Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: *Asymmetry* 18 (2007) 949–962
Tetrahedron: *Asymmetry*

Asymmetric zinc-Reformatsky reaction of Evans chiral imide with acetophenones and its application to the stereoselective synthesis of triazole antifungal agents

Luo-Ting Yu,[a,b,c] Meng-Tsung Ho,[d] Ching-Yao Chang[e] and Teng-Kuei Yang[c,d,*]

[a]*Laboratory of Organo-metallic Chemistry, East China University of Science and Technology, Shanghai 200237, China*
[b]*Department of Pharmaceutical and Biochemical Engineering, Sichuan University, Sichuan 610065, China*
[c]*Wisdom Pharmaceutical Co. Ltd, Haimen, Jiangsu 226100, China*
[d]*Department of Chemistry, National Chung-Hsing University, Taichung 402, Taiwan, ROC*
[e]*Department of Biotechnology and Bioinformatics, Asia University, Wufeng, Taichung 413, Taiwan, ROC*

Received 10 February 2007; accepted 12 March 2007

Abstract—The $Ni(acac)_2$ catalytic $ZnEt_2$-mediated asymmetric Reformatsky-type reaction of Evans chiral imide with various acetophenones was studied. The chiral imido zinc enolate, which was formed through the metal–halogen exchange reaction of chiral α-bromopropionyl-2-oxazolidinones **2** with diethyl zinc under the catalysis of $Ni(acac)_2$, performed the asymmetric zinc-Reformatsky reaction with activated α-haloacetophenones **3** to give the chiral β-hydroxyamide **4** in good yields and high ratios of *syn*-(2*R*,3*R*)-isomers (up to >97%). This new asymmetric synthesis technology affords a practical method to synthesize the versatile chiral building block **5** for triazole antifungal agents, such as Voriconazole, Ravuconazole, TAK-187, and RO-0094815.

1. Introduction

Reformatsky reaction was first discovered in the late 19th century and involves a reaction between an aldehyde (or ketone) and an α-haloester in the presence of metallic zinc.[1] This long historical reaction has the advantage of forming a carbon–carbon bond under mild and neutral conditions. For the asymmetric-type reaction of a prochiral ketone and a chiral metallic enolate, a Reformatsky reaction mediated by a chiral halo-organozinc reagent could afford a chiral β-hydroxyester with better results, compared to the corresponding aldol reaction, which generally requires ultra low temperature and strongly basic conditions.[2] However, a common problem for the traditional Reformatsky reaction is the lack of reactivity for the insertion of zinc into the halogen–carbon bond, so it is necessary to activate the zinc reagent and one often needs to raise reaction temperatures, which generally results in a poor stereoselectivity. A series of metals were used to perform the Reformatsky reaction, but are rarely used in the asymmetric-type reaction.[3] In 1998, Saigo reported using $Ge^{(0)}$ to prepare a chiral imido auxiliary Ge enolate and performed the asymmetric Ge-Reformatsky reaction with aldehydes to give the chiral β-hydroxyesters in good diastereoselectivities.[4] In 2000, Fukuzawa employed chiral 2-oxazolidinones and 'SuperQuat' oxazolidinones as chiral auxiliaries to proceed in the asymmetric Sm-Reformatsky reaction with aldehydes in which high diastereoselectivities were obtained.[5] However, these metals are too expensive to use for practical purpose and these literatures report only using aldehydes as the electrophiles. For ketones as the substrate, the asymmetric Reformatsky reaction generally leads to lower diastereoselectivity, because it is more difficult to distinguish between two substitutive carbon-atoms of a ketone than between one substitutive carbon-atom and one hydrogen-atom of an aldehyde. For the purpose of directly and conveniently preparing β-hydroxyesters with a quaternary β-carbon, the asymmetric Reformatsky reaction of ketones has been a challenging issue. In 2002, Yamano reported an asymmetric Reformatsky reaction of ketones with excellent stereoselectivities by using a cinchona alkaloid as the chiral ligand, but the carbonyl substrate is

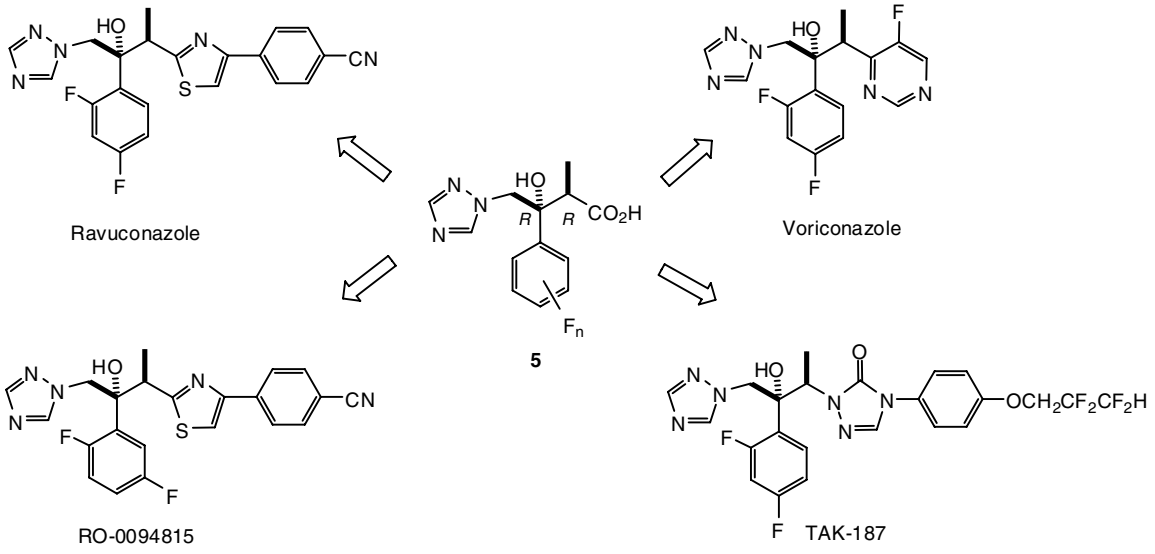
* Corresponding author. Tel.: +86 513 82263281; fax: +86 513 8227902; e-mail addresses: tk@wisdompharma.com; tkyang@mail.nchu.edu.tw

0957-4166/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2007.03.015

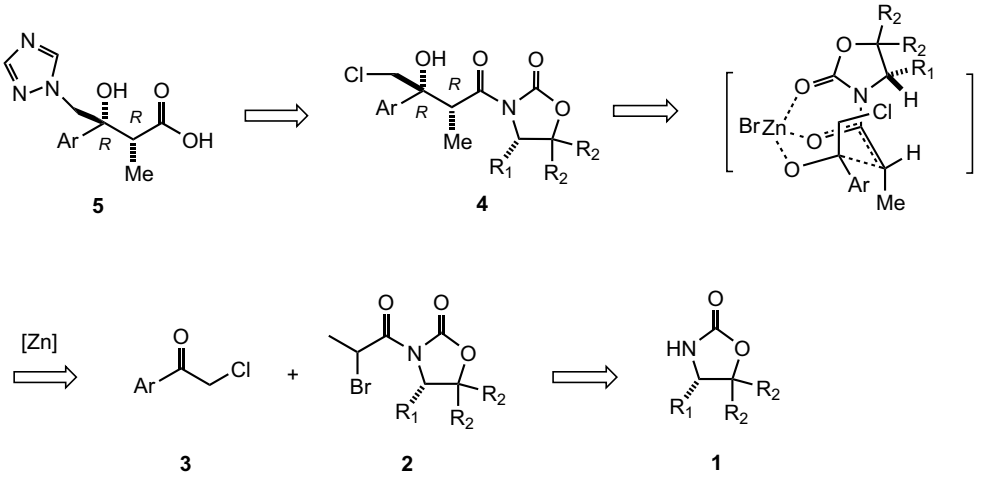
limited to the ketones possessing an adjacent sp^2-nitrogen.[6] On the other hand, Cozzi in 2006 also reported a catalytical asymmetric Reformatsky reaction of ketones with iodo esters by using [ClMn(salen)] as the chiral catalyst to obtain moderate enantioselectivities.[7] Herein, we employ Evans chiral imido zinc enolates and a series of acetophenones to perform the asymmetric Reformatsky reaction. Target compound **5** is a key intermediate in the syntheses of a series of optically active triazole antifungal agents, such as Voriconazole, Ravuconazole, TAK-187, and RO-0094815 (Scheme 1).[8]

In these syntheses, Evans chiral auxiliaries (2-oxazolidinones) **1** served as a useful tool for constructing the vicinal *syn*-stereogenic centers, as required in compound **5** and all of the chiral triazole antifungal drugs. The retrosynthetic analysis in Scheme 2 indicated an asymmetric Reformatsky reaction between acetophenones and a α-halo-organozinc reagent coupled with 2-oxazolidinones, which would give chiral β-hydroxyamide **4** diastereoselectively.

Our investigation covered a detailed study on the asymmetric Reformatsky reaction of various zinc enolates with



Scheme 1.



1a R_1 = Bn ; R_2 = H
1b R_1 = *i*-Pr; R_2 =Ph

2a R_1 = Bn ; R_2 = H
2b R_1 = *i*-Pr; R_2 =Ph

3a Ar = 2,4-difluorophenyl
3b Ar = 2,5-difluorophenyl

4a R_1 = Bn, R_2 = H, Ar = 2,4-difluorophenyl
4b R_1 = Bn, R_2 = H, Ar = 2,5-difluorophenyl
4c R_1 = *i*-Pr, R_2 = Ph, Ar = 2,4-difluorophenyl
4d R_1 = *i*-Pr, R_2 = Ph, Ar = 2,5-difluorophenyl
4e R_1 = *i*-Pr, R_2 = Ph, Ar = Ph

5a Ar = 2,4-difluorophenyl
5b Ar = 2,5-difluorophenyl

Scheme 2.

