Highly Stereoselective Aldol-type Reaction of 2-Bromo-2,3,3,3-tetrafluoropropanamide with Aldehydes Leading to *erythro*-α-Fluoro-α-(trifluoromethyl)-β-hydroxy Amides

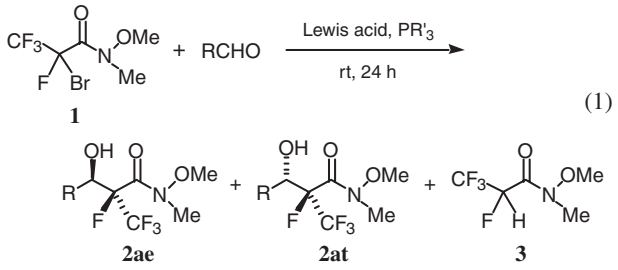
Kei Sato, Takashi Sekiguchi, Takashi Ishihara,* Tsutomu Konno, and Hiroki Yamanaka
Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585

(Received November 7, 2003; CL-031069)

N-Methoxy-*N*-methyl-2-bromo-2,3,3,3-tetrafluoropropanamide underwent highly stereoselective aldol-type reaction with various aldehydes under the influence of triphenylphosphine—a catalytic amount of titanium(IV) isopropoxide at room temperature to give the *erythro*-isomers of α-fluoro-α-(trifluoromethyl)-β-hydroxy amides preferentially in good to excellent yields.

Since the fluorine substituents, such as monofluoro, difluoromethylene, and trifluoromethyl, introduced to organic molecules are frequently recognized to exert specific effects on their biochemical properties,[1] a lot of efforts have continually been made to synthesize many sorts of fluorine-containing biologically active compounds.[2] Stereochemically defined α-fluorinated-β-hydroxy carboxylic acid derivatives are very important fundamental synthetic blocks for preparing various fluorinated analogues of natural compounds.[3] Hence, development of a novel access to the construction of such α-fluorinated-β-hydroxy carbonyl frameworks would be of exceeding value.

In this communication is disclosed a new practical version of the stereoselective aldol-type reaction between 2-bromo-2,3,3,3-tetrafluoropropanamide and aldehydes,[4] which is efficiently promoted by triphenylphosphine and a catalytic quantity of Lewis acid[5] at room temperature to provide preferentially the *erythro*-isomers of α-fluoro-α-(trifluoromethyl)-β-hydroxy amides.



(1)

The treatment of *N*-methoxy-*N*-methyl-2-bromo-2,3,3,3-tetrafluoropropanamide (**1**) with benzaldehyde and triphenylphosphine (PPh_3) (1.2 equiv. each) in dichloromethane (CH_2Cl_2) at ambient temperature for 24 h led to the reduction product **3** in 82% yield, no desired product **2** being formed. When **1** was allowed to react with benzaldehyde in the presence of PPh_3 and boron trifluoride etherate (1.2 equiv. each), the desired β-hydroxy amide **2a** was obtained in 37% yield as a mixture of the *erythro*- and *threo*-isomer,[6] of which the ratio was 67:33. Thereupon were examined other Lewis acids, such as diethylaluminium chloride, aluminium(III) isopropoxide, zinc iodide, titanium(IV) chloride, dichlorotitanium(IV) isopropoxide, and titanium(IV) isopropoxide ($Ti(O\text{-}i\text{-}Pr)_4$). As shown in Table 1, $Ti(O\text{-}i\text{-}Pr)_4$ was found to be the most favorable Lewis acid in terms both of a chemical yield and of stereoselectivity (Entry 7). Thus, the reaction of **1** with benzaldehyde under the influence of PPh_3 and $Ti(O\text{-}i\text{-}Pr)_4$ proceeded in a highly stereoselective manner to provide the *erythro*-isomer of **2a** preferentially (**2ae**:**2at** = 95:5) in 84% yield. Among the phosphorus(III) compounds examined (Entries 7, 9, and 10), such as PPh_3, tributylphosphine, and triethyl phosphite, PPh_3 gave the best result (Entry 7). It can be pointed out that an equimolecular amount of PPh_3 is essential for this reaction, because the absence of PPh_3 did not cause any reactions, resulting in the quantitative recovery of **1** and, in addition, the use of 0.2 equiv. of PPh_3 produced merely 16% yield of **2a** (Entry 8). Examining the solvents, like CH_2Cl_2, acetonitrile, THF, and toluene, revealed that CH_2Cl_2 was the most suitable for the reaction.

