ORGANIC SYNTHESIS UTILIZING BECKMANN FRAGMENTATION: ASYMMETRIC CARBON-CARBON BOND FORMATION VIA CHIRAL ACETAL INTERMEDIATES

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Treatment of racemic α-methoxycycloalkanone oxime acetates **1** with (2*R*,4*R*)-2,4-bistrimethylsilyloxypentane in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) afforded the chiral acetal intermediates **3**, which were reacted with silicon-containing nucleophiles to give the chiral ω-cyano compounds **4**, in a one-pot operation.

KEYWORDS asymmetric synthesis; Beckmann fragmentation; chiral acetal; ω-cyano alcohol; one-pot operation

Although Beckmann fragmentation is one of the long-known reactions, few studies on high-order use of its intermediates have been done so far.[1] As an extension of our effort to develop the organic synthesis utilizing the intermediates of Beckmann fragmentation,[2] we have succeeded in a novel asymmetric carbon-carbon bond formation by combination of Beckmann fragmentation reaction and asymmetric synthesis using a chiral acetal .[3]

The overall transformation is shown in Chart 1. Reaction of racemic α-methoxycycloalkanone oxime acetates **1** with (2*R*,4*R*)-2,4-bistrimethylsilyloxypentane in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) gave the chiral acetals **3**[4] quantitatively *via* oxonium ion intermediates **2**. Reaction of **3** with silicon-containing nucleophiles afforded the ω-cyano compounds **4** in both high diastereomeric excess (de) and chemical yields. These transformations were carried out in a one-pot operation without isolation of **3**.

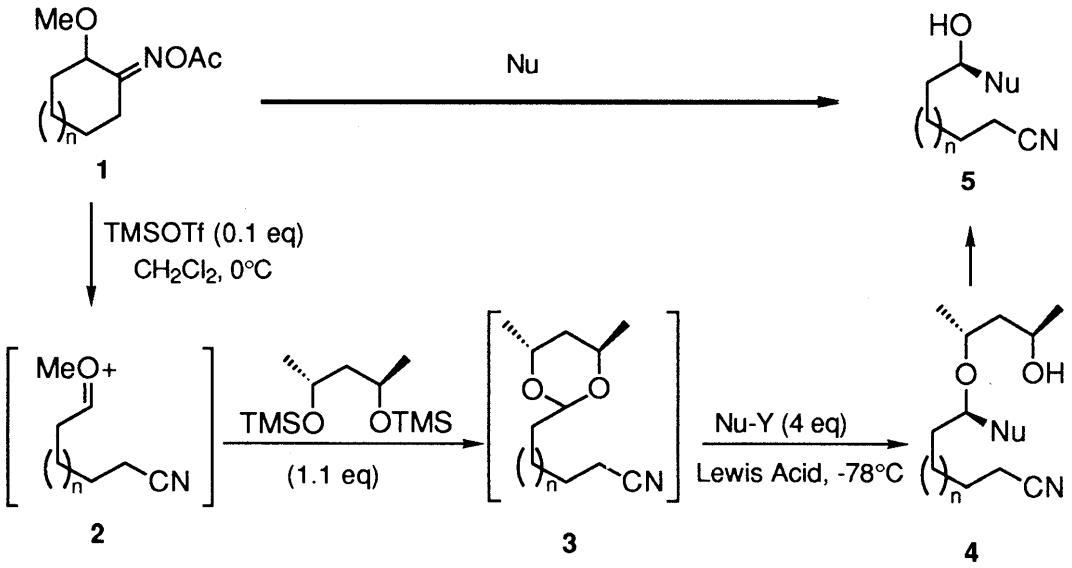
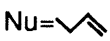
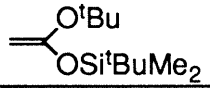


