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Stereodivergent Construction of Aminodiols with a CF_3 Group

Ryusuke Obinata, Tomoko Kawasaki-Takasuka, and Takashi Yamazaki*

Division of Applied Chemistry, Institute of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Nakamachi, Koganei 184-8588, Japan

tyamazak@cc.tuat.ac.jp

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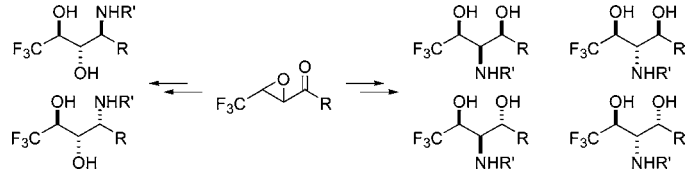
ABSTRACT

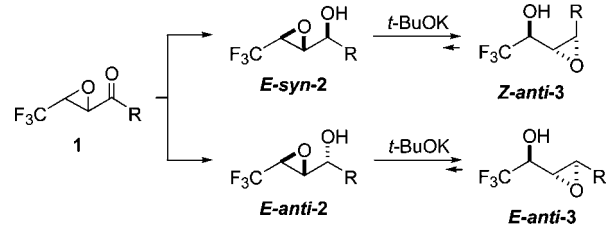


A stereodivergent synthesis of various 2-amino-1,3-diols and 3-amino-1,2-diols from a single intermediate, 2,3-epoxyketones, is described.

Introduction of a fluorine atom or fluorine-containing groups into molecules has attracted significant interest of chemists because such modification sometimes endows enormous change in their physical and/or chemical properties.[1] However, because organofluorine compounds are scarce in nature[2] and this most electronegative element affects reaction courses sometimes very significantly,[3] development of effective methods has been required for construction of organofluorine compounds.

We have previously reported[4] Payne rearrangement[5] of CF_3-containing epoxyalcohols ***E-syn*-2**[6] and ***E-anti*-2** specifically to ***Z-anti*-3** and ***E-anti*-3**, respectively, whose driving force was, from the computational point of view, considered to be the thermodynamic preference of the corresponding alkoxide ion stabilized by a strongly electron-withdrawing CF_3 group (Scheme 1). It is well-known that nucleophilic attack at the CF_3-attached carbon atom is usually restricted[3,7] as a result of the electrostatic characteristics of this group rendering the F_3C-*C*−*O* bond shorter (thus stronger), and nucleophiles approach from the backside of this bond with difficulty. Thus, if this is the case, regioselective reaction to **2** would be readily possible by nucleophilic species. Moreover, if approach of reagents to **3** is intentionally controlled, we could realize new methodology for construction of a variety of regio- and stereoisomeric aminodiols from a single substrate, epoxyketones **1**. In this communication our recent successful results are described on the stereodivergent syntheses of CF_3-containing highly functionalized molecules.

Scheme 1



First, a brief investigation of the reactivity of the isomeric epoxyalcohols ***E-anti*-2a** and **-3a**[4] toward aqueous dimethy-

(1) (a) Yamazaki, T.; Taguchi, T.; Ojima, I. In *Fluorine in Medicinal Chemistry andChemical Biology*; Ojima, I., Ed.; John Wiley & Sons: New York, 2009; p 3. (b) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, NJ, 2008.

(2) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127–133.

(3) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing: Oxford, 2006.

(4) Yamazaki, T.; Ichige, T.; Kitazume, T. *Org. Lett.* **2004**, *6*, 4073–4076.

(5) Hanson, R. M. *Org. React.* **2002**, *60*, 1–15.

(6) Because the DIBAL reduction of **1a** (R = Ph) was found to proceed in an irregularly *anti*-selective manner (61% *anti*), the product, ***E-syn*-2a**was not used throughout this work.

(7) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11.