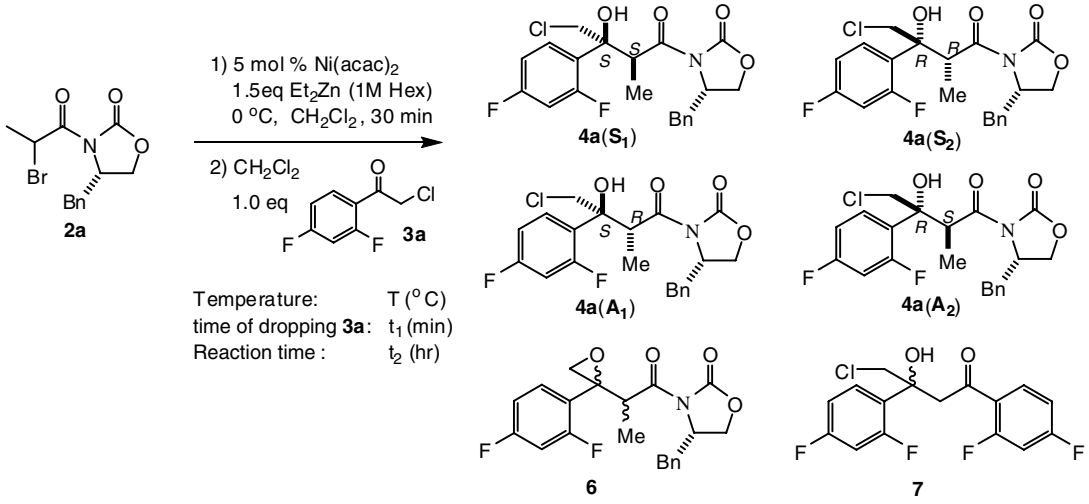
Evans chiral imido auxiliaries and a series of acetophenones, such as α-chloro-2,4-difluoroacetophenone, α-chloro-2,5-difluoroacetophenone, α-chloroacetophenone, acetophenone, 4-methoxyacetophenone, and 4-nitroacetophenone. We found that the chiral α-bromopropionyl-2-oxazolidinones **2** with diethyl zinc under catalysis of $Ni(acac)_2$ performed the asymmetric zinc-Reformatsky reaction with α-chloroacetophenones **3** to give chiral β-hydroxyamides **4** in good yields and high ratios of *syn*-(2*R*,3*R*)-isomers (up to >97%). After the dissociation of the chiral β-hydroxyamides **4** followed by triazole substitution, compounds **5** were obtained in good yields, which provided a practical route to the new triazole antifungal agents, and chiral imido auxiliaries **1** were recycled in high yields.

2. Results and discussion

The traditional zinc dust used in a Reformatsky reaction generally needs to be activated under a higher temperature, which would result in lower stereoselectivity in an asymmetric-type reaction. The idea of a 'catalytic' Reformatsky reaction has been reported on some metals, such as magnesium,[9] cerium,[10] titanium,[11] and nickel,[12] which were employed to facilitate the insertion of zinc into the halogen–carbon bond. Recently, we noticed that Adrian used a catalytic amount of $Ni(acac)_2$ to make diethyl zinc generate a zinc enolate through a metal–halogen exchange process with a good reactivity at room temperature.[13] In the hope of obtaining a good stereoselectivity under a lower reaction temperature, we employed diethyl zinc and a catalytic amount of $Ni(acac)_2$ to generate zinc enolates with 2-oxazolidinone type chiral auxiliaries to perform the asymmetric Reformatsky reaction with acetophenones. We found that the use of Evans chiral auxiliaries in such asymmetric Reformatsky reaction would induce a vicinal *syn* stereogenic center in the resulting β-hydroxyamides. Table 1 shows a typical $Ni(acac)_2$ catalytic, $ZnEt_2$-mediated asymmetric Reformatsky reaction of chiral α-bromoamide **2a** with α-chloro-2,4-difluoroacetophenone **3a** under a wide range of reaction conditions. HPLC analysis of the unpurified reaction mixtures indicates that the *syn*-isomer, $\mathbf{S_2}$, is clearly the major product among the four possible isomers.

The results in Table 1 indicate that side product **7**, generated from the self-addition of **3a**, could be reduced from 25.7% to 6.1%, by decreasing the reaction temperature from 30 to −30 °C (entry 1 vs entry 7). We also found quite good *Si* diastereofacial bias ($\mathbf{S_2}$:$\mathbf{S_1}$ = 41.2:1) and moderate *anti*:*syn* selectivity (3.2:1) under the reaction condition shown in entry 7.

Table 1.



Entry	T (°C)	t_1 (min)	t_2 (h)	Product ratio (HPLC)[a]					$\mathbf{S_2}$:$\mathbf{S_1}$	*syn*:*anti*	Isolated[b] yield (%)
				4a($\mathbf{S_1}$)	**4a**($\mathbf{S_2}$)	**4a**($\mathbf{A_1}$)	**4a**($\mathbf{A_2}$)	**7**			
1	30	60	3	11.8	18.1	39.6	4.8	25.7	1.5:1	0.7:1	10.1
2	0	1	3	2.8	36.5	34.5	4.9	21.3	13.0:1	1.0:1	31.3
3	0	60	3	1.9	51.3	25.5	4.5	16.8	27.0:1	1.8:1	46.5
4	−15	1	3	1.9	55.2	18.3	5.2	19.4	29.1:1	2.4:1	48.7
5	−15	60	3	1.8	65.1	19.5	4.8	8.8	36.2:1	2.8:1	54.5
6	−30	1	4	1.9	63.0	15.6	4.7	14.8	33.2:1	3.2:1	55.2
7	−30	60	4	1.7	70.0	17.6	4.6	6.1	41.2:1	3.2:1	63.6
8	−30	60	0.5	1.8	68.8	16.1	5.5	7.8	38.2:1	3.3:1	48.9
9	−40	60	12	1.5	65.2	16.1	4.4	12.8	43.5:1	3.3:1	60.3
10	−60	60	12	1.5	66.1	15.9	4.3	12.2	44.1:1	3.3:1	30.8

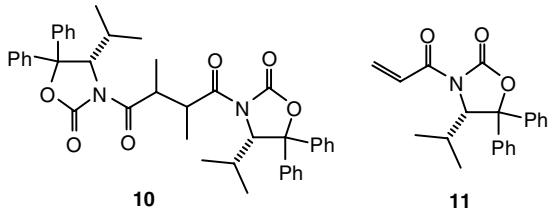
[a] All the products were not purified and the ratios were taken directly from the UV response of the HPLC under the conditions: [column: Lichrospher 100RP18; mobile phase: CH_3CN/H_2O = 64:36; UV: 220 nm; retention time (min): **4a**($\mathbf{A_1}$) (7.6); **4a**($\mathbf{A_2}$) (8.0); **4a**($\mathbf{S_2}$) (11.3); **4a**($\mathbf{S_1}$) (12.5); **7** (10.1)].

[b] The yields of pure compound **4a**($\mathbf{S_2}$) were obtained through flash chromatography.

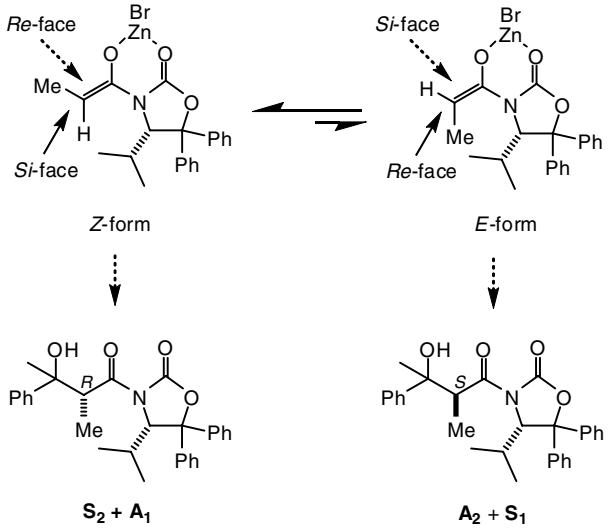
In Table 1, we used dichloromethane as the reaction solvent because it was reported that dichloromethane could provide good reactivity in the exchange between zinc and nickel complex.[13,14] However, the nature of the solvent would exert a great influence on the transition state (TS) of the asymmetric Reformatsky reaction, which has a tight relationship with the stereoselectivity. Therefore, we checked the solvent effect with two types of $ZnEt_2$ solutions. In order to diminish the reaction complexity, we chose acetophenone **8** as a substrate to perform the asymmetric Reformatsky reaction, with the results shown in Table 2.

The results in Table 2 display a quite significant solvent effect, in which we can find that polar solvents give better stereoselectivities (entries 1 and 2). Conversely, those solvents, such as THF and CH_3CN, which can act as good ligands to the metal, might interfere with the coordination structure of the transition state of the asymmetric Reformatsky reaction, thus leading to poor stereoselectivities (entries 6 and 7). Furthermore, the major product was the self-addition product **10** in THF or the dehydrohalogenation product **11** in CH_3CN, respectively (Scheme 3). On the other hand, non-polar solvents, such as benzene and toluene, give moderate stereoselectivities (entries 3–5). Nevertheless, all reactions give very good yields if the non-coordinating solvents are used.