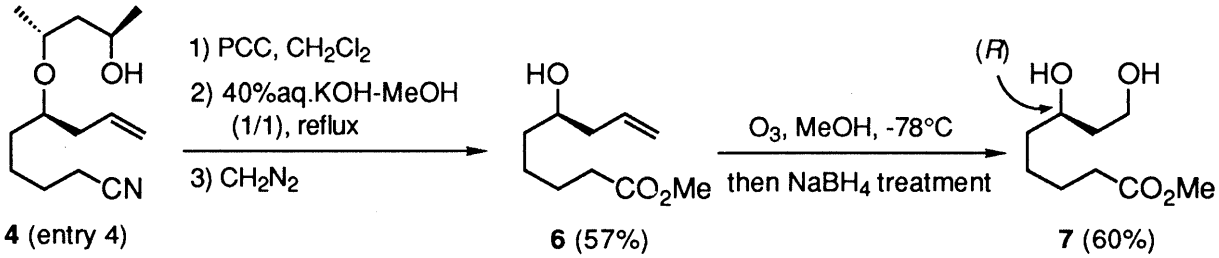
Chart 1

Reaction of **3** (n=1) with allyltrimethylsilane in the absence of Lewis acid gave no **4** (n=1) (Table, entry 1). However, the addition of Lewis acid promoted the conversion of **3** (n=1) to **4** (n=1) (entries 2-4), and slow addition of the mixed Ti-catalyst [$6TiCl_4 \cdot 5Ti(O\text{-}i\text{-}Pr)_4$][5] gave the best result (entry 4).[6] The reaction also worked well for medium and large ring systems (entries 5 and 6).[6] Other silicon-containing nucleophiles similarly reacted with **3** (n=1) in a highly diastereoselective manner. In these cases the mixed Ti-catalyst was ineffective and the use of $TiCl_4$ gave good results (entries 7 and 8).[7] The stereochemistries of the products were determined as follows. The absolute configurations of the products in entries 1-4 were determined by converting the product in entry 4 to the key intermediate **7** for the synthesis of α-(*R*)-lipoic acid (Chart 2). Thus, pyridinium chlorochromate (PCC) oxidation of **4** (94% de) in entry 4 followed by aqueous alkaline treatment under reflux conditions and methylation of the resulting acid afforded the hydroxy methylester **6**. Ozonolysis of **6** followed by $NaBH_4$ treatment gave the dihydroxy methylester **7.** The value of the specific rotation ($[\alpha]_D$ +3.6°) of **7** showed good agreement with the reported one ($[\alpha]_D$ -3.9°)[8] except for the sign. The stereochemistries of the products in entries 5-8 were tentatively assigned by assuming the same sense of diastereoselection as observed for the products in entries 3 and 4 and also by referring to the results in the usual asymmetric synthesis using this chiral acetal.[5,7] The method of converting **4** to the chiral ω-cyano alcohols **5**, oxidation/β-elimination procedure, has already been established.[5,7] In fact, conversion of the product in entry 5 to **5** (n=3, Nu=allyl, $[\alpha]_D$ +9.4°) by the usual procedure [PCC, CH_2Cl_2/40%aq.KOH-MeOH (1/1), r.t.] proceeded in 92% overall yield without any

Table

Entry	Substrate **1**	Nu-Y	Lewis acid(eq)	Product **4**	Yield(%)	de (%) of **4**
1	n=1		None		No reaction	
2			TMSOTf (2)	Nu= 	32	29[a)b)]
3			$TiCl_4$ (2)		88	68[b)]
4			$6TiCl_4 \cdot 5Ti(O\text{-}i\text{-}Pr)_4$ (30)		92	94[b)]
5	n=3		$6TiCl_4 \cdot 5Ti(O\text{-}i\text{-}Pr)_4$ (30)		79	94[b)]
6	n=7		$6TiCl_4 \cdot 5Ti(O\text{-}i\text{-}Pr)_4$ (30)		94	92[b)]
7	n=1	TMS—≡—TMS	$TiCl_4$ (4)	Nu=	77	≥95[c)]
8			$TiCl_4$ (4)	$Nu=CH_2CO_2{}^tBu$	66	≥95[c)]

a) Obtained with *S* configuration, predominantly. b) Determined by GC on a 25m HiCap-CBP 1 capillary column. c) Determined by 500MHz ^{1}H-NMR.



