Pergamon

Tetrahedron Letters 42 (2001) 423–427

TETRAHEDRON LETTERS

Regio- and stereoselective installation of alkyl groups onto *cis* 4-cyclopentene-1,3-diol monoacetate by using reagents derived from alkylmagnesium halides

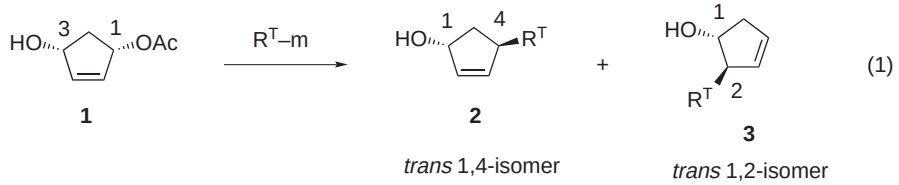
Michiko Ito, Modachur G. Murugesh and Yuichi Kobayashi*

Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan

Received 29 September 2000; revised 1 November 2000; accepted 2 November 2000

Abstract—Reaction of *cis* 4-cyclopentene-1,3-diol monoacetate with alkyl reagents derived from RMgX and CuCN furnished either *trans* 4-alkyl-2-cyclopenten-1-ols (1,4-isomers) or *trans* 2-alkyl-3-cyclopenten-1-ols (1,2-isomers) depending upon the stoichiometry of RMgX/CuCN and the solvents used (Et_2O or THF).

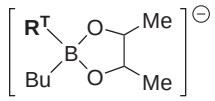
The ready availability of 4-cyclopentene-1,3-diol monoacetate (**1**) in an enantiomerically enriched form of >95% ee as well as the chemically stable nature of **1** makes it attractive as a starting compound for the synthesis of cyclopentanoids.[1] Regio- and stereoselective installation of carbon-based nucleophiles onto the cyclopentene ring is a critical step to this end. It was surprising, therefore, to find that only the palladium-catalyzed reaction with soft nucleophiles[2] and the Heck reaction[3] have been applied to **1** and the derivatives,[4] when we commenced the investigation of this issue with aryl- and alkenyl borates, which resulted in the development of the regioselective and stereospecific formation of *trans* 1,4-isomers **2** possessing an sp^2-carbon-based group as the major regioisomers (Eq. (1)).[5–7] Thereafter, products **2** have been utilized in the synthesis of the primary PG intermediates,[6] aristeromycin,[8] and brefeldin.[9] Further investigation with the borates, however, was unsuccessful for installation of an alkyl group. We then explored reagents based on copper.[10] Herein, we present the first achievement of installation of the *alkyl* groups onto **1** to produce *either*



1 **2** **3**

trans 1,4-isomer *trans* 1,2-isomer

ref. 5 and 6



R^T: aryl and alkenyl groups giving **2**

present investigation

R^T–MgX/CuX R^T: alkyl group giving either **2** or **3**

for **1**–**3**: **a**, *n*-Bu; **b**, Et; **c**, $(CH_2)_3Ph$; **d**, $(CH_2)_9CH{=}CH_2$; **e**, *c*-C_6H_{11}

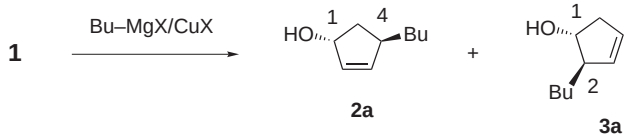
Keywords: alkylation; copper and compounds; coupling reactions; cyclopentenes; Grignard reactions/reagents.

* Corresponding author. Tel./fax: +81 45 924 5789; e-mail: ykobayas@bio.titech.ac.jp

0040-4039/01/$ - see front matter
PII: S0040-4039(00)01983-3

regioisomer in a *trans* stereofashion using the reagents derived from alkylmagnesium halides (RMgX) and CuX (Eq. (1)).

A butyl group (Bu) was chosen as a representative alkyl group for the present investigation with **1**. Reactions were examined with reagents derived in situ from BuMgX (X = Cl, Br) and CuX (X = CN, I) (in stoichiometric or catalytic amounts) in THF or Et_2O at temperatures between −18°C and room temperature (Eq. (2)).[7] We found that, in most cases, the reactions were completed within 2–5 h (monitored by TLC), furnishing the regioisomers **2a** and/or **3a**. The regioselectivity of **2a**/**3a** was dependent upon the halogen atom in BuMgX, the stoichiometry of BuMgX/CuX, and the solvent used. The corresponding *cis* isomers were not detected in all cases by ^{1}H NMR (300 MHz) spectroscopy.[11] Results with the reagents derived from BuMgCl and BuMgBr are summarized in Tables 1 and 2, respectively, in which 'calculated yields' (regioselectivity × combined yield) are given to assess the efficiency of the reactions.