From a mechanistic view, we propose that the zinc enolate has both an *E*-form and a *Z*-form configuration in which the *Z*-form enolate is more preferred and produces the (*R*)-configuration at the β-carbon of the adduct (Scheme 4). As the

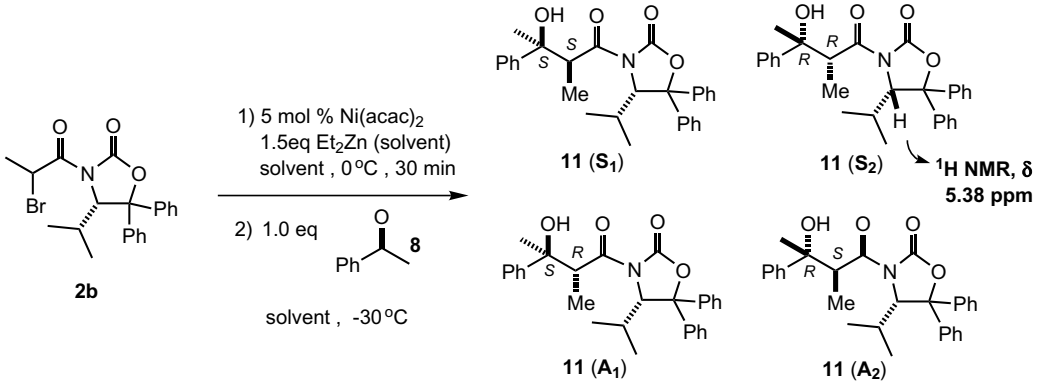


Scheme 3.



Scheme 4.

Table 2.



Entry	Et_2Zn solvent	Reaction solvent	^1H NMR[a]							Isolated[b] yield (%)
			9(S_1)	**9**(S_2)	**9**(A_1)	**9**(A_2)	S_2:S_1	*syn*:*anti*	(S_2+A_1):(S_1+A_2)	
1	*n*-Hexane	CH_2Cl_2	2.0	95.5	2.3	0.2	47.8:1	39.0:1	40.7:1	83.7
2	Toluene	CH_2Cl_2	2.1	95.3	2.3	0.3	45.4:1	37.5:1	40.7:1	83.1
3	*n*-Hexane	Benzene	4.2	85.2	9.5	1.1	20.3:1	8.4:1	17.9:1	78.4
4	Toluene	Toluene	3.3	89.1	7.1	0.5	27.0:1	12.2:1	25.3:1	84.3
5	*n*-Hexane	Toluene	3.0	90.5	6.2	0.3	30.2:1	14.4:1	29.3:1	82.7
6	*n*-Hexane	THF	11.3	45.6	37.3	5.8	4.0:1	1.3:1	4.8:1	25.5[c]
7	*n*-Hexane	CH_3CN	—	—	—	—	—	—	—	[d]

[a] The ratios were taken directly from the characteristic ^1H NMR peaks of the four diastereomers for [δ (ppm): **9**(S_1) (5.35); **9**(S_2) (5.38); **9**(A_1) (5.50); **9**(A_2) (5.15)].

[b] The yields of the mixture, which consisted of all the four diastereomers were obtained through simple purification by flash chromatography.

[c] The main product was compound **10** (see Scheme 3).

[d] The main product was compound **11**.

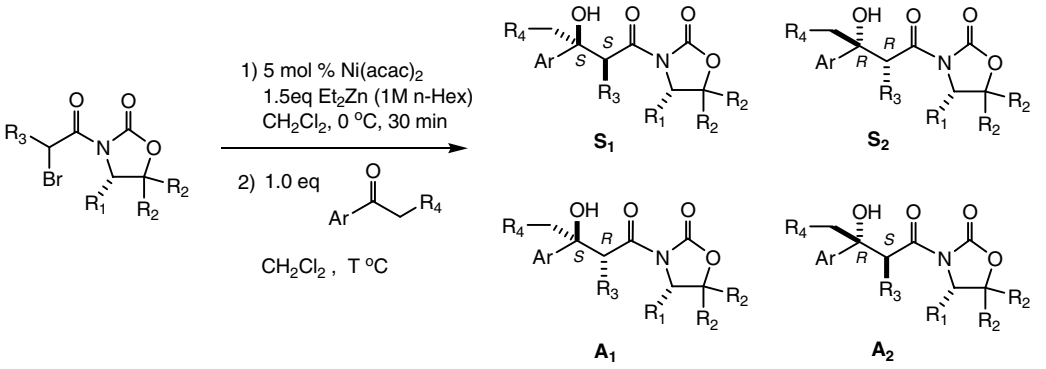
isopropyl group of the chiral auxiliary moiety blocks the *Re*-face of the zinc enolate, the carbonyl molecule preferably approaches the *Si*-face of the zinc enolate, which gives the diastereoselectivities appeared as $(\mathbf{S_2}+\mathbf{A_1}):(\mathbf{S_1}+\mathbf{A_2}) = 40.7{:}1$ in the best cases (entries 1 and 2).

After the study of Table 2, we decided to broaden our investigations on the asymmetric Reformatsky reaction with various Evans chiral auxiliaries and acetophenones at different temperatures, as shown in Table 3.

Our observations indicate that the reaction temperature is an important factor in the stereoselectivity and chemical yield of the asymmetric Reformatsky reaction. In general, lowering the reaction temperature would make the coordination structure of the transition state more stable, which benefits the favorable space tropism in the asymmetric reaction. However, too low a temperature (−60 °C) would not only greatly reduce the reactivity but also make the reaction sluggish enough to lower the reaction yield. The optimal reaction temperature was −30 °C in our study, which gave the best diastereoselectivities with the highest isolated yields.

On the other hand, we also studied the effect of various Evans chiral auxiliaries and acetophenones on the asymmetric Reformatsky reaction. As described in Table 3 (entries 12 and 16), a sterically more crowded chiral auxiliary **1b** ($R_1 = i$-Pr, $R_2 =$ Ph) displays a better diastereoselectivity with the best ratio of $\mathbf{S_2}$ up to 97.2%. The variation of acetophenones was also investigated. From the results given in Table 3, we observed that the electron withdrawing substitution of acetophenones would increase the reactivity of the carbonyl group, which gave better

Table 3.



Entry	$\mathbf{S_2}$	T (°C)	Ar	R_1	R_2	R_3	R_4	^{1}H NMR[a] and HPLC[b]						Isolated[c] yield (%)
								$\mathbf{S_1}$	$\mathbf{S_2}$	$\mathbf{A_1}$	$\mathbf{A_2}$	$\mathbf{S_2}$:$\mathbf{S_1}$	*syn*:*anti*	
1	**9**	30	Ph	*i*-Pr	Ph	Me	H	20.3	31.5	39.2	9.0	1.6:1	1.1:1	48.2
2	**9**	0	Ph	*i*-Pr	Ph	Me	H	5.2	84.8	7.9	2.1	11.5:1	9.0:1	76.8
3	**9**	−30	Ph	*i*-Pr	Ph	Me	H	2.0	95.5	2.3	0.2	47.8:1	39.0:1	83.7
4	**4e**	30	Ph	*i*-Pr	Ph	Me	Cl	8.1	72.3	13.3	6.3	8.9:1	4.1:1	68.9
5	**4e**	0	Ph	*i*-Pr	Ph	Me	Cl	4.2	88.1	5.7	2.0	21.0:1	12.0:1	77.9
6	**4e**	−30	Ph	*i*-Pr	Ph	Me	Cl	2.0	95.9	1.9	0.2	48.0:1	46.6:1	82.2
7	**4a**	30	2,4-Difluorophenyl	Bn	H	Me	Cl	16.1	24.2	50.6	9.1	1.5:1	0.7:1	10.1
8	**4a**	0	2,4-Difluorophenyl	Bn	H	Me	Cl	2.3	62.1	29.5	6.1	27.0:1	1.8:1	54.2
9	**4a**	−30	2,4-Difluorophenyl	Bn	H	Me	Cl	1.8	74.2	18.8	5.2	41.2:1	3.2:1	63.6
10	**4a**	−60	2,4-Difluorophenyl	Bn	H	Me	Cl	1.7	75.0	18.3	5.0	44.1:1	3.3:1	23.3
11	**4b**	0	2,5-Difluorophenyl	Bn	H	Me	Cl	1.7	49.6	43.9	4.8	29.2:1	1.1:1	44.5
12	**4b**	−30	2,5-Difluorophenyl	Bn	H	Me	Cl	2.0	74.2	18.6	5.2	37.1:1	3.2:1	64.9
13	**4c**	0	2,4-Difluorophenyl	*i*-Pr	Ph	Me	Cl	2.4	92.9	3.4	1.3	38.7:1	20.3:1	72.1
14	**4c**	−30	2,4-Difluorophenyl	*i*-Pr	Ph	Me	Cl	1.2	97.1	1.4	0.3	80.9:1	57.8:1	78.6
15	**4d**	0	2,5-Difluorophenyl	*i*-Pr	Ph	Me	Cl	2.9	91.2	3.9	2.0	31.4:1	15.9:1	76.5
16	**4d**	−30	2,5-Difluorophenyl	*i*-Pr	Ph	Me	Cl	1.1	97.2	1.2	0.5	88.4:1	57.8:1	76.7
17	**12**	−30	Ph	*i*-Pr	Ph	Me	[d]	4.4	42.5	51.4	1.6	9.4:1	0.9:1	65.7
18	**13**	−30	4-Methoxyphenyl	*i*-Pr	Ph	Me	H	3.5	92.3	4.2	0.1	25.6:1	22.3:1	74.8
19	**14**	−30	4-Nitrophenyl	*i*-Pr	Ph	Me	H	1.8	97.1	0.9	0.2	53.9:1	89.9:1	72.6
20	**15**	−30	2,4-Difluorophenyl	*i*-Pr	Ph	Et	Cl	1.8	88.9	7.9	1.5	49.3:1	9.6:1	71.2

[a] Product ratios were taken directly from the ^{1}H NMR characteristic peaks of the four diastereomers for: **9** [δ (ppm): $\mathbf{S_1}$ (5.35); $\mathbf{S_2}$ (5.38); $\mathbf{A_1}$ (5.50); $\mathbf{A_2}$ (5.15)]; **4e** [δ (ppm): $\mathbf{S_1}$ (5.30); $\mathbf{S_2}$ (5.35); $\mathbf{A_1}$ (5.50); $\mathbf{A_2}$ (5.24)]; **4c** [δ (ppm): $\mathbf{S_1}$ (5.40); $\mathbf{S_2}$ (5.33); $\mathbf{A_1}$ (5.44); $\mathbf{A_2}$ (5.24)]; **4d** [δ (ppm): $\mathbf{S_1}$ (5.38); $\mathbf{S_2}$ (5.33); $\mathbf{A_1}$ (5.46); $\mathbf{A_2}$ (5.28)]; **12** [δ (ppm): $\mathbf{S_1}$ (5.39); $\mathbf{S_2}$ (5.42); $\mathbf{A_1}$ (5.57); $\mathbf{A_2}$ (5.55)]; **13** [δ (ppm): $\mathbf{S_1}$ (5.32); $\mathbf{S_2}$ (5.37); $\mathbf{A_1}$ (5.49); $\mathbf{A_2}$ (5.19)]; **14** [δ (ppm): $\mathbf{S_1}$ (5.32); $\mathbf{S_2}$ (5.37); $\mathbf{A_1}$ (5.50); $\mathbf{A_2}$ (5.19)]; **15** [δ (ppm): $\mathbf{S_1}$ (5.34); $\mathbf{S_2}$ (5.38); $\mathbf{A_1}$ (5.23); $\mathbf{A_2}$ (5.20)].

