Regioselective Epoxide Opening

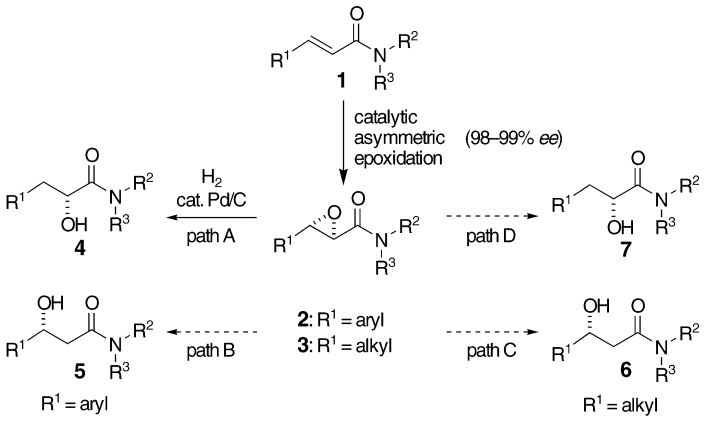
Efficient Synthesis of Chiral α- and β-Hydroxy Amides: Application to the Synthesis of (*R*)-Fluoxetine**

*Hiroyuki Kakei, Tetsuhiro Nemoto, Takashi Ohshima, and Masakatsu Shibasaki**

Chiral α- and β-hydroxy amides are useful building blocks for the synthesis of biologically active compounds.[1] The synthesis of these intermediates in both a regio- and stereoselective manner, however, is difficult. There are only a few methods for the synthesis of such chiral units, and their substrate scope and selectivity remain unsatisfactory.[2] The regioselective epoxide-opening reaction of optically active α,β-epoxy amides is one of the most attractive approaches to this problem. We[3] and Aggarwal's group[4] recently succeeded in developing efficient strategies to obtain α,β-epoxy amides in a highly enantioselective manner. There are no reports, however, on regioselective epoxide-opening reactions of α,β-epoxy amides,[3,5] in contrast to the success with α,β-epoxy ketones.[6] We report herein a new synthesis of nearly enantiomerically pure α- and β-hydroxy amides with high substrate generality, which consists of a novel highly regioselective epoxide opening of both β-alkyl- and β-aryl-substituted α,β-epoxy amides (Scheme 1). An efficient enantioselective synthesis of (*R*)-fluoxetine, using the newly developed method, is also described.

To realize the highly regioselective epoxide-opening reactions of α,β-epoxy amides, it is important to control the relative reactivity of the α- and β-positions, which depends on the β-substituent. Thus, we discuss the reactions of the β-aryl-substituted amide (paths A and B) and of the β-alkyl-substituted amide (paths C and D).

We recently described the highly enantio- and regioselective synthesis of β-aryl α-hydroxy amides using a one-pot, tandem process consisting of catalytic asymmetric epoxidation and a Pd-catalyzed epoxide opening (path A). The selectivity was based on the higher reactivity of the β-position (benzyl position) over that of the α-position.[3] The higher reactivity of the β-position, however, make it difficult to obtain β-hydroxy amides through cleavage of the C_α–O bond (path B). Indeed, the general conditions for selective cleavage of the C_α–O bond in α,β-epoxy ketones, such as SmI_2 and $[Cp_2TiCl_2]/Zn$,[6,7] gave unsatisfactory results (trace amounts) with α,β-unsaturated and -saturated amides as the major



Scheme 1. Strategy to obtain α- and β-hydroxy amides from α,β-epoxy amides by regioselective epoxide opening.

products. To overcome this difficulty, we examined a so-called intramolecular hydride transfer using Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride),[1c,8] which might react with N–H first to produce a N–Al species; the remaining hydride attacks the α-position of the epoxy amide (see Figure 1). As we expected, the reduction of **2a** with Red-Al gave β-hydroxy amide **5a**[7] as the major product in moderate yield (Table 1, entry 1). This result prompted us to optimize the reaction conditions.