2a **3a** (2)

Reaction of **1** with BuCu(CN)(MgCl) in THF at 0°C afforded the *trans* 1,2-isomer **3a** (Table 1, entry 1) with a high efficiency of 90% calculated yield. On the other hand, $Bu_2Cu(CN)(MgCl)_2$ and BuMgCl/CuCN (10 mol%) furnished the 1,4-isomer **2a** with calculated yields of 87 and 94%, respectively (entries 2 and 3). Surprisingly, the regioselectivity for $Bu_2Cu(CN)(MgCl)_2$ and BuMgCl/CuCN (cat.) was reversed in Et_2O to afford **3a**, and their efficiency in giving **3a** was among the best of the reactions (entries 5 and 6). On the other hand, BuCu(CN)(MgCl) in Et_2O produced a mixture of unidentified compounds, although **3a** was a major product (entry 4). We also examined CuI-based reagents (entries 7–10). In all cases, the same sense of selectivity as for the CuCN-based reagents was ob-

Table 1. Reaction of **1** with reagents derived from BuMgCl

Entry	Reagent[a]	Solvent	Temp. (°C)	Time (h)	Ratio of **2a**:**3a**[b]	Combined yield (%)[c]	Calcd yield (%)[d]	
							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 (cat.)[e]	THF	−18	5	94:6	100	94 (85)	6
4	BuCu(CN)(MgCl)	Et_2O	rt	5	14:86	37	5	32
5	$Bu_2Cu(CN)(MgCl)_2$	Et_2O	−18	2	7:93	85	6	79
6	BuMgCl, CuCN (cat.)[e]	Et_2O	−18	2	8:92	82	7	75
7	BuCu (from CuI)	THF	0	4	40:60	22[f]	9	13
8	BuMgCl, CuI (cat.)[e]	THF	−18	3	92:8	100	92	8
9	BuCu (from CuI)	Et_2O	0	5	13:87	22[f]	3	19
10	BuMgCl, CuI (cat.)[e]	Et_2O	−18	5	19:81	85	16	69

[a] Three (3) equiv.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR with pyridine.
[d] Isolated yields are given in parentheses.
[e] 10 mol%.
[f] Acetate **1** was recovered.

Table 2. Reaction of **1** with reagents derived from BuMgBr

Entry	Reagent[a]	Solvent	Temp. (°C)	Time (h)	Ratio of **2**:**3**[b]	Combined yield (%)[c]	Calcd yield (%)	
							2	**3**[b]
1	BuCu(CN)(MgBr)	THF	0	5	10:90	89	9	80
2	$Bu_2Cu(CN)(MgBr)_2$	THF	−18	3	71:29	98	70	28
3	BuMgBr, CuCN (cat.)[d]	THF	−18	3	73:27	96	70	26
4	BuCu(CN)(MgBr)	Et_2O	0	4	7:93	71[e]	5	66
5	$Bu_2Cu(CN)(MgBr)_2$	Et_2O	−18	3	6:94	88	5	83
6	BuMgBr, CuCN (cat.)[d]	Et_2O	−18	3	5:95	94	5	89

[a] Three (3) equiv.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR with pyridine.
[d] 10 mol%.
[e] Acetate **1** was recovered.

served. However, the efficiency was good only in the case with BuMgCl/CuI (cat.) in THF giving the 1,4-isomer **2a** (entry 8), while the reagents in Et_2O showed moderate selectivity (entry 10). Reactions with BuCu, derived from CuI and BuMgCl, were not completed both in THF and in Et_2O (entries 7 and 9).

The BuMgBr-based reagents, BuCu(CN)(MgBr), $Bu_2Cu(CN)(MgBr)_2$, BuMgBr/CuCN (10 mol%), showed the same tendency for the selectivity (**2a**/**3a**) and a similar reactivity (Table 2). Among them, good efficiency furnishing the 1,2-isomer **3a** was recorded with BuCu(CN)(MgBr) in THF, $Bu_2Cu(CN)(MgBr)_2$ in Et_2O, and BuMgBr/CuCN (cat.) in Et_2O (entries 1, 5, and 6). However, the selectivity and/or the yield were somewhat lower in entries 2–4.

The efficient reaction conditions developed above (Tables 1 and 2) were applied to other alkylmagnesium halides (Eq. (1)). As summarized in Table 3, Et, $(CH_2)_3Ph$, $(CH_2)_9CH{=}CH_2$, and c-C_6H_{11} groups were installed onto **1** with good efficiency furnishing 1,4-isomers **2b**–**e** or 1,2-isomers **3b**–**e** depending upon the conditions. In these experiments, no *cis* products were detected by ^1H NMR spectroscopy.

