COMMUNICATION

Chelation controlled *cis*-selective acylation of 2-(alkoxycarbonyl)-cyclopentylzinc iodides

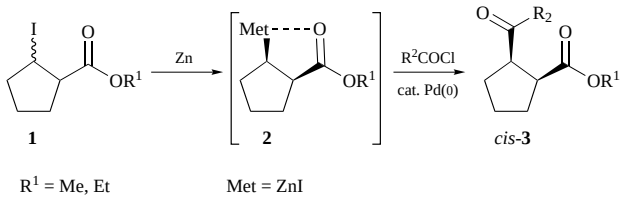
Morio Asaoka,*[a] Akiko Kosaka,[a] Michiko Tanaka,[a] Tsuyoshi Ueda,[b] Takashi Houkawa[b] and Hisashi Takei[b]

[a] *Department of Chemical and Biological Sciences, Faculty of Science, Japan Women's University, Mejirodai 2-8-1 Bunkyoku, Tokyo 112, Japan*
[b] *Interdisciplinary Graduate School of Science and Engineering, Tokyo Institute of Technology, Midoriku, Yokohama 226, Japan*

The Pd(0) catalyzed acylation of 2-(alkoxycarbonyl)cyclopentylzinc iodides gives *cis*-products preferentially.

Stereocontrol at sp^3 carbanionic centers is one of the most fundamental and essential subjects in organic synthesis. Generally, thermodynamically more stable *trans*-substituted products with good to high diastereomeric ratios (80:20 ~ >99:1) are obtained by the reactions of 2-substituted cyclopentyl- and cyclohexyl-zinc or copper species with electrophiles such as benzoyl chloride, allylic halides and vinyl iodides.[1]

In contrast, we report here a highly *cis*-selective reaction of 2-(alkoxycarbonyl)cyclopentylzinc iodide **2** (Scheme 1). In connection with our work on the stereocontrolled S_E reaction of chiral organometallic compounds,[2] we examined a chelation controlled acylation of a cyclic system. The iodo ester **1** was chosen as a starting material, since the intramolecular chelation of its organometallic derivative **2** was expected to fix the configuration in the *cis*-form and result in a *cis*-selective introduction of substituents. The zinc reagent **2** (Met = ZnI) was prepared by the treatment of iodide **1** (R^1 = Et) with activated zinc (3.2 equiv.) in dry 1,4-dioxane at 40 °C for 1.5 h in the presence of chlorotrimethylsilane (0.2 equiv.).[3] Benzoylation of **2** (R^1 = Et) with benzoyl chloride in the presence of 5 mol% of $Pd[(o\text{-tol})_3P]_4$ at room temperature for 14 h gave the expected *cis*-**3a** (R^1 = Et, R^2 = Ph) in 90% isolated yield (Table 1, entry 1). Since use of the corresponding methyl ester as a starting material gave an inferior result (entry 2), the ethyl ester was used for the following study. Other benzoyl chloride derivatives gave the corresponding compounds *cis*-**3c**–**e** in good yields (entries 3–5).† Under the same reaction conditions, pivaloyl chloride gave *cis*-**3f** in good yield (entry 6), however, the more reactive phenylacetyl chloride afforded *cis*-**3g** in a moderate yield. A slight improvement of the yield was observed (entry 7) when the reaction was carried out under milder conditions (10–15 °C, for 2.5 h). Attempted acylation with ethyl chloroformate under various reaction conditions resulted in failure (entry 8).



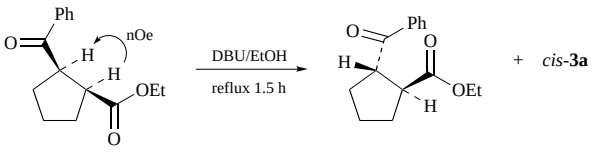
Scheme 1

† Careful examination of the ^1H NMR spectra (400 MHz) of the crude products indicated the formation of a small amount of *trans*-**3** (less than 5% yield), which was easily separated by column chromatography.

Table 1 Chelation controlled *cis*-acylation of **2**

Entry	R^1	R^2	*cis*-**3**	Yield (%)
1	Et	C_6H_5	**3a**	90
2	Me	C_6H_5	**3b**	77
3	Et	$p\text{-}CH_3C_6H_4$	**3c**	71
4	Et	$m\text{-}ClC_6H_4$	**3d**	74
5	Et	$p\text{-}CH_3OC_6H_4$	**3e**	55
6	Et	Bu^t	**3f**	73
7	Et	$C_6H_5CH_2$	**3g**	51
8	Et	OEt	**3h**	—

To confirm the stereostructure of the products (*cis*-**3**), isomerization under basic conditions was examined. Treatment of *cis*-**3a** with a catalytic amount of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in EtOH at reflux for 1.5 h gave thermodynamically more stable *trans*-**3a** in 84% yield, and 6% of *cis*-**3a** was recovered.‡ The configurations of *cis*-**3a** and *trans*-**3a** were also confirmed by NOE experiments (Scheme 2).



