **3a** (R = Ph) (Table 1, entries 1–3). The lower order (LO)[6] reagent (entry 1) was less reactive, producing *cis* 3,4-isomer **5a** only in 18% yield. On the other hand, the

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Table 1. Butylation of *trans* acetates **3a** and **3b**

Entry	Acetate	Reagent[a]	Solvent	Temp. (°C)	Time (h)	Major product	Combined yield[b,c]	Ratio of **4**:**5**[d]	Other compds. (%)	
									Acetate[e]	Alcohol[f]
1	**3a**	BuCu(CN)(MgCl)	THF	0	5	**5a**	18	1:>99	90	–
2	**3a**	$Bu_2Cu(CN)(MgCl)_2$	THF	−18	5	**4a**	82 (71)	83:17	–	13
3	**3a**	BuMgCl, CuCN (cat.)[g]	THF	−18	8	**4a**	19	87:13	29	52
4	**3a**	BuCu(CN)(MgCl)	Et_2O	0	10	**5a**	74	1:>99	26	–
5	**3a**	$Bu_2Cu(CN)(MgCl)_2$	Et_2O	−18	5	**5a**	90	7:93	–	15
6	**3a**	BuCu(CN)(MgBr)	THF	0	5	**5a**	20	1:>99	80	7
7	**3a**	$Bu_2Cu(CN)(MgBr)_2$	THF	−18	5	**5a**	52	47:53	13	23
8	**3a**	BuCu(CN)(MgBr)	Et_2O	0	5	**5a**	97 (91)	1:>99	–	–
9	**3a**	$Bu_2Cu(CN)(MgBr)_2$	Et_2O	−18	5	**5a**	100 (94)	1:>99	–	–
10	**3b**	BuCu(CN)(MgCl)	THF	0	7	**5b**	50	1:>99	49	–
11	**3b**	$Bu_2Cu(CN)(MgCl)_2$	THF	−18	5	**4b**	84	91:9	–	2
12	**3b**	BuMgCl, CuCN (cat.)[g]	THF	−18	5	**4b**	42	91:9	–	54
13	**3b**	BuCu(CN)(MgBr)	Et_2O	0	5	**5b**	99 (85)	2:98	–	–
14	**3b**	$Bu_2Cu(CN)(MgBr)_2$	Et_2O	−18	5	**5b**	93 (73)	2:98	–	–

[a] Three equiv. of the reagents were used.
[b] Determined by ^{1}H NMR with pyridine as a standard.
[c] Isolated yields are given in parentheses.
[d] Determined by ^{1}H NMR spectroscopy.
[e] **3a** for entries 1, 3, 4, 6, and 7; **3b** for entries 10 and 12.
[f] **2a** for entries 2, 3, and 5–7; **2b** for entries 11 and 12.
[g] 10 mol%.

higher order (HO)[6] and CuCN-catalyzed reagents produced *cis* 1,4-isomer **4a** though alcohol **2a** and/or acetate **3a** were co-produced with **4a**. In entry 2, the isolated yield was 71%.[7] These results are beyond our prediction.[8] Since the yield of 3,4-isomer **5a** obtained in THF was quite low (entry 1), the LO and HO reagents were re-examined in Et_2O (entries 4 and 5). Both reagents furnished **5a** with high product selectivity; of the two reagents, higher reactivity and higher yield were obtained with the HO reagent (entry 5). We also checked the BuMgBr-based reagents in THF and in Et_2O (entries 6–9). Among them, the best results were provided with Et_2O (entries 8 and 9), giving **5a** in 91 and 94% isolated yields, respectively.[9]

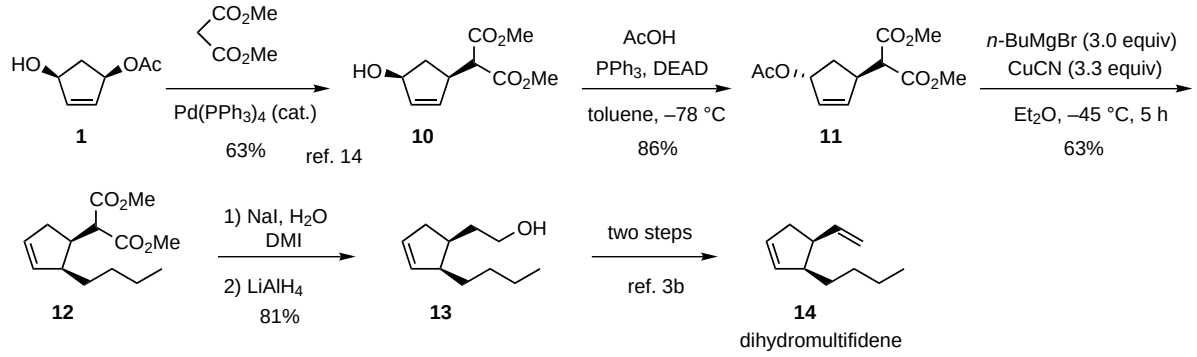
Although it was conceived that the best conditions elucidated for the butylation of **3a** (R = Ph) are applicable to that of **3b** (R = *n*-Bu), the conditions given in entries 1–9 were investigated for butylation of **3b**. Similar tendencies for the reactivity and the regioselectivity were observed through the experiments; some of the results are presented in entries 10–14. The regioisomers **4b** and **5b** were best synthesized in entry 11 for **4b** and in entries 13, 14 for **5b**, respectively.