[b] The ratios of the four diastereomers for **4a** and **4b** were taken directly from the UV response of the HPLC detector. See Table 1.

[c] The enantiomerically pure compounds **4a**($\mathbf{S_2}$) and **4b**($\mathbf{S_2}$) were obtained through chromatography. The mixtures containing all the four diastereomers for **9**, **4e**, **4c**, **4d**, **12**, **13**, **14**, **15** were obtained, respectively, by purification through flash chromatography.

[d] Triazole group.

stereoselectivities. On the other hand, the electron donating or sterically bulky substitution of acetophenones would reduce the reactivity of the carbonyl group, which resulted in poor stereoselectivity. The results obtaind from our studies are shown in Table 4.

Attention was then focused on the effect of the catalysis. Although nickel complexes have been reported to have good effect on activating diethyl zinc in the Reformatsky reaction, it was necessary for further investigations on the stoichiometry of the catalyst, different kinds of metals and Lewis acid effects, as shown in Table 5.

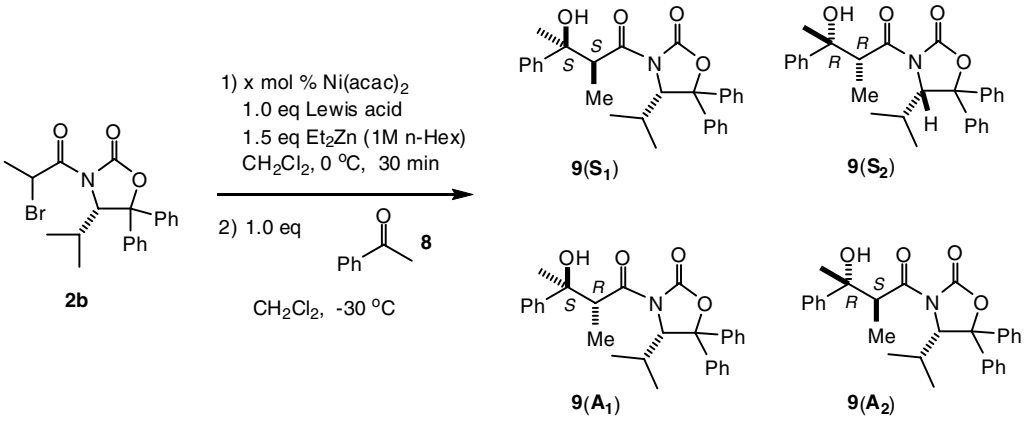
As the amount of catalyst $Ni(acac)_2$ was increased from 5 to 50 mol %, the diastereoselectivity was significantly reduced, which could be rationalized due to the interference of excess Ni^{2+} in the complexation of Zn^{2+} and chiral imide **2b**. The mechanism can be interpreted in a catalytic cycle described in Scheme 5.[13] The Ni^{2+} is reduced into $Ni^{(0)}$ by diethyl zinc and then the $Ni^{(0)}$ reacts with chiral imide **2b** to form the imido nickel enolate at room temperature. The exchange between Ni^{2+} and Zn^{2+} generates the imido zinc enolate, which performs the asymmetric Reformatsky reaction with acetophenone **8**. We believed that the differences amongst the various nickel ligands resulted from the different solubilities of these nickel complexes in dichloromethane, which influenced the exchange rates of zinc and nickel complexes (Table 5, entries 1 and 7–9). Other metal complex catalysts gave poor results in both reactivity and stereoselectivity, compared to the nickel

Table 4.

Entry[a]	Changes[b]	Stereoselectivity	Reasons
14, 16, 19	Electron withdrawing groups on Ar	↑	Electronic effect
18	Electron donating groups on Ar	↓	Electronic effect
3, 6	R_4 changed from H to Cl	↑	Electronic effect
6, 17	R_4 changed from Cl to triazole	↓	Steric effect
16, 20	R_3 changed from Me to Et	↓	Steric effect

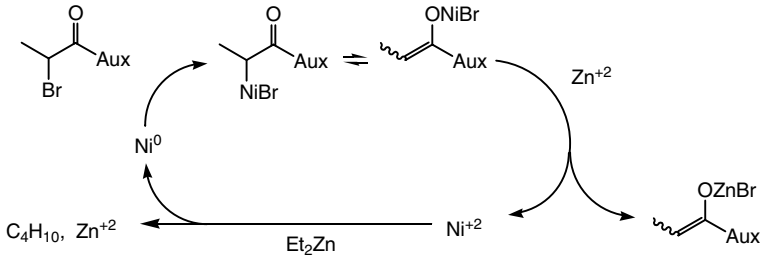
[a] See Table 3.
[b] See the formula of Table 3.

Table 5.



Entry	*X* (mol %)	Catalyst	Lewis acid 1.0 equiv	^{1}H NMR[a]						Isolated[b] yield (%)
				9(S$_1$)	**9(S$_2$)**	**9(A$_1$)**	**9(A$_2$)**	**S$_2$:S$_1$**	*syn*:*anti*	
1	5	$Ni(acac)_2$		2.0	95.5	2.3	0.2	47.8:1	39.0:1	83.7
2	10	$Ni(acac)_2$		3.5	92.0	4.2	0.3	26.3:1	21.2:1	81.4
3	50	$Ni(acac)_2$		8.7	81.3	9.1	0.9	9.3:1	9.0:1	66.7
4	5	$Ni(acac)_2$	LiBr	2.8	87.1	9.7	0.4	31.1:1	8.9:1	32.7
5	5	$Ni(acac)_2$	$MgBr_2$	—	—	—	—	—	—	[c]
6	5	$Ni(acac)_2$	$ZnBr_2$	3.1	95.5	1.1	0.3	30.8:1	70.4:1	70.1
7	5	$Ni(acac)_2(PPh_3)_2$[d]		3.4	90.9	5.4	0.3	26.7:1	16.5:1	68.3
8	5	$NiCl_2$		4.9	80.6	12.5	2.0	16.4:1	5.9:1	43.6
9	5	$NiCl_2(PPh_3)_2$		3.0	93.4	3.4	0.2	31.1:1	26.8:1	81.9
10	5	$Cu(OTf)_2$		24.3	35.2	29.7	10.8	1.4:1	1.5:1	10.5
11	5	$PdCl_2(CH_3CN)_2$		13.8	25.3	53.8	7.1	1.8:1	0.6:1	36.2

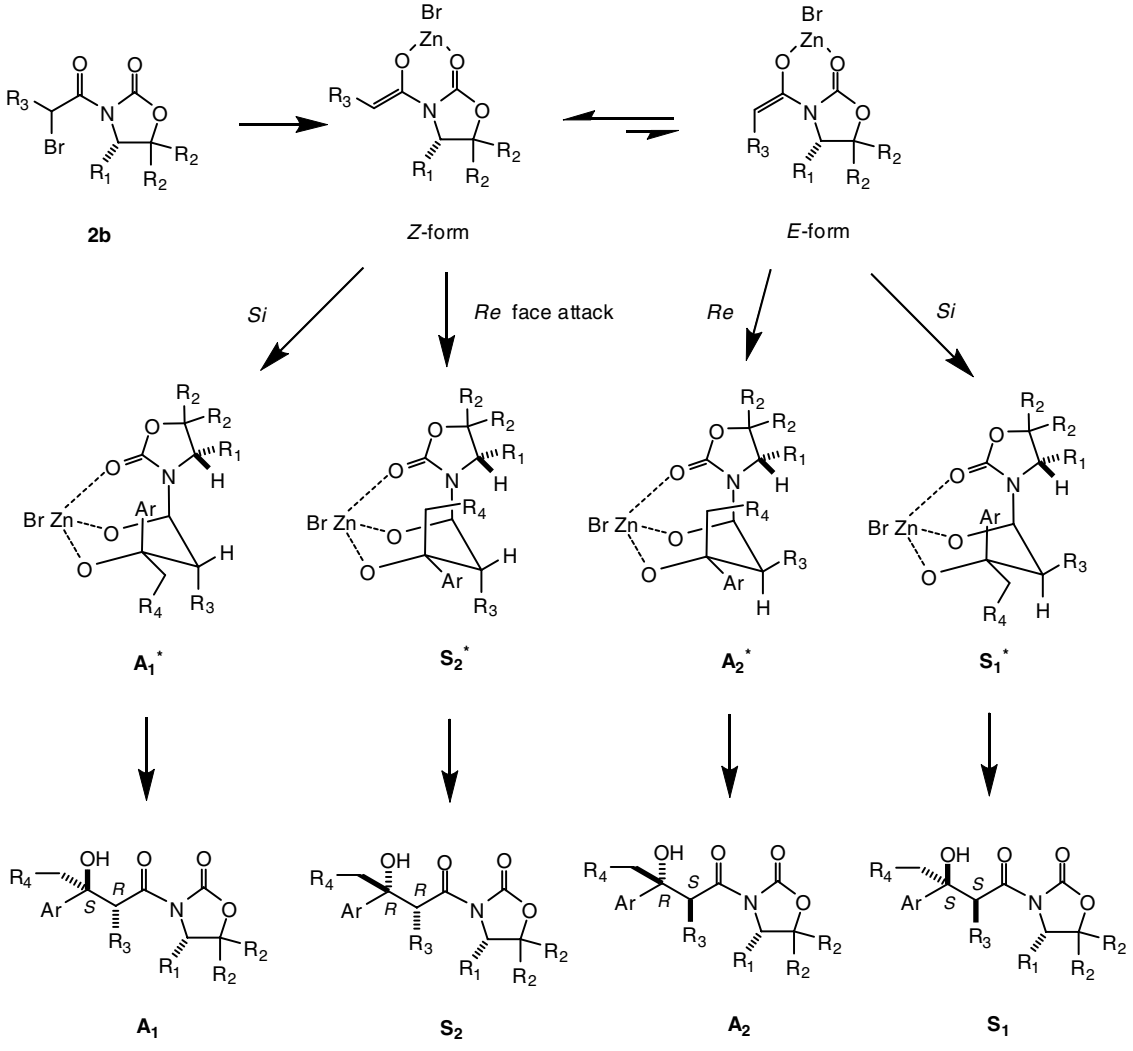
[a] Product ratios were taken directly from the ^{1}HNMR characteristic peaks of the four diastereomers for: [δ (ppm): **9(S$_1$)** (5.35); **9(S$_2$)** (5.38); **9(A$_1$)** (5.50); **9(A$_2$)** (5.15)].
[b] The yields of the mixture, which consisted of all the four diastereomers were obtained through purification by flash chromatography.
[c] The main product was compound **10**.
[d] 10 mol % PPh_3 was added in the reaction.