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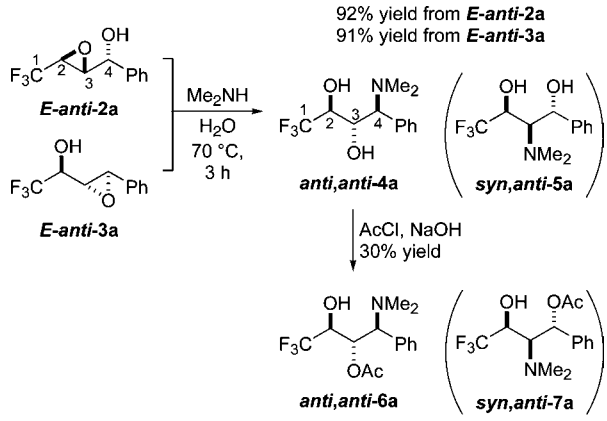
lamine was carried out (Scheme 2). Independent utilization of both substrates interestingly furnished the identical product

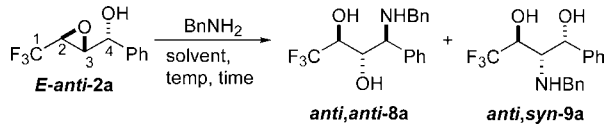
Scheme 2. Reaction of ***E-anti*-2a** and **-3a** with Me_2NH



in excellent yields. We anticipated that the reaction under this basic condition proceeded via Payne rearrangement, conversion of ***E-anti*-2a** to ***E-anti*-3a**, and then regioselective epoxy ring-opening. In fact, the product was confirmed as ***anti*,*anti*-4a**, not ***syn*,*anti*-5a**, which was understood to be a consequence of the $HNMe_2$ attack at the more reactive benzylic site of ***E-anti*-3a** exclusively.[8,9]

With this basic information in hand, benzylamine was selected as the next convenient nucleophile (Table 1). In this

Table 1. Reaction of ***E-anti*-2a** with Benzylamine



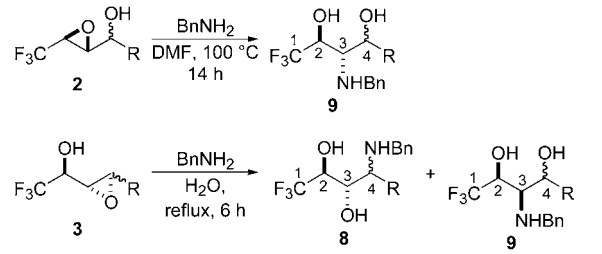
				^{19}F NMR yield (%)	
entry	solvent	temp (°C)	time (h)	**8a**	**9a**
1	toluene	60	6	0	4
2	toluene	80	6	0	21
3	toluene	80	14	0	42
4	toluene	100	14	0	84
5	THF	refl	6	0	21
6	DMF	100	6	0	37
7	DMF	100	14	0	92
8	DMF/H_2O^a	100	6	84	0
9	H_2O	refl	6	quant	0
10	*n*-PrOH	refl	14	trace	90

[a] DMF/H_2O = 1:1 (v/v).

instance, yields of the products seemed to be dependent on the temperature and time of the reactions rather than the polarity of the solvents employed, and overnight heating of the model epoxyalcohol ***E-anti*-2a** at 100 °C afforded the aminodiol in 92% yield with complete regioselectivity (entry 7). Quite interestingly, its structure was found to be different from that of the product obtained when H_2O was used as a (co)solvent (entries 8 and 9). The Me_2NH results are described in Scheme 2. We expected that the latter product was ***anti*,*anti*-8a** by the $BnNH_2$ attack after Payne rearrangement of ***E-anti*-2a** to ***E-anti*-3a**,while the former ***anti*,*syn*-9a** was obtained as the consequence of the direct and regiospecific C−N bond formation at C^3 in an S_N2 fashion. It is noteworthy that this alteration of the product selectivity was observed only for water as the solvent, and *n*-propanol with a similar boiling point of 97 °C did not show such effect, furnishing ***anti*,*syn*-9a** in excellent yield without Payne rearrangement (entry 10). Due to the lower ability to accept hydrogen bonding compared with *n*-propanol, H_2O would lead to more effective activation of the epoxy ring as the Brønsted acid and thus ready intramolecular nucleophilic attack of the OH group to facilitate Payne rearrangement.[10]

These two independent solvents, DMF and H_2O (entries 7 and 9 in Table 1, respectively), furnished excellent results for the introduction of $BnNH_2$ to ***E-anti*-2a** and were applied to other substrate series **2** and **3**, the results of which are summarized in Table 2. As expected, attainment of regio-