To gain insight into the reaction mechanism, especially for the counterion effects, calculations were performed by means of the hybrid density functional method (B3LYP[9]) using a 6-31G(d) basis set. As shown in Figure 1, the coordination of a sodium ion to the epoxide and carbonyl oxygen atoms should weaken the C_β–O bond ($\Delta_\beta = 0.0315$ Å) more effectively than the C_α–O bond ($\Delta_\alpha = 0.0092$ Å).[10] In an attempt to overcome this drawback, we added [15]crown-5 to trap sodium ions. Both regioselectivity and reactivity improved (entries 2–4, and 6). The best selectivity was obtained with a 1:1 ratio of Red-Al and [15]crown-5 (entry 4). The use of [18]crown-6 gave a comparable result (entry 5). Solvents and temperatures were also investigated; the use of dimethoxyethane (DME) and a lower reaction temperature gave much better results (entries 7 and 8).[11] This mixture of reagents, Red-Al and crown ether, was applicable to the selective conversion of various β-aryl α,β-epoxy amides **2b–d** into β-aryl β-hydroxy amides **5b–d** (entries 12–14).[7]

The Red-Al/crown ether strategy was applicable to the regioselective epoxide-opening reaction of β-*alkyl*-substituted amides (Scheme 1, path C). In contrast to β-*aryl*-substituted amides, these substrates have higher reactivity at the α-position than at the β-position, and β-hydroxy amides were obtained with much higher regioselectivity (Table 2, entry 1). Thus, satisfactory selectivity was achieved even when simple reaction reagents, such as DIBAL (diisobutylaluminum hydride, entry 2), were employed. The scope and limitations of this reaction were also examined with various substrates prepared from primary amines **3b**,**c**,**f**,**g** (entries 3, 4, 7, and 8) and α-branched primary amines **3d**,**e** (entries 5 and 6). When two equivalents of DIBAL were used, β-alkyl α,β-epoxy amides were successfully converted into the corre-

[*] H. Kakei, T. Nemoto, Dr. T. Ohshima, Prof. Dr. M. Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113–0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: mshibasa@mol.f.u-tokyo.ac.jp

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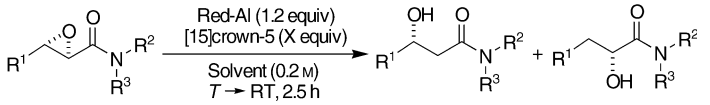
Table 1: Selective epoxide-opening reaction of β-aryl α,β-epoxy amides (Scheme 1, path B).



2a–d: R^1 = aryl **5a–d** **4a–d**

Entry		Substrate[a] R^1	R^2NR^3	[15]crown-5 [equiv]	Solvent	T [°C]	Yield [%][b]	5:4[c]
1	**2a**	Ph	MeNH	0	DME	4	72	2:1
2	**2a**	Ph	MeNH	0.5	DME	4	78	4:1
3	**2a**	Ph	MeNH	1.0	DME	4	91	7:1
4	**2a**	Ph	MeNH	1.2	DME	4	89	8:1
5	**2a**	Ph	MeNH	1.2[d]	DME	4	86	8:1
6	**2a**	Ph	MeNH	2.0	DME	4	84	8:1
7	**2a**	Ph	MeNH	1.2	DME	−20	87	16:1
8	**2a**	Ph	MeNH	1.2	DME	−40	87	18:1
9	**2a**	Ph	MeNH	1.2	THF	4	80	6:1
10	**2a**	Ph	MeNH	1.2	toluene	4	73	3:1
11	**2a**	Ph	MeNH	1.2	CH_2Cl_2	4	88	3:1
12	**2b**	4-Me-C_6H_4	MeNH	1.2	DME	−20	85	10:1
13	**2c**	4-F-C_6H_4	MeNH	1.2	DME	−20	90	14:1
14[e]	**2d**	Ph	BnNH	1.2	DME	−20	87	5:1

[a] Substrate purity in all cases 99% *ee*. [b] Yield of **4** and **5**. [c] The ratio was determined by ^{1}H NMR analysis of the crude sample. [d] [18]Crown-6 was used instead of [15]crown-5. [e] Reaction time was 5.0 h.