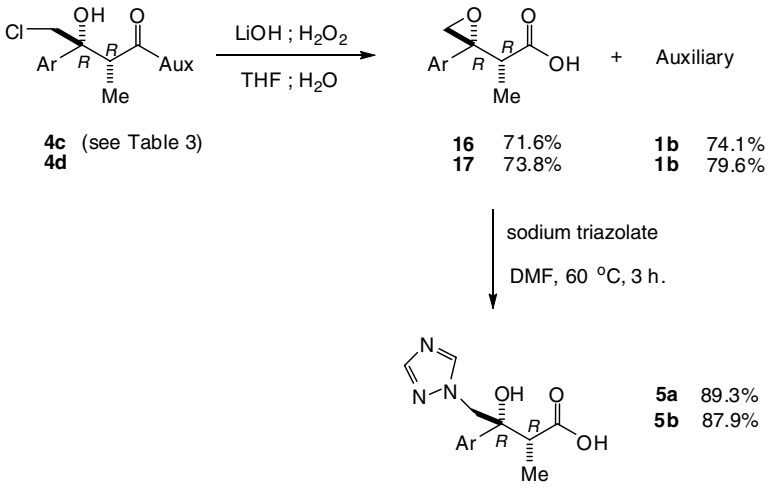
Scheme 5.

complex (Table 5, entries 10 and 11). The addition of Lewis acids does not have much positive effect on this reaction with the exception of $ZnBr_2$, which improved the *syn*:*anti* selectivity due to facilitation of the Ni^{2+}–Zn^{2+} exchange of the enolates at lower temperatures.

On the basis of the results obtained above, the $\mathbf{S_2}$-predominated trends of the asymmetric Reformatsky reaction can now be rationalized by the Zimmerman–Traxler chair pericyclic transition state model[15] as shown in Scheme 6. As we mentioned before, the predominated (*Z*)-form zinc enolate preferably attacked the acetophenone from its *Si*-face in order to avoid the steric congestion of the isopropyl group of the 2-oxazolidinone moiety. This proposal is proven by the constant high ratios of $(\mathbf{S_2}+\mathbf{A_1}):(\mathbf{S_1}+\mathbf{A_2})$. In addition, $\mathbf{S_2}$ is more preferred than $\mathbf{A_1}$ because the axial aryl group of transition state $\mathbf{A_1^*}$ is more sterically crowded than that of $\mathbf{S_2^*}$. Some of the absolute structures of the asymmetric



Scheme 6.



Scheme 7.

Reformatsky reaction adducts, **4a**($\mathbf{S_2}$), **9**($\mathbf{S_2}$) and **4b**($\mathbf{A_1}$), have been confirmed by X-ray single-crystal diffractometry analysis (see Section 4).

After our successful studies on finding the best way to create the correct vicinal *syn*-stereogenic centers, the subsequent process toward target compound **5** was the removal of the Evans chiral auxiliary moiety of β-hydroxyamide **4** under the reported condition (LiOH, H_2O_2, THF, then Na_2SO_3 and HCl)[16] to obtain the epoxy acid and then treatment with excess sodium triazolate (Scheme 7). The Evans chiral auxiliaries were recovered in yields of 74–80%.

3. Conclusion

In conclusion, we have reported a new asymmetric synthesis of chiral β-hydroxyamide **4** through an asymmetric zinc-Reformatsky reaction. Our study demonstrated that the zinc enolates of Evans chiral imides, which formed through the metal–halogen exchange reaction of chiral α-bromoamide **2** and diethyl zinc in the presence of $Ni(acac)_2$ catalyst, reacted with acetophenones with good facial diastereoselectivity and *syn*:*anti* selectivity. Under the optimized condition, the desired $\mathbf{S_2}$ diastereoisomer was obtained in a ratio of >97%, which was transformed into target compound **5** efficiently in a high yield with a good recovery of the chiral auxiliary. These results have offered a very prominent route to the industrial by useful chirally building block **5**, which is known as a key intermediate to several triazole antifungal drugs.

4. Experimental

Acetophenone **8**, α-chloroacetophenone, 4-methoxyacetophenone, 4-nitro-acetophenone, α-chloro-2,4-difluoroacetophenone **3a**, (*S*)-4-benzyl-2-oxazolidinone **1a**, and other starting materials were obtained from commercial suppliers and used without further purification unless otherwise stated. Diethyl zinc (1.0 M in *n*-hexane and 1.2 M in toluene) was purchased from Aldrich Chemical Co. and used as received. THF, benzene and toluene were dried by distillation under nitrogen from sodium metal, and dichloromethane was distilled under nitrogen from calcium hydride. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh). Melting points were recorded on a Fargo Mp-1D. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Infrared spectra were recorded on a Bruker FT-IR Equinox 55 Infrared Spectrophotometer. NMR spectra were recorded on a Varian Mercury 400 or Varian Inova 600, and the chemical shifts were reported as δ value in parts per million relative to TMS in $CDCl_3$ ($\delta = 0$), used as internal standard for ^1H NMR spectra, and the center peak of $CDCl_3$ ($\delta = 77.0$ ppm) used as the internal standard in the ^{13}C NMR spectra. Analytical HPLC was performed on Varian Star (UV detector 310) chromatograph equipped with a 4 mm × 25 cm Lichrospher 100RP18 5 μm column coupled to a UV detector (210 nm) using an acetonitrile/water mixture of 64:36 as the eluent or a 4.6 mm × 25 cm Chiralcel OD-H column (UV 210 nm, eluent IPA/*n*-Hex mixture of 10:90). HRMS-FAB mass were collected on Finnigan, Thermo Quest MAT 95XL. X-ray single-crystal diffractometer analysis was performed on a Bruker AXS SMART-1000.

4.1. (*S*)-4-Isopropyl-5,5-diphenyl-2-oxazolidinone, 1b

To a cold solution (0 °C) of L-valine (25.00 g, 0.21 mol), H_2O (200 mL), and 1 M NaOH (200 mL) in an ice bath was slowly added ethyl chloroformate (20.5 mL, 0.21 mol) within pH 9–10 and then stirred for 1 h at room temperature. After the reaction mixture was extracted with ethyl acetate (3 × 100 mL), the aqueous phases were adjusted to pH 3–4 with 1 M HCl at 0 °C in an ice bath and then extracted again with ethyl acetate (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL), brine (200 mL), dried over anhydrous $MgSO_4$, and concentrated to give (*S*)-2-(ethoxycarbonyl)-3-methylbutanoic acid as a white solid (39.77 g). To the solution of (*S*)-2-(ethoxycarbonyl)-3-methylbutanoic acid (39.77 g, 0.23 mol) and MeOH (400 mL) was slowly added dropwise $SOCl_2$ (30.14 g, 0.25 mol) at 0 °C in an ice bath and stirred for 3 h at room temperature. Having been concentrated,

the resulting mixture was extracted with ethyl acetate (3×200 mL) and the combined organic phases were washed, respectively, with H_2O (100 mL), saturated aqueous $NaHCO_3$ (100 mL), brine (200 mL), dried over anhydrous $MgSO_4$, and concentrated to give (*S*)-methyl 2-(ethoxycarbonyl)-3-methylbutanoate as a white solid (41.91 g). To a solution of (*S*)-methyl 2-(ethoxycarbonyl)-3-methylbutanoate (41.91 g, 0.22 mol) and THF (600 mL) was slowly added dropwise PhMgBr (0.66 mol, freshly prepared from Mg and PhBr) at 0 °C in an ice bath and then stirred for 2 h at room temperature. To the resulting mixture was slowly added dropwise 1 M NaOH (200 mL) at 0 °C and stirred for 3 h in an ice bath and then concentrated. The resulting mixture was filtered to give a white solid and the filtrate extracted with $CHCl_3$ (3×100 mL). The filtered solid was dissolved again into the combined organic phases and recrystallization (ethyl acetate/hexane) was carried out to give Evans auxiliary **1b** as a white solid (53.35 g, 90.3% yield): $[\alpha]_D = -255.2$ (*c* 0.20, $CHCl_3$); mp 252–253 °C; IR (neat): 3456, 2976, 1757, 1501, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.53 (m, 2H), 7.43–7.22 (m, 8H), 6.44 (s, 1H), 4.36 (d, $J = 3.6$ Hz, 1H), 1.91–1.83 (m, 1H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.69 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.77, 143.92, 139.26, 128.53, 128.21, 128.07, 127.68, 126.30, 125.68, 89.41, 65.81, 29.59, 20.86, 15.62; MS (EI): 281, 238, 194, 183, 165, 77; HRMS (EI): calcd for $C_{11}H_9NO_5$ MH^+ 281.1416, found MH^+ 281.1413; The enantiomer ratio was determined by anal. HPLC (Chiralcel OD-H column) to be >99% ee.