Table 2. Reactions of **2** and **3** with $BnNH_2$



a: R = Ph, b: R = $PhCH_2CH_2$, c: R = *n*-C_6H_{13}

			compound **9**[b]		
entry	substrate	ratio[a]	yield (%)	ratio[c]	major isomer[d]
1	***E*-anti-2a**	87:13	92	90:10	*syn*
2	***E*-anti-2b**	89:11	82	90:10	*syn*
3	***E*-anti-2c**	91:9	80	89:11	*syn*
4	***E*-syn-2b**	9:91	95	9:91	*anti*
5	***E*-syn-2c**	12:88	49	8:92	*anti*
6	***E*-anti-3a**	83:17	[>99]	[90:10]	[*anti*]
7	***E*-anti-3b**	90:10	[77]	[90:10]	[*anti*]
8	***E*-anti-3c**	89:11	9 [63]	[86:14]	[*anti*]
9	***Z*-anti-3b**	11:89	[71]	[6:94]	[*syn*]
10	***Z*-anti-3c**	14:86	16 [69]	[8:92]	[*syn*]

[a] Isomeric ratios of *anti*:*syn* for compounds **2** and *E*:*Z* for **3**. [b] In the brackets are shown the corresponding data of compound **8**. [c] Isomeric ratio between C^3−C^4. [d] Relative stereochemistry between C^3−C^4.

and stereospecific ring-opening of aminodiols **8** and **9** was realized by way of a clean S_N2 mechanism.

As shown above, because we successfully found the conditions to access 2-amino-1,3-diols ***anti*,*anti*-** and

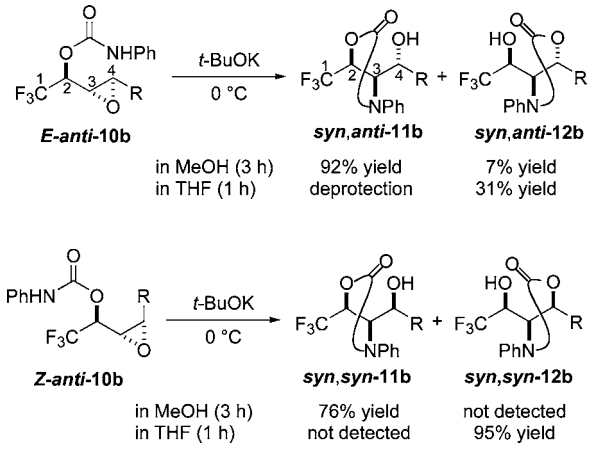
(8) The same 3-amino-1,2-diol selectivity was also confirmed by ***E*-anti-2b** and **-3b**.

***anti*,*syn*-9** in addition to 3-amino-1,2-diols ***anti*,*anti*-** and ***anti*,*syn*-8**, the diastereomeric **9** with a C^2-C^3 *syn* stereochemical relationship was set as the next target to be prepared for completion of the stereodivergent preparation of all isomeric 2-amino-1,3-diols from single substrates. For this purpose, extension of our previous method[11] was performed by way of intramolecular S_N2-type ring-opening after conversion of **3** into the corresponding carbamates **10**.

Requisite substrates **10** for this process were prepared on the basis of a standard protocol using phenylisocyanate in the presence of triethylamine at 0 °C (Table S1 in Supporting Information). Stereoisomerically pure carbamates ***Z*-*anti*-10b** and **-10c** were fortunately obtained from ***Z*-*anti*-3b** and **-3c** by only their simple recrystallization. This is also the case for ***E*-** and ***Z*-*anti*-10a**, which were readily separable by silica gel column chromatography, but ***E*-*anti*-10b** and **-10c** should be employed for the next intramolecular oxirane ring-opening as the isomeric mixtures.

Applicaion of our slightly modified previous conditions to ***E*-*anti*-10b** smoothly afforded the oxazolidinone ***syn*,*anti*-11b** in excellent yield along with a small amount of the isomeric ***syn*,*anti*-12b** when the reaction was conducted in MeOH (Scheme 3). However, the aprotic solvent THF