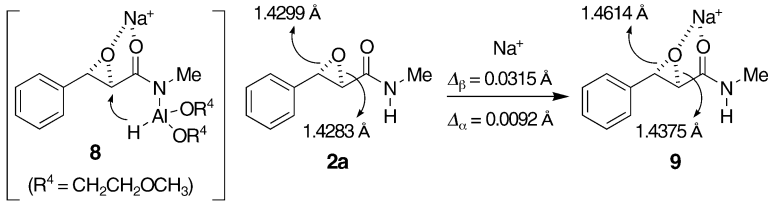
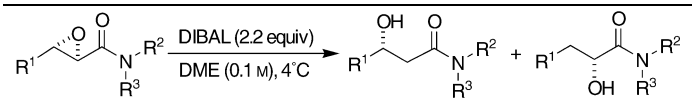


Figure 1. The effects of a sodium ion on the C–O bonds of α,β-epoxy amides **2a** during reduction with Red-Al.

Table 2: Selective epoxide-opening reaction of β-alkyl α,β-epoxy amides (Scheme 1, path C).



3a–g: R^1 = alkyl **6a–g** **7a–g**

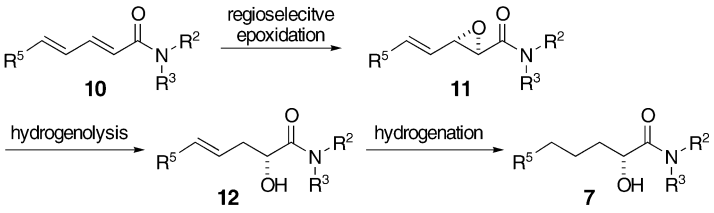
Entry		Substrate[a] R^1	R^2NR^3	t [h]	Yield [%][b]	6:7[c]
1[d]	**3a**	$Ph(CH_2)_2$	MeNH	2.5	95	40:1
2	**3a**	$Ph(CH_2)_2$	MeNH	1.0	94	22:1
3	**3b**	$Ph(CH_2)_2$	BnNH	1.5	88	21:1
4	**3c**	$Ph(CH_2)_2$	AllylNH	1.5	89	20:1
5	**3d**	$Ph(CH_2)_2$	*c*HexNH[e]	1.5	89	28:1
6	**3e**	$Ph(CH_2)_2$	*t*BuNH	1.5	92	>50:1
7	**3f**	$Ph(CH_2)_4$	MeNH	1.5	93	12:1
8	**3g**	*c*Hex[e]	BnNH	1.5	89	11:1

[a] Substrate purity in all cases 99% *ee* except for substrate **3c** (98% *ee*). [b] Yield of **6** and **7**. [c] The ratio was determined by ^{1}H NMR analysis of the crude sample. [d] Red-Al/crown ether conditions shown in Table 1 (entry 6) were used. [e] *c*Hex = cyclohexyl.

sponding β-hydroxy amides **6a–g** in excellent yields and selectivities.[7]

The transformation of β-*alkyl*-substituted α,β-epoxy amides into α-hydroxy amides (Scheme 1, path D) is extremely challenging because the β-position is much less reactive than the α-position. After intensive examination, we obtained α-hydroxy amide **7a** with moderate selectivity (2.7:1) by using $LiAlH_4$.[11] To obtain α-hydroxy amides efficiently, we used a new synthetic strategy with α,β,γ,δ-unsaturated amides, as shown in Scheme 2. In this process, the α,β-selective epoxidation of α,β,γ,δ-unsaturated amides through the intramolecular transfer of peroxide from La to the β-position and hydrogenolysis of the corresponding γ,δ-unsaturated α,β-epoxy amides were key steps.