4.2. α-Chloro-2,5-difluoroacetophenone, 3b

To a cooled (0 °C) mixture of 1,4-difluorobenzene (35.00 g, 0.31 mol) and $AlCl_3$ (62.00 g, 0.46 mol) was added dropwise chloroacetyl chloride (27.0 mL, 0.34 mol), and the resulting mixture stirred at 0 °C for 1 h and at 60 °C for 1 h. The resulting mixture was added carefully to concentrated HC1 (70 mL) and ice water (200 mL) and stirred for a few minutes, after which it was extracted by CH_2Cl_2 (3×100 mL). The organic phase was washed with water (50 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated. The residual oil was evaporated under reduced pressure to get the product as a white solid (49.28 g, 84.3% yield): mp 48–49 °C; IR (neat): 1696, 1601, 538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.62 (m, 1H), 7.33–7.27 (m, 1H), 7.19 (dt, $J = 10.0$, 4.0 Hz, 1H), 4.73 (d, $J = 3.2$ Hz, 2H).

4.3. (4*S*)-4-Benzyl-3-(2-bromopropanoyl)-2-oxazolidinone, 2a

To a solution of (*S*)-4-benzyl-2-oxazolidinone **1a** (10.00 g, 56.43 mmol) in THF (50 mL) was added 60% NaH (3.4 g, 85.00 mmol) at room temperature and the reaction mixture stirred for 1 h. After the resulting mixture was cooled to −30 °C, the solution of 2-bromopropionyl bromide (41.6 mL, 85.0 mmol) in THF (250 mL) was added dropwise, and then stirred for 1 h at −30 °C and 1 h at 0 °C. The reaction was quenched with saturated aqueous NaH_2PO_4 (200 mL) and the mixture was concentrated. The resulting mixture was extracted with ethyl acetate (4×100 mL) and the combined organic phases were washed, respectively, with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate = 10:1) to give target compound **2a** (14.70 g, 83.6% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 5.73 (q, $J = 6.4$ Hz, 1H), 4.75–4.71 (m, 1H), 4.27–4.21 (m, 2H), 3.22 (dd, $J = 13.2$, 3.2 Hz, 1H), 2.80 (dd, $J = 13.2$, 9.6 Hz, 1H), 1.88 (d, $J = 6.4$ Hz, 3H).

4.4. (4*S*)-3-(2-Bromopropanoyl)-4-isopropyl-5,5-diphenyl-2-oxazolidinone, 2b

Following the procedure described above, but using another Evans auxiliary (*S*)-4-(1-methylethyl)-5,5-diphenyl-2-oxazolidinone **1b** as the reactant, product **2b** was obtained (racemic mixtures, 88.5% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.26 (m, 10H), 5.64–5.58 (m, 1H), 5.50 (d, $J = 2.4$ Hz, 1H), 5.35 (d, $J = 3.6$ Hz, 1H), 2.05–1.99 (m, 1H), 1.82 (d, $J = 6.8$ Hz, 3H), 1.72 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.77 (d, $J = 6.8$ Hz, 3H).

4.5. Asymmetric Reformatsky reactions

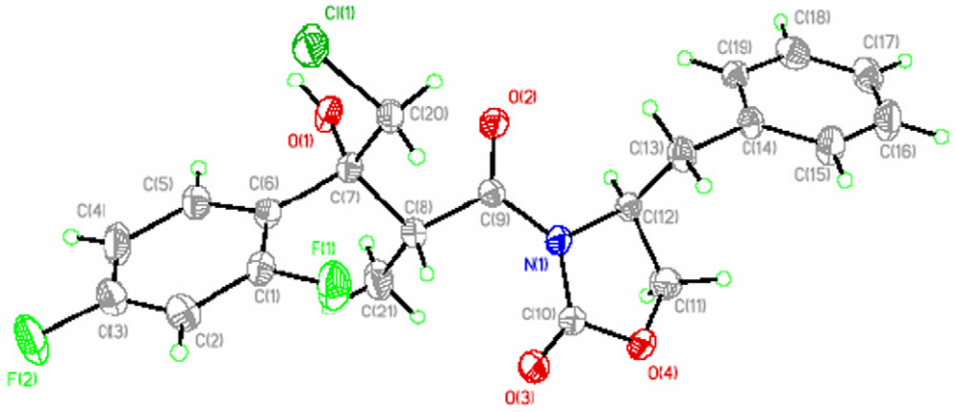
All reactions were carried out under a nitrogen atmosphere using a Schlenk tube with standard techniques for air-sensitive materials. The following description provides a typical experimental procedure for the Reformatsky reaction of Evans chiral imide zinc enolates with a series of acetophenones. $Ni(acac)_2$ (0.05 mmol) and an Evans chiral imide (1.00 mmol) were placed in a 20-mL Schlenk tube equipped with a magnetic stirring bar and dried in vacuo. Under the nitrogen atmosphere, dry CH_2Cl_2 (2.0 mL) was added to the Schlenk tube to dissolve the mixture and the resulting solution was adjusted to 0 °C in an ice bath. $ZnEt_2$ (1.0 M in *n*-Hex, 1.50 mL) was added dropwise to the Schlenk tube at 0 °C and the resulting solution was stirred for 30 min. Then the Schlenk tube was adjusted to a designed temperature in a constant temperature regulator and a solution of an acetophenones-type compound (1.00 mmol) in dry CH_2Cl_2 (2.0 mL) was slowly dropwise injected over a designed time. The resulting solution was stirred for several hours, monitored by anal. HPLC (UV 210 nm). The resulting solution was hydrolyzed with saturated aqueous KH_2PO_4 (2.0 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were washed with H_2O (5 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was measured and analyzed. Simple purification was done by flash chromatography to afford a mixture consisting of all the four diastereomers. Optical pure diastereomers were, respectively, isolated by recrystallization (ether/hexane) or by flash chromatography (ethyl acetate/hexane). The yields and the ratios of the diastereomers of each experiments are listed in the tables above.

4.5.1. [3(2*R*,3*R*),4*S*]-4-Benzyl-3-[4-chloro-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone, 4a(S_2).

The product was obtained by using **2a** and **3a** to perform the asymmetric Reformatsky reaction and

purification by flash chromatography (ethyl acetate/hexane 1:5). Mp 108–110 °C; $[\alpha]_D = +9.9$ (c 1.0, CH_2Cl_2); IR (neat): 3466, 1786, 1669, 1501, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dt, $J = 8.8$, 6.4 Hz, 1H), 7.39–7.25 (m, 5H), 6.96–6.71 (m, 2H), 5.01 (s, 1H), 4.77 (q, $J = 6.8$ Hz, 1H), 4.73–4.67 (m, 1H), 4,21 (d, $J = 4.8$ Hz, 1H), 4.05 (d, $J = 11.2$ Hz, 1H), 3.96 (dd, $J = 11.2$, 0.8 Hz, 1H), 3.48 (dd, $J = 13.6$, 3.6 Hz, 1H), 2.74 (dd, $J = 13.2$, 10.4 Hz, 1H), 1.04 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.60, 163.59, 163.51, 161.94, 161.86, 159.53, 159.45, 157.88, 157.80, 152.80, 135.02, 130.86, 130.82, 130.80, 130.76, 129.35, 129.01, 127.52, 123.62, 123.60, 123.54, 123.52, 111.36, 111.24, 104.38, 104.20, 104.03, 77.38, 77.34, 66.17, 55.69, 51.80, 51.76, 40.89, 40.86, 37.69, 14.66; MS (FAB): 406, 370, 191, 136, 91, 77; HRMS (FAB): calcd for $C_{21}H_{20}ClF_2NO_4$ MH^+ 424.1127, found MH^+ 424.1133. The absolute configuration was determined using single crystal X-ray crystallography diffractometer, as shown below.

X-ray crystal data for **4a(S_2)**: $C_{21}H_{20}ClF_2NO_4$, MW = 423.83, Monoclinic, Space group: $P2(1)$, $a = 14.486(3)$ Å, $\alpha = 90°$, $b = 7.0875(13)$ Å, $\beta = 97.275(4)°$, $c = 20.257(4)$ Å, $\gamma = 90°$, Volume 2063.0(6) $Å^3$, $T = 293(2)$ K, $Z = 4$, $D_c = 1.203$ mg m^{-3}, Absorption coefficient: 0.230 mm^{-1}, Wavelength: 0.71073 Å, $F(000)$: 880, Crystal size: $0.32 \times 0.28 \times 0.14$ mm^3, Independent reflections: 7726 [R(int) = 0.0480], Reflections collected: 11,768; Refinement method: Full-matrix least-squares on F^2, Goodness-of-fit on F^2: 1.008, Final R indices [$I > 2\sigma(I)$]: $R1 = 0.0529$, $wR2 = 0.1090$, SADABS. CCDC No. 642377.