Table 1. Screening of the reaction conditions[a]

Entry	Lewis acid	PR'_3	Yield[b]/% of **2a**	Ratio[b] of **2ae**:**2at**	Yield[b]/% of **3**
1	$BF_3{\cdot}OEt_2$	PPh_3	37	67:33	44
2	Et_2AlCl	PPh_3	84	67:33	7
3	$Al(O\text{-}i\text{-}Pr)_3$	PPh_3	tr	-	97
4	ZnI_2	PPh_3	0	-	86
5	$TiCl_4$	PPh_3	-	-	16
6	$TiCl_2(O\text{-}i\text{-}Pr)_2$	PPh_3	26	96:4	65
7	$Ti(O\text{-}i\text{-}Pr)_4$	PPh_3	84	97:3	15
8	$Ti(O\text{-}i\text{-}Pr)_4$	PPh_3[c]	16	95:5	6
9	$Ti(O\text{-}i\text{-}Pr)_4$	PBu_3	30	43:57	43
10	$Ti(O\text{-}i\text{-}Pr)_4$	$P(OEt)_3$	0	-	29

[a]Unless otherwise noted, the mole ratio is **1**:Lewis acid:PR_3 = 1:1.2:1.2. [b]Determined by ^{19}F NMR. [c]0.2 equiv. of PPh_3.

Thus, the aldol-type reaction of **1** with various aldehydes was conducted as follows. To a CH_2Cl_2 solution of $Ti(O\text{-}i\text{-}Pr)_4$ (1.2 equiv.) were successively added in the order CH_2Cl_2 solutions of aldehyde (1.2 equiv.), PPh_3 (1.2 equiv.), and of the amide **1** at ambient temperature. The whole mixture was stirred at room temperature under argon. After 24 h, the reaction was quenched with a saturated NH_4Cl aqueous solution and the resultant mixture was extracted three times with CH_2Cl_2. The organic extracts were washed with a brine, followed by drying over Na_2SO_4, filtration, and concentration in vacuo to leave an oily residue, which was chromatographed on a silica-gel column to give analytically pure product **2**.[7] The results of these reactions are summarized in Table 2.

A variety of aldehydes, including aromatic, aliphatic, and α,β-unsaturated aldehydes, took part very nicely in the reaction of **1** to afford the corresponding α-fluoro-α-(trifluoromethyl)-β-hydroxy amides **2** in good to excellent yields, together with small amounts (6–27%) of the reduction product **3**. The reactions with sterically hindered aldehydes, 2-methylpropanal and 2,2-dimethylpropanal, were somewhat reluctant to result in a slight decrease in the yield of **2** (Entries 16 and 18). Significantly, all of

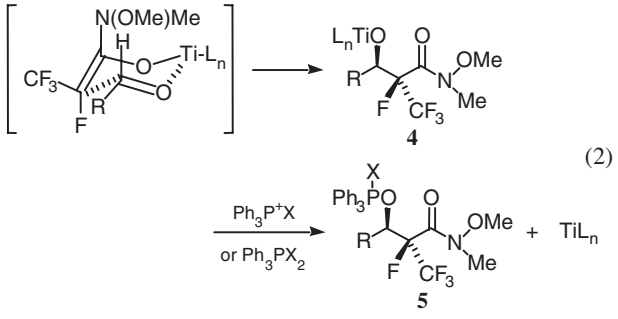
Table 2. Aldol-type reaction of **1** with various aldehydes

Entry	R		Yield[a]/% of **2**	Ratio[b] of **2e**:**2t**	Yield[b]/% of **3**
1	Ph	(**a**)	84 (73)	97:3	15
2[c]			87 (82)	96:4	7
3	*p*-MeC_6H_4	(**b**)	79 (73)	98:2	12
4[c]			84	96:4	9
5	*p*-$MeOC_6H_4$	(**c**)	77	96:4	22
6[c]			91 (83)	95:5	5
7	*p*-ClC_6H_4	(**d**)	90 (78)	96:4	6
8	*p*-FC_6H_4	(**f**)	82	97:3	13
9[c]			83 (81)	97:3	16
10	MeCH=CH	(**g**)	74	95:5	15
11[c]			80 (75)	89:11	12
12	PhCH=CH	(**h**)	76 (68)	95:5	17
13[c]			87	87:13	9
14	Pr	(**i**)	72	96:4	27
15[c]			84 (68)	90:10	11
16	*i*-Pr	(**j**)	65 (53)	95:5	22
17[c]			50	86:14	37
18	*t*-Bu	(**k**)	53 (43)	95:5	25
19[c]			20	87:13	37

[a]Determined by ^{19}F NMR. Values in parentheses are of isolated yields. [b]Determined by ^{19}F NMR. [c]Conducted in the presence of 0.1 equiv. of Ti(O-*i*-Pr)$_4$ and 1.2 equiv. of PPh_3.

the reactions between **1** and aldehydes occurred stereoselectively to afford the *erythro*-isomers of the products preferentially. To be mentioned is that the esters and dialkylamides of 2-bromo-2,3,3,3-tetrafluoropropanoic acid did not efficiently undergo the present aldol-type reaction mediated by phosphine–Lewis acid reagents, leading to less than 20% yields of the products.