We first investigated the catalytic asymmetric epoxidation of α,β,γ,δ-unsaturated amides **10a** using Sm–(*S*)-binol–Ph_3As=O (1:1:1) complex **13** (binol = 2,2′-dihydroxy-1,1′-binaphthyl), which is a useful catalyst for the asymmetric epoxidation of α,β-unsaturated amides.[3] The reaction proceeded to afford **11a** with complete α,β-selectivity; however, the reactivity was not satisfactory (Table 3, entry 1). Thus, we further tested a number of other lanthanum complexes.[11] Finally, the Gd–(*S*)-binol–Ph_3As=O complex **14** was determined to be the best in this system (entry 2), and activation of 4-Å molecular sieves was necessary to improve the reactivity (entry 3). This catalytic system was applicable to various α,β-selective epoxidations of α,β,γ,δ-unsaturated amides **10a–f**

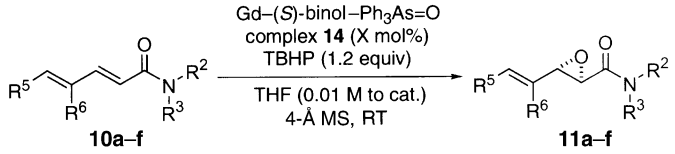


Scheme 2. Strategy to obtain β-alkyl,α-hydroxy amides (Scheme 1, path D)

(entries 5–9). When 10 to 20 mol% of Gd–(*S*)-binol–Ph_3As=O complex **14** was used, amides prepared from primary amines (**10a,b,e,f**), a secondary amine (**10c**), and an α-branched primary amine (**10d**) were epoxidized to afford γ,δ-unsaturated α,β-epoxy amides in good yield and excellent selectivity.[12]

Moreover, these γ,δ-unsaturated α,β-epoxy amides **11a–f** were easily converted into γ,δ-unsaturated α-hydroxy amides **12a–f** via a π-allyl palladium intermediate (Table 4).[13]

Table 3: Catalytic asymmetric epoxidation of α,β,γ,δ-unsaturated amides.

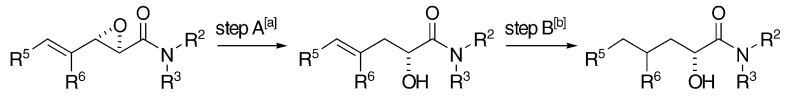


10a–f **11a–f**

Entry		Substrate			Cond.[a]	**14** [mol%]	*t* [h]	Yield [%]	*ee* [%]
		R^5	R^6	R^2NR^3					
1[b]	**10a**	Ph	H	MeNH	A	10	48	48	97
2	**10a**	Ph	H	MeNH	A	10	48	61	99
3	**10a**	Ph	H	MeNH	B	10	48	78	99
4	**10a**	Ph	H	MeNH	B	15	48	85	96
5	**10b**	Ph	H	BnNH	B	10	21	89	99
6	**10c**	Ph	H	MeNMe	B	10	12	90	99
7	**10d**	Ph	H	*c*HexNH	B	15	48	94	99
8	**10e**	Me	H	BnNH	B	20	48	85	99
9	**10f**	-$(CH_2)_4$-		BnNH	B	20	48	76	99

[a] Conditions A: TBHP in decane, 4-Å molecular sieves not dried. Conditions B: TBHP in toluene, 4-Å molecular sieves dried for 3 h at 180°C under reduced pressure. [b] Sm was used as a central metal.