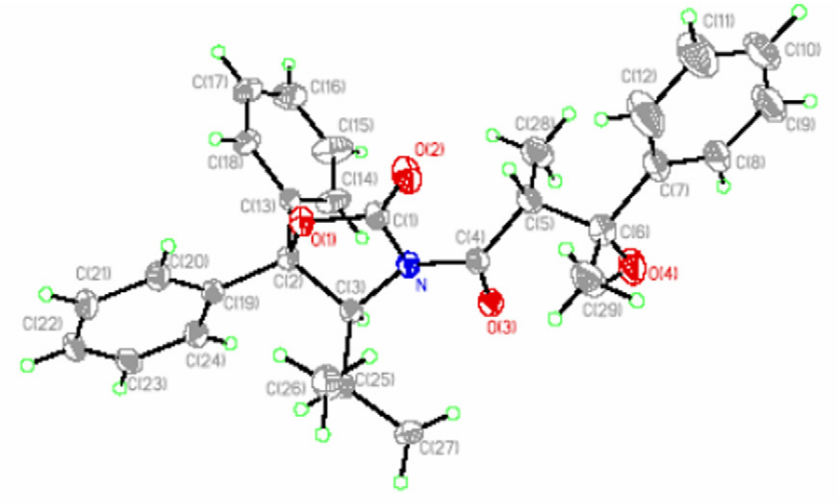
4a(S_2)

4.5.2. [3(2*R*,3*S*),4*S*]-4-Benzyl-3-[4-chloro-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone, 4a(A_1). The product was obtained by using **2a** and **3a** to perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:5). Oil; $[\alpha]_D = +32.8$ (c 1.0, CH_2Cl_2); IR (neat): 3460, 1789, 1673, 1498, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (dt, $J = 6.8$, 2.0 Hz, 1H), 7.30–7.25 (m, 5H), 6.97–6.82 (m, 2H), 5.00 (d, $J = 6.8$ Hz, 1H), 4.85 (q, $J = 6.8$ Hz, 1H), 4.53–4.49 (m, 1H), 4.14–3.96 (m, 4H), 2.64 (dd, $J = 13.2$, 3.2 Hz, 1H), 2.09 (dd, $J = 13.6$, 9.6 Hz, 1H), 1.42 (d, $J = 4.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.59, 159.70, 158.10, 155.37, 153.77, 152.75, 135.00, 129.78, 129.73, 129.69, 129.64, 129.35, 129.10, 127.53, 117.09, 117.04, 116.92, 116.86, 116.67, 116.50, 116.47, 116.26, 116.20, 116.10, 116.04, 66.20, 55.69, 51.50, 51.46, 40.69, 40.66, 37.70, 14.71; MS (FAB): 406, 370, 191, 136, 91, 77; HRMS (FAB): calcd for $C_{21}H_{20}ClF_2NO_4$ MH^+ 424.1127, found MH^+ 424.1133.

4.5.3. [3(2*R*,3*R*),4*S*]-5,5-Diphenyl-4-isopropyl-3-(3-phenyl-3-hydroxy-2-methyl-1-oxobutyl)-2-oxazolidinone, 9(S_2). The product was obtained by using **2b** and **8** to perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:6). Mp 192–194 °C; $[\alpha]_D = -127.3$ (c 1.0, CH_2Cl_2); IR (neat): 3450, 1781, 1669, 1476, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.20 (m, 15H), 5.38 (d, $J = 3.2$ Hz, 1H), 4.26 (s, 1H), 4.22 (q, $J = 6.8$ Hz, 1H), 2.06–2.02 (m, 1H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.48 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.31, 152.90, 145.14, 141.92, 137.59, 128.84, 128.69, 128.46, 128.10, 12800, 126.54, 125.78, 125.45, 124.90, 89.73, 74.77, 65.26, 45.38, 30.24, 29.52, 21.79, 16.63, 12.66; MS (FAB): 458, 440, 238, 121, 77; HRMS (FAB): calcd for $C_{29}H_{31}NO_4$ MH^+ 458.2331, found MH^+ 458.2341. The absolute configuration was determined using single crystal X-ray crystallography diffractometer, as shown below.

X-ray crystal data for **9(S_2)**: $C_{29}H_{31}NO_4$, MW = 457.55, Orthorhombic, Space group: $P2(1)2(1)2$, $a = 8.2983(7)$ Å, $\alpha = 90°$, $b = 23.271(2)$ Å, $\beta = 90°$, $c = 6.4644(7)$ Å, $\gamma = 90°$, Volume 2525.6(5) $Å^3$, $T = 293(2)$ K, $Z = 4$, $D_c = 1.365$ mg m^{-3}, absorption coefficient: 0.080 mm^{-1}, Wavelength: 0.71073 Å, $F(000)$: 976, Crystal size: $0.55 \times 0.52 \times 0.47$ mm^3, Independent reflections: 4947 [R(int) = 0.0696], Reflections collected: 14314; Refinement method: Full-matrix least-squares on F^2, Goodness-of-fit on F^2: 1.184, Final R indices [$I > 2\sigma(I)$]: R1 = 0.0660, wR2 = 0.1781, SADABS. CCDC No. 642379.

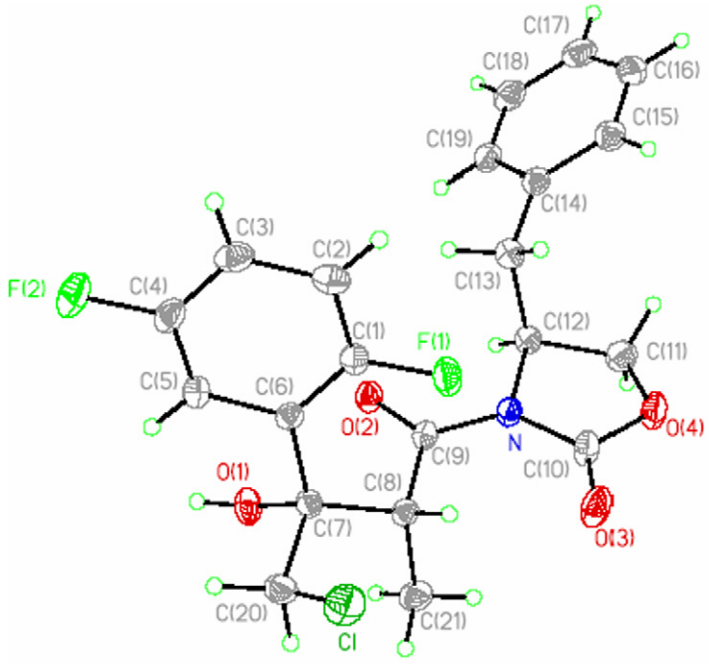
4.5.4. [3(2*R*,3*R*),4*S*]-4-Benzyl-3-[4-chloro-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone, 4b(S_2). The product was obtained by using **2a** and **3b** to



9(S_2)

perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:5). Oil; $[\alpha]_D = +7.7$ (c 1.0, CH_2Cl_2); IR (neat): 3457, 1784, 1669, 1488, 1388 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–6.99 (m, 8H), 5.06 (s, 1H), 4.79 (q, $J = 7.2$ Hz, 1H), 4.73–4.62 (m, 1H), 4.22 (d, $J = 4.8$ Hz, 2H), 4.06 (d, $J = 11.2$ Hz, 1H), 3.96 (d, $J = 11.2$ Hz, 1H), 3.48 (dd, $J = 13.2$, 4.0 Hz, 1H), 2.74 (dd, $J = 13.2$, 10.0 Hz, 1H), 1.05 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.59, 159.70, 158.10, 155.37, 153.77, 152.75, 135.00, 129.78, 129.73, 129.69, 129.64, 129.35, 129.10, 127.53, 117.09, 117.04, 116.92, 116.86, 116.67, 116.50, 116.47, 116.26, 116.20, 116.10, 116.04, 66.20, 55.69, 51.50, 51.46, 40.69, 40.66, 37.70, 14.71; MS (FAB): m/z 424 (MH^+), 406, 374, 229, 178, 91, 77; HRMS (FAB): calcd for $C_{21}H_{20}ClF_2NO_4$ MH^+ 424.1127, found MH^+ 424.1116.

4.5.5. [3(2*R*,3*S*),4*S*]-4-Benzyl-3-[4-chloro-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone, 4b(A_1). The product was obtained by using **2a** and **3b** to perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:5). Mp 109–111 °C; $[\alpha]_D = +41.4$ (c 1.0, CH_2Cl_2); IR (neat): 3460, 1790, 1669, 1486, 1386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.40 (m, 1H), 7.28–7.21 (m, 3H), 7.06–6.92 (m, 4H), 5.03 (s, 1H), 4.87 (q, $J = 6.8$ Hz, 1H), 4.54–4.50 (m, 1H), 4.12–3.94 (m, 4H), 2.64 (dd, $J = 13.6$, 3.2 Hz, 1H), 2.13 (dd, $J = 13.2$, 9.6 Hz 1H), 1.41 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.80, 159.78, 157.36, 155.86, 153.46, 152.17, 134.48, 131.86, 131.78, 131.71, 128.92, 128.77, 127.22, 117.05, 116.97, 116.78, 116.73, 116.70, 116.52, 116.47, 116.14, 116.05, 115.90, 115.81, 76.55, 76.50, 65.67, 54.41, 49.08,



4b(A_1)

49.04, 42.21, 42.16, 36.95, 11.97; MS (FAB): *m/z* 424 (MH^+), 406, 370, 229, 178, 91, 77; HRMS (FAB): calcd for $C_{21}H_{20}ClF_2NO_4$ MH^+ 424.1127, found MH^+ 424.1123. The absolute configuration was determined using a single crystal X-ray crystallography diffractometer, as shown below.