Next, butylation of *cis* acetates **6a** (R = Ph) and **6b** (R = Bu) was investigated using the LO and HO reagents. Among the eight experiments with **6a** (combination of LO or HO, X = Cl or Br, and THF or Et_2O), the BuMgCl-based HO reagent in THF and the BuMgBr-based LO reagent in Et_2O provided the best results producing *trans* **7a** and **8a**, respectively (Table 2,

Table 2. Butylation of *cis* acetates **6a** and **6b**

Entry	Acetate	Reagent[a]	Solvent	Temp. (°C)	Time (h)	Major product	Combined yield[b]	Ratio of **7**:**8**[c]	Other compds. (%)	
									Acetate[d]	Alcohol[e]
1	**6a**	$Bu_2Cu(CN)(MgCl)_2$	THF	−18	5	**7a**	96	67:33	–	2
2	**6a**	BuCu(CN)(MgBr)	Et_2O	0	7	**8a**	100 (90)[f]	3:97	–	–
3	**6b**	$Bu_2Cu(CN)(MgCl)_2$	THF	−18	5	**7b**	96	55:45	–	–
4	**6b**	BuCu(CN)(MgBr)	Et_2O	0	7	**8b**	100	5:95	–	–

[a] Three equiv. of the reagents were used.
[b] Determined by ^{1}H NMR with pyridine as a standard.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Acetates **6a** and **6b** were not recovered in entries 1–4.
[e] **9a** for entry 1. In other entries, the corresponding alcohol **9a** or **9b** were not detected.
[f] Isolated yield.



Scheme 2. Racemic synthesis of dihydromultifidene.

entries 1 and 2), though the regioselectivity for the former was moderate. Regarding *cis* acetate **6b**, *trans* 1,4-isomer **7b** was obtained with the HO reagent, but with a poor regioselectivity (entry 3), while 3,4-isomer **8b** was produced in high ratio and yield (entry 4).

9a: R = Ph
9b: R = Bu

The stereochemistry of the 1,4-regioisomers **4a**,**b** and **7a**,**b** was easily determined by ^{1}H NMR spectroscopy: in general, differences in chemical shifts between the geminal protons at C(5) of *cis* and *trans* 1,4-disubstituted 2-cyclopentenes are >1 and <0.3 ppm, respectively.[10] In the spectra of **4a** and **4b**, the differences in question were 1.3 and 1 ppm, respectively, thus supporting the *cis* stereochemistry for them, while those measured for **7a** and **7b** were 0.1 and 0[11] ppm, respectively, by which the *trans* stereochemistry was assigned for them (**7a** and **7b**). These stereochemical outcomes strongly suggest the inversion and the *anti* S_N2' reactions to be involved depending on the ratio of BuMgX/CuCN and the solvent, the same reaction mode as that observed for the alkylation of monoacetate **1**.[2] Furthermore, with the ^{1}H NMR spectra of these products, no contamination of the corresponding stereoisomers in the entries of Tables 1 and 2 was confirmed. Regarding 3,4-isomers, the *cis* stereochemistry of **5a** was determined by an NOE experiment,[12] while stereochemistries of the other products **5b**, **8a**, and **8b** were assigned by analogy to the above assignments.