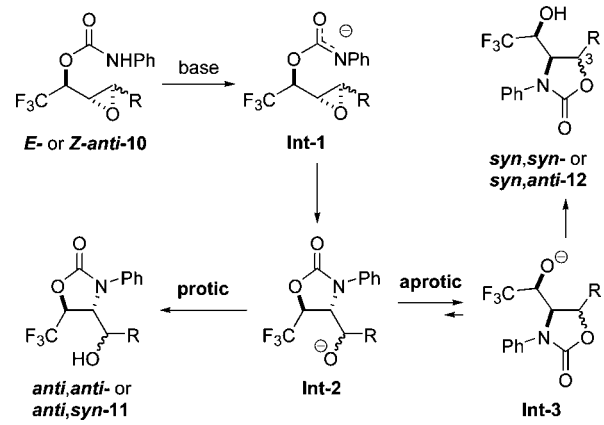
Scheme 3. Intramolecular Epoxy Ring-Opening of ***E*-** and ***Z*-*anti*-10b** (R = $PhCH_2CH_2$)



drastically altered the product selectivity, and ***syn*,*anti*-12b** became the major product but only in low yield, and one of the byproducts in the mixture seemed to be the deprotected aminodiol. When ***Z*-*anti*-10b** was used as the substrate, the same trend was observed with attainment of a much higher chemical yield of ***syn*,*syn*-12b** in THF.

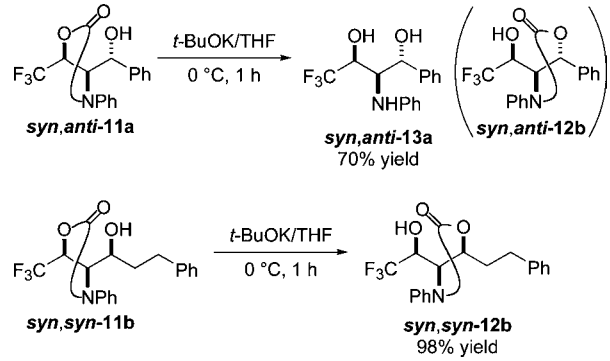
Near quantitative formation of ***syn*,*syn*-12b** instead of the isomeric ***syn*,*syn*-11b** was unexpected from our experience[11] and would be understood by the proposed mechanism depicted in Scheme 4. Thus, subjection of ***E*-*anti*-10** to a solution

Scheme 4. Possible Reaction Mechanism



containing *t*-BuOK should convert it to the anionic species **Int-1**. This intermediate would experience epoxy ring-opening in a 5-*exo*-*tet*[12] fashion to yield **Int-2** whose spontaneous protonation would allow us to construct the final product ***syn*,*anti*-11** when a protic solvent was used. On the other hand, under the condition where no proton source was found in a reaction mixture, the alkoxide in **Int-2** would intramolecularly attack the oxazolidinone carbonyl carbon atom to produce ***syn*,*anti*-12** by way of **Int-3**. The driving force of this isomerization would be the same as in the case of Payne rearrangemnet, furnishing the thermodynamically more stable anionic species. The two neighboring substituents with an energetically less favorable *cis* relationship in the oxazolidinone ring would cause the low yield of the product ***syn*,*anti*-12**. On the contrary, because ***Z*-*anti*-10** under the latter aprotic system led to the *trans* five-membered ring structure without suffering from steric hindrance, its chemical yield would be increased to as high as 95%. Actually, treatment of the isolated ***syn*,*anti*-11a** with *t*-BuOK in THF at 0 °C for 1 h allowed us to obtain the totally deprotected ***syn*,*anti*-13a** in 70% yield without observation of ***syn*,*anti*-12b** with the *cis*-configured oxazolidinone ring (Scheme 5). On the other

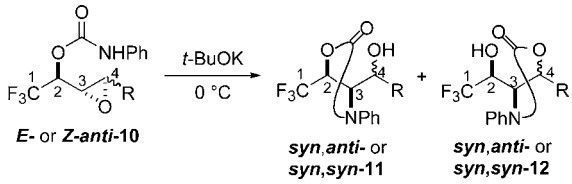
Scheme 5



(9) An excess amount of NaOH converted the aminodiol into the corresponding dianionic species whose less stable OH group remote from the CF_3 moiety should be trapped more readily and quickly. The acetylated OH group was identified by the lower field shift (ca. 1 ppm) of the proton at the same carbon by ^1H NMR. The coupling pattern of the shifted proton (dd, not d) led to an unambiguous conclusion that the product was ***anti*,*anti*-4a**. For the detailed experimental procedure and spectroscopic data, see the Supporting Information.

hand, the diastereomeric ***syn*,*syn*-11b** experienced a facile conversion to ***syn*,*syn*-12b** in quantitative yield. These two independent reactions well supported the above hypothesis.