Previously, 1,4-isomers **2** have been synthesized by the reaction of cyclopentadiene monoepoxide (**4**) with $R^TCu(CN)Li$,[12a] and $[R^TZnMe_2]Li$/MeCu(CN)Li (cat.).[12b] On the other hand, hydroboration of 5-alkyl-1,3-cyclopentadienes with (+)- or (−)-$(Ipc)_2BH$ furnishes 1,2-isomers **3** with a synthetically acceptable level of enantiomeric excesses.[13] However, these methods suffer from serious problems such as follows: (1) the former method is not applicable, at present, for synthesis of 1,4-isomers **2** with sufficient % ee for organic synthesis since only a moderate enantiomeric excess of 64% is reported in the asymmetric synthesis of the monoepoxide **4**,[14] (2) for the latter method, the preparation of 5-alkyl-1,3-cyclopentadiene requires harsh conditions keeping temperature at −78°C for extremely long periods (16–20 h) and the tedious isolation procedure after the hydroboration to separate the co-produced Ipc-OH. On the contrary, the present reaction provides both of the regioisomers, 1,4-isomers **2** and 1,2-isomers **3**, from acetate **1** with high efficiency within several hours at the mild temperatures between −18 and 0°C,[15] and both enantiomers of **1** are easily available.[1] Entries 2, 3, and 8 in Table 1 are suitable for the production of **2**, while entries 1, 5, and 6 in Table 1 and entries 1, 5, and 6 in Table 2 are recommended for the preparation of **3**. Moreover, the success in the installation of the c-C_6H_{11} group shows applicability of the present reaction to other secondary alkyl groups. In addition, the regioisomeric products **2** and **3** are easily purified by chromatography on silica gel as the differences in the ΔR_f value on TLC are large enough to allow the separation (ca. 0.1).

The relative stereochemistry of **2a** was determined to be *trans* by comparison of their ^1H NMR spectra with those prepared from cyclopentadiene monoepoxide by Marino,[12a] who elucidated the stereochemistry on the basis of the difference in the chemical shift between the geminal protons at C(5): $\Delta\delta$ for *trans* and *cis* isomers being <0.3 ppm and >1 ppm, respectively.[16] In the same way, the *trans* stereochemistry was assigned to

Table 3. Reaction of **1** with reagents derived from R^TMgX and CuCN

Entry	Reagent[a]	Solvent	Temp. (°C)	Time (h)	Ratio of **2**:**3**[b]	Combined yield (%)[c]	Calcd yield (%)[d]	
							2[b]	**3**[b]
1	EtCu(CN)(MgCl)	THF	0	5	5:95	87	4	83
2	EtMgCl, CuCN (cat.)[e]	THF	−18	3	94:6	91	86	5
3	$[Ph(CH_2)_3]_2Cu(CN)(MgBr)_2$	Et_2O	−18	5	3:97	97	3	94 (96)
4	$Ph(CH_2)_3MgCl$, CuCN (cat.)[e]	THF	−18	5	91:9	100	91 (87)	9
5	$[CH_2{=}CH(CH_2)_9]$-Cu(CN)(MgCl)	THF	0	5	4:96	100	4	96 (91)
6	$CH_2{=}CH(CH_2)_9MgCl$, CuCN (cat.)[e]	THF	−18	5	95:5	102	97 (90)	5
7	$(c$-$C_6H_{11})_2Cu(CN)$-$(MgCl)_2$	Et_2O	−18	4	7:93	85	6	79
8	$(c$-$C_6H_{11})MgCl$, CuCN (cat.)[e]	Et_2O	−18	4	9:91	91	8	83
9	$(c$-$C_6H_{11})MgCl$, CuCN (cat.)[e]	THF	−18	5	89:11	78	69	9

[a] Three (3) equiv.
[b] Determined by ^1H NMR.
[c] Determined by ^1H NMR with pyridine.
[d] Isolated yields are given in parentheses.
[e] 10 mol%.

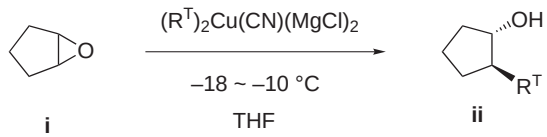
other 1,4-products **2b**–**e** successfully. Regarding 1,2-regioisomers, the *trans* stereochemistry for **3a**–**c** was determined by comparison of the ^{1}H NMR spectra of the corresponding saturated alcohols (synthesized by hydrogenation) with those of the authentic compounds prepared by another method.[17] The same (*trans*) stereochemistry was assigned for **3d** and **3e** by analogy.[18–20]

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture Government of Japan.