Scheme 2

In conclusion, the Pd(0) catalyzed acylation of **2** with aromatic and aliphatic acid chlorides proceeded in a highly diastereoselective manner aided by intramolecular chelation to give the thermodynamically unstable *cis*-substituted cyclopentanecarboxylates (*cis*-**3**) in good yields. Since the basic isomerization gives thermodynamically more stable *trans*-isomers, the above method offers a diastereodivergent route to 2-acylated cyclopentanecarboxylates. Further extension and synthetic applications of the above types of chelation controlled S_E reactions are currently underway.

‡ Ethyl 2-benzoylcyclopentane-1-carboxylate *cis*-**3a**: δ_H(400 MHz, $CDCl_3$; *J* values are given in Hz) 1.05 (3 H, t, *J* 7.1), 1.54–2.25 (6 H, m), 3.08 (1 H, q, *J* 8.3, C*H*CO_2Et), 3.94–4.00 (2 H, m), 4.07–4.13 (1 H, m, C*H*COPh), 7.43–7.57 (3 H, m), 7.92–7.95 (2 H, m); δ_C(100 MHz, $CDCl_3$) 13.5, 23.8, 28.0, 29.6, 47.3, 48.5, 59.7, 128.0, 128.1, 132.4, 136.4, 173.4, 200.5. *trans*-**3a**: δ_H(400 MHz, $CDCl_3$) 1.18 (3 H, t, *J* 7.1), 1.72–2.18 (6 H, m), 3.40 (1 H, q, *J* 8.3, C*H*CO_2Et), 4.06–4.14 (3 H, m, $CO_2CH_2CH_3$ and C*H*COPh), 7.43–7.56 (3 H, m), 7.97–8.00 (2 H, m); δ_C(100 MHz, $CDCl_3$) 14.0, 25.7, 30.5, 31.4, 46.4, 49.4, 60.4, 128.5, 132.9, 136.6, 175.2, 201.4.

Experimental

Typical procedure for the preparation of *cis*-3

To a suspension of activated zinc (312 mg, 4.8 mmol) in dry 1,4-dioxane (2 cm^3) was added 1,2-dibromoethane (34.4×10^{-3} cm^3, 0.4 mmol). The mixture was heated at 65 °C for 5 min. After the addition of chlorotrimethylsilane (40×10^{-3} cm^3, 0.32 mmol), the mixture was stirred at room temperature for 15 min and then a 1,4-dioxane (6 cm^3) solution of **1** (570 mg, 1.5 mmol) was added to the mixture. The mixture was stirred at 40 °C for 1.5 h and cooled to room temperature. To the mixture were added a 1,4-dioxane (1.5 cm^3) solution of $Pd[(o\text{-tol})_3P]_4$, which was prepared by mixing $Pd_2(dba)_3(CHCl_3)$ (41 mg, 0.07 mmol) and $(o\text{-tol})_3P$ (93 mg, 0.31 mmol) in dry 1,4-dioxane at room temperature for 0.5 h, and benzoyl chloride (158.5 mg, 1.12 mmol). After stirring at room temperature for 14 h, the mixture was filtered through a short pad of Celite. Extraction with ethyl acetate and concentration under reduced pressure gave a crude mixture. Formation of the *trans*-isomer was estimated by 400 MHz NMR spectroscopy at this stage. Purification by flash column chromatography on silica gel (hexane–ethyl acetate = 17 : 1) gave *cis*-**3a** (247 mg, 90%).

Acknowledgements

We thank Professor Seizo Takahashi in this University for his help with the NOE experiments.

References

1 L. Micouin, M. Oestreich and P. Knochel, *Angew. Chem.*, *Int. Ed. Engl.*, 1997, **36**, 245; R. Duddu, M. Eckhardt, M. Furlong, H. P. Knoess, S. Berger and P. Knochel, *Tetrahedron*, 1994, **50**, 2415; T. N. Majid, M. C. P. Yeh and P. Knochel, *Tetrahedron Lett.*, 1989, **30**, 5069.

2 T. Houkawa, T. Ueda, S. Sakami, M. Asaoka and H. Takei, *Tetrahedron Lett.*, 1996, **37**, 1045.

3 Generation and reactions of organozinc iodides: P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93**, 2117 and references cited therein.

Paper 7/05554D
Received 31*st July* 1997
Accepted 1*st September* 1997