Noticeably, even use of PPh_3 and catalytic Ti(O-*i*-Pr)$_4$ reagents was found to facilitate efficiently the aldol-type reaction of **1** with aldehydes in an *erythro*-selective fashion, providing the products **2** in good yields. As listed in Table 2, the results were almost comparable to those employing 1.2 equiv. each of PPh_3 and Ti(O-*i*-Pr)$_4$ reagents, though an appreciable decrease in the stereoselectivity was observed for the reactions with α,β-unsaturated or aliphatic aldehydes.



A plausible mechanism of the present reaction is proposed as follows. Thus, the amide **1**, coordinated with Ti(O-*i*-Pr)$_4$, undergoes a bromine abstraction with PPh_3 to generate a titanium enolate[8] which may have the Z configuration. This enolate reacts with aldehyde via a cyclic chair-like transition state, leading preferentially to the *erythro*-isomer of a titanium aldolate **4**. The aldolate would be subject to the exchange reaction with in situ formed phosphonium or phosphorane species to produce a phosphonium or phosphorane aldolate **5** and titanium Lewis acid. The former is finally transformed to the product **2** by quenching, whereas the latter may be recycled in the reaction of **1**. The more exact mechanistic explanation should await further investigations.

In summary, we have developed a new version of the aldol-type reaction of 2-bromo-2,3,3,3-tetrafluoropropanamide **1** with aldehydes, which is effectively promoted by PPh_3-catalytic Ti(O-*i*-Pr)$_4$ reagents to give preferentially the *erythro*-isomers of α-fluoro-α-(trifluoromethyl)-β-hydroxy amides **2** in good yields. The present reaction will serve as a key step for preparing a number of regio- and stereoselectively fluorinated compounds of biological interest.

This work was financially supported in part by a Grant-in-Aid for Scientific Research (No. 14550808) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and Notes

1 a) "Biomedical Aspects of Fluorine Chemistry," ed. by R. Filler and Y. Kobayashi, Kodansha & Elsevier Biomedical, Tokyo (1982). b) J. T. Welch, *Tetrahedron*, **43**, 3123 (1987). c) J. T. Welch and S. Eswarakrishnan, "Fluorine in Bioorganic Chemistry," John Wiley & Sons, New York (1991). d) I. Ojima, J. R. McCarthy, and J. T. Welch, "Biomedical Frontiers of Fluorine Chemistry," American Chemical Society, Washington, D.C. (1996).

2 a) T. Yamazaki and T. Kitazume, *J. Synth. Org. Chem. Jpn.*, **49**, 721 (1991). b) T. Yamazaki, K. Mizutani, and T. Kitazume, *J. Synth. Org. Chem. Jpn.*, **52**, 734 (1994). c) "Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications," ed. by R. Filler, Y. Kobayashi, and L. M. Yagupolskii, Elsevier, Amsterdam (1993). d) "Fluorine-containing Amino Acids. Synthesis and Properties," ed. by V. P. Kukhar and V. A. Soloshonok, John Wiley and Sons, Chichester (1995).

3 "Enantiocontrolled Synthesis of Fluoro-Organic Compounds, Stereochemical Challenges and Biomedical Targets," ed. by V. A. Soloshonok, John Wiley & Sons, New York (1999).

4 For the aldol reaction of *N*,*N*-dialkyltetrafluoropropanamides: a) M. Kuroboshi and T. Ishihara, *Bull. Chem. Soc. Jpn.*, **63**, 1191 (1990). b) T. Ishihara, *J. Synth. Org. Chem. Jpn.*, **50**, 347 (1992).

5 A stoichiometric combination of triphenylphosphine and Lewis acid is reported to facilitate the aldol-type reaction of α-bromo carbonyl compounds, in which the use of α-bromo carbonyl compounds is limited to *N*,*N*-diphenylamide, thioesters, and ketones. H. Kagoshima, Y. Hashimoto, and K. Saigo, *Tetrahedron Lett.*, **39**, 8465 (1998); Y. Hashimoto and S. Kikuchi, *Chem. Lett.*, **2002**, 126.

6 The relative stereochemical nomenclature proposed by Noyori *et al.* is applied in this work. R. Noyori, I. Ishida, and J. Sakata, *J. Am. Chem. Soc.*, **105**, 1598 (1983).

7 The spectral and analytical data of the products **2** were in good accord with the assigned structures. The stereochemical determination was made by the single-crystal X-ray diffraction method for the major isomer of **2c**, whose data were collected on a Rigaku AFCR7R diffractometer with graphite monochromated Cu Kα radiation and a rotating anode generator.

8 A Lewis acid-assisted generation of enolates via the reductive dehalogenation is proposed. Ref. 5; K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 7705 (1977).

Published on the web (Advance View) January 14, 2004; DOI 10.1246/cl.2004.154