References

1. (a) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480–492; (b) Sugai, T.; Mori, K. *Synthesis* **1988**, 19–22; (c) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1298–1299; (d) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875–5878; (e) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695–3696.
2. (a) Deardorff, D. R.; Linde II, R. G.; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759–2762; (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776–5788; (c) Deardorff, D. R.; Savin, K. A.; Justman, C. J.; Karanjawala, Z. E.; Sheppeck II, J. E.; Hager, D. C.; Aydin, N. *J. Org. Chem.* **1996**, *61*, 3616–3622.
3. Torii, S.; Okumoto, H.; Akahoshi, F.; Kotani, T. *J. Am. Chem. Soc.* **1989**, *111*, 8932–8934.
4. For the construction of specific compounds, the Claisen rearrangement,[1c,d,4a] intramolecular radical reaction,[4b,c] and metathesis reaction[4d] of **1** has been developed: (a) Nara, M.; Terashima, S.; Yamada, S. *Tetrahedron* **1980**, *36*, 3161–3170; (b) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384–6385; (c) Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958–2960; (d) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179–8188.
5. (a) Kobayashi, Y.; Takahisa, E.; Usmani, S. B. *Tetrahedron Lett.* **1998**, *39*, 597–600; (b) Kobayashi, Y. *J. Synth. Org. Chem.* **1999**, *57*, 845–855.
6. Usmani, S. B.; Takahisa, E.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 601–604.
7. One enantiomer is shown to indicate the relative stereochemistries properly. For convenience, racemic **1** was used for the present investigation.
8. Tokoro, Y.; Kobayashi, Y. *Chem. Commun.* **1999**, 807–808.
9. Kobayashi, Y.; Watatani, K.; Kikori, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 6125–6128.
10. (a) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318–2325; (b) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986–3990; (c) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056–8066; (d) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864–4872; (e) Kang, S.-K.; Lee, D.-H.; Sim, H.-S.; Lim, J.-S. *Tetrahedron Lett.* **1993**, *34*, 91–94.
11. The *cis* isomers corresponding to **2a** and **3a** were prepared by the Mitsunobu reaction.
12. (a) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898–4913; (b) Lipshutz, B. H.; Woo, K.; Gross, T.; Buzard, D. J.; Tirado, R. *Synlett* **1997**, 477–478.
13. (a) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532–540; (b) Grethe, G.; Sereno, J.; Williams, T. H.; Uskokovic, M. R. *J. Org. Chem.* **1983**, *48*, 5315–5317; (c) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 7171–7172; (d) Chadha, N. K.; Batcho, A. D.; Tang, P. C.; Courtney, L. F.; Cook, C. M.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1991**, *56*, 4714–4718.
14. Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669–672.
15. Representative experiment: **Reaction with Bu-Cu(CN)(MgCl)** (Table 1, entry 1): To a slurry of CuCN (224 mg, 2.50 mmol, from Aldrich) in THF (4.5 mL) was added *n*-BuMgCl (1.4 mL, 1.49 M in THF, 2.09 mmol) slowly at −18°C (ice/NaCl). After 20 min of stirring at −18°C, acetate **1** (100 mg, 0.70 mmol) dissolved in THF (0.5 mL) was added dropwise under an argon atmosphere. The reaction mixture was stirred at 0°C for 4 h. The reaction was quenched by the addition of saturated NH_4Cl and 28% NH_4OH, and the resulting mixture was extracted several times with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated by evaporation to afford a crude 7:93 mixture of **2a** and **3a** as determined by ^{1}H NMR spectroscopy. The product was purified by chromatography to give **3a** (87 mg) in 89% yield. **Reaction with BuMgCl/CuCN (cat.)** (Table 1, entry 3): To a slurry of CuCN (63 mg, 0.70 mmol) in THF (14 mL) was added *n*-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. The product was isolated as described above and was a 94:6 mixture of **2a** and **3a**, as determined by ^{1}H NMR spectroscopy. Chromatography of the crude product furnished **2a** (832 mg) in 85% yield.
16. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730–4743.
17. Prepared by the epoxide ring opening of cyclopentene oxide (**i**) with $(R^T)_2Cu(CN)(MgCl)_2$ (R^T = Et, Bu, $(CH_2)_3Ph$).



18. The observed stereoselectivity is in accordance with the previous papers: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063–3066; (b) Gendreau, Y.; Normant, J. F. *Tetrahedron* **1979**, *35*, 1517–1521.
19. Attempted phenylation using PhCu(CN)(MgCl) in THF at 0°C for 7 h gave a mixture of the corresponding 1,4- and 1,2-isomers in a rather low yield of 41%.

20. Dependence of the hydroxyl group present in **1** on this reaction was supported by the reactions of **1** and the MOM ether of **1** using (PrO)$SiMe_2CH_2MgCl$ and CuI (15 mol%) in THF. The 1,4-isomer was obtained selectively in 87% isolated yield from **1**, while the MOM ether afforded a 1:2 mixture of the 1,4- and 1,2-isomers, which were marginally separated by chromatography (unpublished result of M. Matsuumi in our laboratory).