Table 3. Epoxy Ring-Opening of ***E***- and ***Z*-*anti*-10**



entry	substrate	*E*:*Z*	conditions[a]	**11**[b] (%)	*syn*:*anti*[b,c]
1	***E*-*anti*-10a**	>99:<1	A	trace	
2	***E*-*anti*-10b**	91:9	A	[31]	[70:30]
3	***E*-*anti*-10c**	88:12	A	[50]	[73:27]
4	***Z*-*anti*-10a**	<1:>99	A	[91]	[<1:>99]
5	***Z*-*anti*-10b**	<1:>99	A	[95]	[<1:>99]
6	***Z*-*anti*-10c**	<1:>99	A	[94]	[<1:>99]
7	***E*-*anti*-10a**	>99:<1	B	62	<1:>99
8	***E*-*anti*-10b**	91:9	B	87	5:95
9	***E*-*anti*-10c**	88:12	B	83	8:92
10	***Z*-*anti*-10a**	<1:>99	B	59	>99:<1
11	***Z*-*anti*-10b**	<1:>99	B	72	>99:<1
12	***Z*-*anti*-10c**	<1:>99	B	68	>99:<1

[a] See the text. [b] In the brackets are shown the data for compounds **12**. [c] Relative stereochemical relationship between C^3-C^4.

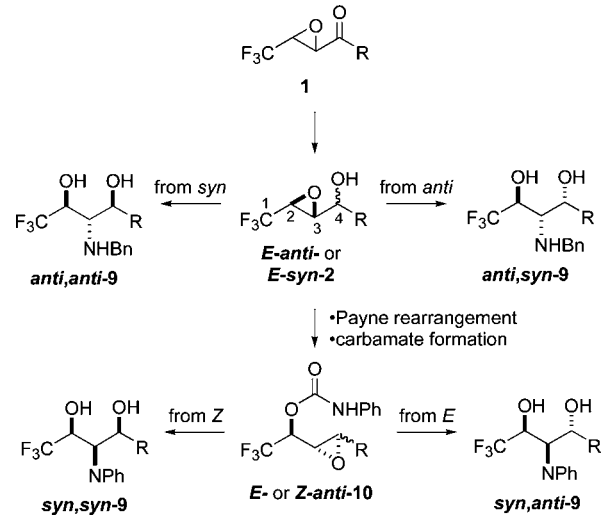
Table 3 summarizes the data for the carbamate-mediated epoxy ring-opening under two reaction conditions, in THF for 1 h (condition A) or in MeOH for 3 h (condition B). As explained above, although ***E*-*anti*-10** under the condition A led to sluggish results, the corresponding *Z*-isomers cleanly afforded ***syn*,*syn*-12** as the sole products by virtue of their stereospecific reaction course and usage of the pure ***Z*-*anti*-10**. In the case of the condition B, both substrates smoothly constructed the *trans*-oxazolidinone rings in good to excellent yields with excellent stereoselectivity. Deprotection of these products was smoothly performed by NaOH in EtOH, and 99% isolated yield was attained for ***syn*,*syn*-13a** with total retention of the stereochemical integrity when ***syn*,*syn*-11a** was used as the substrate.

(10) Kamlet, M. J.; Abboud, J.-L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877–2887. Because the β value for the hydrogen-bonding accepting ability of *n*-propanol was missing, the values of ethanol and *n*-butanol were referred to for the discussion.

(11) Yamazaki, T.; Iwatsubo, H.; Kitazume, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1823–1830.

(12) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736–738.

In summary, we have successfully demonstrated new pathways to access all stereoisomeric 2-amino-1,3-diol structures **9** with a CF_3 group starting from single materials, 3-CF_3-2,3-epoxyketones **1**, by appropriate utilization of the characteristic nature of epoxyalcohols **2** accepting nucleophilic attack in a regiospecific manner only at the 3 position with complete inversion of stereochemistry. Moreover, following an electronically driven Payne rearrangement we have already reported previously,[4] conversion of **3** to the corresponding carbamates **10** allowed selective cyclization to the oxazolidinone ring, which unambiguously determined the stereochemistry of the products **11** and **12** whose ring structure was found to be easily opened by treatment of an ethanolic alkaline-solution in excellent yields. As summarized below, a combination of these methods enabled us to readily synthesize 2-amino-1,3-diols in a stereodivergent fashion within 5 facile steps, and further application of this strategy is underway in this laboratory.



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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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