4 (entry 4) **6** (57%) **7** (60%)

Chart 2

trouble.

In conclusion, we opened a novel way to get optically active ω-cyano alcohols **5** from the readily available racemic cyclic α-methoxy cycloalkanone oxime acetates **1**.

REFERENCES AND NOTES

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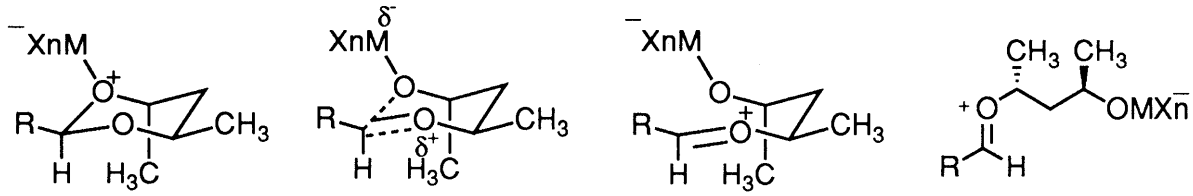
2) a) H. Fujioka, M. Miyazaki, T. Yamanaka, H. Yamamoto and Y. Kita, *Tetrahedron Lett.*, **31**, 5951 (1990); b) H. Fujioka, T. Yamanaka, K. Takuma, M. Miyazaki and Y. Kita, *J. Chem. Soc., Chem. Commun.*, **1991**, 533; c) H. Fujioka, H. Yamamoto, M. Miyazaki, T. Yamanaka, K. Takuma and Y. Kita, *Tetrahedron Lett.*, **32**, 5367 (1991).

3) For reviews on the asymmetric synthesis using the chiral C_2-symmetric acetals, see: a) A. Alexakis and P. Mangeny, *Tetrahedron: Asymmetry*, **1**, 477 (1990); b) H. Fujioka and Y. Kita, "Studies in Natural Product Chemistry", ed by Atta-ur-Rahman, Elsevier, Amsterdam, in press.

4) Compound **3** (n=1) was isolated and its structure was determined by spectroscopic data.

5) W. S. Johnson, P. H. Crackett and J. D. Elliott, *Tetrahedron Lett.*, **25**, 3951 (1984).

6) These phenomena observed in entries 2-6 were explained as follows: the reactions proceed through three different ion pairs **ii-iv** formed from Lewis acid-acetal complex **i**; and (1) the reaction with weak Lewis acid involves the intimate ion pair **ii** and shows extremely high stereoselectivity by inversive substitution (entries 4-6), (2) the reaction with stronger Lewis acid proceeds with modest selectivity through transition state **iii** (entry 3), and (3) the reaction with very powerful Lewis acid involves separated ion pair **iv** and affords the product with no selectivity. [*cf.* S. E. Denmark and N. G. Almstead, *J. Am. Chem. Soc.*, **113**, 8089 (1991); idem, *J. Org. Chem.*, **56**, 6485 (1991).]



Lewis acid acetal complex **i** | intimate ion pair **ii** | external ion pair **iii** | oxonium ion **iv**

7) a) W. S. Johnson, R. Elliott and J. D. Elliott, *J. Am. Chem. Soc.*, **105**, 2904 (1983). b) J. D. Elliott, J. Steele and W. S. Johnson, *Tetrahedron Lett.*, **26**, 2535 (1985). Although high selectivities were obtained even by use of $TiCl_4$ in entries 7 and 8 (*vs* entry 3), these results might be due to difference of nucleophilicity of the reagents: see Y. Yamamoto, H. Abe, S. Nishii, J. Yamada, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 3253.

8) M. H. Brookes, B. T. Golding and A. T. Hudson, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 9.

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