With the establishment of the product prediction in the reaction of acetates **3a**,**b** and **6a**,**b**, application in organic synthesis has now become quite feasible. As an example, synthesis of alcohol **13** was achieved as summarized in Scheme 2. This alcohol is the key intermediate[3b] for synthesis of dihydromultifidene (**14**), which is a pheromone of the brown algae, *Dictyopteris acrostichoides*.[13]

According to the literature,[14] racemic acetate **1** was converted into alcohol **10**, which upon Mitsunobu inversion with AcOH furnished **11** stereoselectively in 86% yield. Installation of the Bu group was carried out using the LO reagent in Et_2O (the conditions of entry 8 in Table 1), which required lower temperature of –45°C to obtain a high diastereomeric ratio (91:1) of **12** and an isomer.[15,16] The acidic proton at the malonate part did not quench the reagent. Demethoxycarbonylation of **12** followed by reduction afforded alcohol **13** in good yield. Finally, **13** was converted into **14** according to the literature procedure.[3b] The ^{1}H NMR spectra of synthetic **14** was consistent with the data reported.[3c,17]

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3. Previous syntheses: (a) Boland, W.; Mertes, K. *Helv. Chim. Acta* **1984**, *67*, 616–624; (b) Kramp, P.; Helmchen, G.; Holmes, A. B. *J. Chem. Soc., Chem. Commun*. **1993**, 551–552; (c) Lebreton, J.; Alphand, V.; Furstoss, R. *Tetrahedron* **1997**, *53*, 145–160.
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5. For information in detail, see Table 1 of Ref. 2.
6. Although the structures of copper reagents derived from butylmagnesium halides and Cu(I) salt are not determined, the terms 'LO, HO, and CuCN-catalyzed reagents' are conveniently used to indicate the ratios of 1:1, 2:1, and 10:1 for the reagents derived from BuMgX and CuCN. For the original LO and HO reagents derived from RLi and CuCN, see the following: Liptshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1994; Chapter 4, p. 283.
7. To a slurry of CuCN (65 mg, 0.73 mmol) in THF (1 mL) was added a solution of BuMgCl (1.0 mL, 1.50 M in THF, 1.50 mmol) at –18°C. After 20 min of stirring,

acetate **3a** (50 mg, 0.25 mmol) in THF (0.2 mL) was injected. The reaction was carried out at −18°C for 5 h, and quenched by addition of saturated NH_4Cl and 28% NH_3. The resulting mixture was extracted with Et_2O three times, and the crude product was purified by chromatography to afford 71% yield (36 mg) of **4a** and **5a** in a 83:17 ratio: ^{1}H NMR of **4a** (300 MHz, $CDCl_3$) δ 0.89 (t, $J=7$ Hz, 3H), 1.1–1.4 (m, 7H), 2.58 (dt, $J=15$, 8 Hz, 1H), 2.71 (br s, 1H), 3.80–3.91 (m, 1H), 5.72 (dt, $J=5$, 2 Hz, 1H), 5.87 (dt, $J=5$, 2 Hz, 1H), 7.15–7.30 (m, 5H).

8. We had expected efficient (yield and regioselectivity) production of **5a** from entry 1 and **4a** from entries 2 and 3 on the basis of the previous results.[2]
9. According to the procedure described in Ref. 7, butylation of **3a** (50 mg, 0.25 mmol) was performed with BuMgBr (0.82 mL, 0.92 M in Et_2O, 0.75 mmol), CuCN (81 mg, 0.90 mmol), and Et_2O (1.2 mL) at 0°C for 5 h to afford **5a** in 91% yield (46 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, $J=7$ Hz, 3H), 0.82–0.99 (m, 2H), 0.99–1.26 (m, 4H), 2.65 (dm, $J=8$ Hz, 2H), 2.76–2.88 (m, 1H), 3.55 (q, $J=8$ Hz, 1H), 5.88 (s, 2H), 7.15–7.30 (m, 5H).
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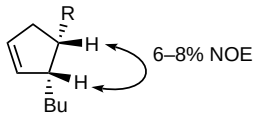
11. Due to the existence of the C_2 symmetry axis.
12. NOE experiment of **5a**:



5a

13. Wirth, D.; Fischer-Lui, I.; Boland, W.; Icheln, D.; Runge, T.; König, W. A.; Phillips, J.; Clayton, M. *Helv. Chim. Acta* **1992**, *75*, 734–744.
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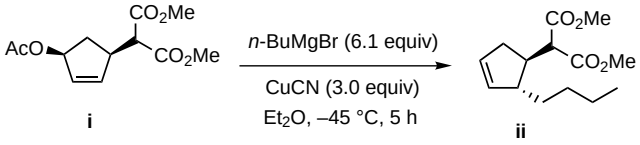
15. Probably the regioisomer. However, the full structure was not characterized.
16. Reaction of acetate **i** derived from **10** (Ac_2O, pyridine) with the LO reagent efficiently afforded isomer **ii**, with the supposed *trans* stereochemistry; the ^{1}H NMR spectrum of **ii** is different from that of **12**.



i **ii**

17. This result and that of Ref. 16 indirectly support the stereochemical outcome for the 3,4-isomers synthesized in Tables 1 and 2.