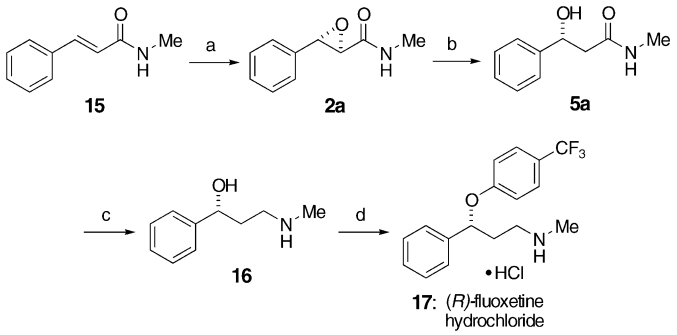
Table 4: Conversion to β-alkyl α-hydroxy amides (Scheme 1, path D).



11a–f **12a–f** **7a–f**

Entry		Substrate			*t* [h]		Yield [%]	
		R^5	R^6	R^2NR^3	step A	step B	step A	step B
1	**11a**	Ph	H	MeNH	1	1	91	95
2	**11b**	Ph	H	BnNH	1	1	90	95
3	**11c**	Ph	H	MeNMe	1	1	87	94
4	**11d**	Ph	H	*c*HexNH	1	1	94	92
5	**11e**	Me	H	BnNH	2	1	94[c]	94
6	**11f**	-$(CH_2)_4$-		BnNH	12	12	94	86

[a] Conditions: $[Pd_2(dba)_3]\cdot CHCl_3$ (2.6 mol%), Bu_3P (2.6 mol%), Et_3N (2 equiv), HCO_2H (5 equiv), THF, RT. [b] Conditions: Pd/C (5 mol%), H_2 (1 atm), THF/MeOH (2:1), RT. [c] A mixture of three olefin isomers was obtained.



Scheme 3. Asymmetric synthesis of (*R*)-fluoxetine hydrochloride (**17**). a) Sm–(S)-binol–Ph_3As=O (**13**) (10 mol%), TBHP (1.2 equiv), THF, 4-Å molecular sieves, RT, 91%, 99% ee; b) Red-Al (1.2 equiv), [15]crown-5 (1.2 equiv), DME (0.2 M), −40°C to RT, 80% (yield of β-OH product isolated), β-OH/α-OH >20:1; c) $LiAlH_4$, THF, reflux, quantitative; d) NaH, DMSO, 4-chlorobenzotrifluoride; HCl, 92% (lit.[14e]). DMSO = dimethyl sulfoxide, RT = room temperature, TBHP = *tert*-butyl hydroperoxide.

Finally, reduction of the C–C double bonds proceeded smoothly with Pd/C and H_2, producing β-*alkyl* α-hydroxy amides **7a–f** efficiently.[7]

To demonstrate the usefulness of our methodology, an asymmetric synthesis of (*R*)-fluoxetine (**17**) was executed on a multigram scale (Scheme 3). Fluoxetine (Prozac, Eli Lilly Co.), marketed as a racemate, is an antidepressant drug and many groups have intensively studied an efficient synthesis of the enantiomerically pure form.[14,15] Catalytic asymmetric epoxidation of **15** (5-g scale) gave enantiomerically pure α,β-epoxy amides **2a** in 91% yield and 99% *ee*. The Red-Al/crown ether strategy was used to convert this epoxide into β-hydroxy amide **5a**.[16] The resulting amide was reduced to the known key intermediate **16** with $LiAlH_4$, and **16** was coupled with 4-chlorobenzotrifluoride to give **17** as the hydrochloride salt.[15d,e]

In summary, regioselective epoxide-opening processes for α,β-epoxy amides to give both α- and β-hydroxy amides have been developed. Moreover, this reaction was successfully applied to an asymmetric synthesis of (*R*)-fluoxetine, demonstrating the power of the newly developed reaction. We are currently investigating more detailed mechanisms of the epoxide-opening reaction and more difficult tasks such as the regioselective epoxide opening of α,β-epoxy amides by carbon nucleophiles and other nucleophiles.

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Keywords: asymmetric synthesis · epoxides · regioselectivity · synthetic methods

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