X-ray crystal data for **4b(A₁)**: $C_{21}H_{20}ClF_2NO_4$, MW = 423.83, Orthorhombic, Space group: $P2(1)2(1)2$, a = 16.7882(18) Å, $\alpha = 90°$, b = 11.1748(9) Å, $\beta = 90°$, c = 21.3114(17) Å, $\gamma = 90°$, Volume 1976.2(3) Å^3, T = 293(2) K, $Z = 4$, $D_c = 1.424$ mg m^{-3}, Absorption coefficient: 0.240 mm^{-1}, Wavelength: 0.71073 Å, $F(000)$: 880, Crystal size: $0.49 \times 0.36 \times 0.27$ mm^3, Independent reflections: 3872 [R(int) = 0.0412], Reflections collected: 11,259; Refinement method: Full-matrix least-squares on F^2, Goodness-of-fit on F^2: 1.046, Final R indices [$I > 2\sigma(I)$]: $R1 = 0.0401$, $wR2 = 0.0911$, SADABS. CCDC No. 642378.

4.5.6. [3(2*R*,3*R*),4*S*]-5,5-Diphenyl-4-isopropyl-3-[4-chloro-3-(2,4-difluorophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone, 4c(S₂). The product was obtained by using **2b** and **3a** to perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:5). Oil; $[\alpha]_D = -110.7$ (*c* 1.0, CH_2Cl_2); IR (neat): 3455, 1787, 1673, 1490, 1451, 1391 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (dt, J = 6.0, 4.4 Hz, 1H), 7.46–7.25 (m, 10H), 6.90–6.87 (m, 1H), 6.79–6.76 (m, 1H), 5.33 (d, J = 2.0 Hz, 1H), 5.09 (s, 1H), 4.77 (q, J = 4.8 Hz, 1H), 4.14 (d, J = 7.2 Hz, 1H), 3.89 (d, J = 11.2, 0.8 Hz, 1H), 2.06–2.03 (m, 1H), 0.94 (d, J = 4.8 Hz, 3H), 0.85 (d, J = 4.4 Hz, 3H), 0.49 (d, J = 4.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.55, 163.47, 163.39, 161.82, 161.73, 159.42, 159.34, 157.77, 157.69, 152.57, 141.83, 137.29, 130.99, 130.95, 130.93, 130.89, 128.91, 128.79, 128.53, 128.21, 125.68, 125.36, 123.42, 123.37, 111.19, 111.05, 111.03, 104.23, 104.05, 103.88, 89.96, 77.07, 77.04, 65.55, 51.49, 51.45, 40.57, 40.54, 29.53, 21.80, 16.63, 13.87; MS (FAB): *m/z* 528 (MH^+), 510, 238, 154, 77; HRMS (FAB): calcd for $C_{29}H_{28}ClF_2NO_4$ MH^+ 528.1753, found MH^+ 528.1758.

4.5.7. [3(2*R*,3*R*),4*S*]-5,5-Diphenyl-4-isopropyl-3-[4-chloro-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone, 4d(S₂). The product was obtained by using **2b** and **3b** to perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:5). Oil; $[\alpha]_D = -109.1$ (*c* 1.0, CH_2Cl_2); IR (neat): 3456, 1790, 1672, 1500, 1391 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–6.94 (m, 13H), 5.33 (d, J = 3.2 Hz, 1H), 5.12 (s, 1H), 4.57 (q, J = 6.8 Hz, 1H), 4.15 (d, J = 11.2 Hz, 1H), 3.89 (dd, J = 11.6, 1.2 Hz, 1H), 2.07–2.03 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.50 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.54, 159.71, 156.38, 155.98, 154.96, 159.34, 157.77, 157.69, 152.57, 141.83, 137.29, 130.99, 130.95, 130.93, 130.89, 128.91, 128.79, 128.53, 128.21, 125.68, 125.36, 123.42, 123.37, 111.19, 111.05, 111.03, 104.23, 104.05, 103.88, 89.96, 65.58, 51.79, 51.75, 40.76, 40.73, 29.57, 21.83, 16.65, 13.92; MS (FAB): *m/z* 528 (MH^+), 510, 238, 154, 77; HRMS (FAB): calcd for $C_{29}H_{28}ClF_2NO_4$ MH^+ 528.1753, found MH^+ 528.1758.

4.5.8. [3(2*R*,3*R*),4*S*]-5,5-Diphenyl-4-isopropyl-3-(4-chloro-3-phenyl-3-hydroxy-2-methyl-1-oxobutyl)-2-oxazolidinone, 4e(S₂). The product was obtained by using **2b** and α-chloro-acetophenone to perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:6). Mp 216–217 °C; $[\alpha]_D = -112.5$ (*c* 1.0, CH_2Cl_2); IR (neat): 3471, 1792, 1677, 1498, 1384 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.25 (m, 15H), 5.35 (d, J = 3.2 Hz, 1H), 4.71 (s, 1H), 4.54 (q, J = 7.2 Hz, 1H), 3.91 (d, J = 11.2 Hz, 1H), 3.76 (d, J = 10.8 Hz, 1H), 2.06–2.02 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.59, 152.74, 141.97, 140.91, 137.52, 128.92, 128.78, 128.52, 128.16, 127.51, 125.77, 125.53, 125.44, 89.84, 77.31, 65.33, 52.38, 41.66, 29.74, 21.76, 16.38, 13.04; MS (FAB): *m/z* 492 (MH^+), 474, 282, 256, 91, 77; HRMS (FAB): calcd for $C_{29}H_{30}ClNO_4$ MH^+ 492.1941, found MH^+ 492.1948.

4.5.9. [3(2*R*,3*R*),4*S*]-5,5-Diphenyl-4-isopropyl-3-[3-(4-methoxyphenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone, 13(S₂). The product was obtained by using **2b** and 4-methoxyl-acetophenone to perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:6). Oil; $[\alpha]_D = -124.2$ (*c* 1.0, CH_2Cl_2); IR (neat): 3499, 1784, 1677, 1512, 1451, 1366 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.25 (m, 12H), 6.85 (d, J = 8.8 Hz, 2H), 5.37 (d, J = 3.6 Hz, 1H), 4.20 (s, 1H), 4.16 (q, J = 7.2 Hz, 1H), 3.79 (s, 3H), 2.05–2.01 (m, 1H), 1.61 (s, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 7.2 Hz, 3H), 0.49 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.39, 158.21, 152.96, 141.93, 137.64, 137.37, 128.87, 128.72, 128.48, 128.12, 126.11, 125.81, 125.49, 113.33, 89.74, 74.60, 65.24, 55.19, 45.51, 30.31, 29.56, 21.82, 16.64, 12.70; MS (FAB): *m/z* 488 (MH^+), 470, 426, 256, 121, 77; HRMS (FAB): calcd for $C_{30}H_{33}NO_5$ MH^+ 488.2437, found MH^+ 488.2444.

4.5.10. [3(2*R*,3*R*),4*S*]-5,5-Diphenyl-4-isopropyl-3-[3-(4-nitrophenyl)-3-hydroxy-2-methyl-1-oxobutyl]-2-oxazolidinone, 14(S₂). The product was obtained by using **2b** and 4-nitro-acetophenone to perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:6). Oil; $[\alpha]_D = -101.4$ (*c* 1.0, CH_2Cl_2); IR (neat): 3503, 1753, 1669, 1505, 1350, 1324 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 9.2 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.45–7.26 (m, 10H), 5.37 (d, J = 3.2 Hz, 1H), 4.44 (s, 1H), 4.24 (q, J = 7.2 Hz, 1H), 2.08–2.04 (m, 1H), 1.63 (s, 3H), 0.96 (d, J = 7.2 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 0.45 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.68, 152.99, 152.62, 146.85, 141.80, 137.42, 128.95, 128.85, 128.56, 128.26, 126.11, 125.78, 125.44, 123.36, 90.04, 74.88, 65.49, 45.02, 30.08, 29.52, 21.86, 16.70, 12.59; MS (FAB): *m/z* 502 (MH^+), 484, 282, 91, 77; HRMS (FAB): calcd for $C_{29}H_{30}N_2O_6$ MH^+ 502.2182, found MH^+ 502.2184.

4.5.11. [3(2*R*,3*R*),4*S*]-5,5-Diphenyl-4-isopropyl-3-[4-chloro-3-(2,4-difluorophenyl)-3-hydroxy-2-ethyl-1-oxobutyl]-2-oxazolidinone, 15(S₂). The product was obtained by using (4*S*)-3-(2-bromobutanoyl)-4-isopropyl-5,5-diphenyl-2-oxa-

zolidinone and **3a** to perform the asymmetric Reformatsky reaction and purification by flash chromatography (ethyl acetate/hexane 1:5). Oil; $[\alpha]_D = -148.6$ (*c* 1.0, CH_2Cl_2); IR (neat): 3454, 1779, 1671, 1503, 1390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dt, $J = 8.8$, 6.8 Hz, 1H), 7.54 (d, $J = 7.2$ Hz, 2H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.38–7.22 (m, 6H), 6.91–6.76 (m, 2H), 5.39 (d, $J = 2.8$ Hz, 1H), 4.71 (s, 1H), 4.56 (dd, $J = 10.8$, 3.6 Hz, 1H), 4.24 (d, $J = 11.2$ Hz, 1H), 3.80 (dd, $J = 11.6$, 1.2 Hz, 1H), 2.12–2.08 (m, 1H), 1.46–1.25 (m, 2H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.4$ Hz, 3H), −0.11 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.35, 163.51, 163.44, 161.86, 161.77, 159.52, 159.44, 157.87, 157.80, 152.99, 142.27, 137.33, 131.15, 131.11, 131.08, 131.05, 128.98, 128.72, 128.58, 128.12, 125.48, 125.07, 123.56, 123.54, 123.48, 123.46, 111.12, 110.98, 104.2, 104.10, 103.93, 89.64, 66.61, 51.78, 51.74, 47.88, 29.90, 29.69, 22.76, 22.02, 16.51, 9.72.

4.6. (2*R*,3*R*)-3-[3-(2,4-Difluorophenyl)-3,4-epoxy-2-methyl]-butanoic acid, 16

To a cooled (−10 °C) solution of chlorohydrin imide **4c** (3.00 g, 5.69 mmol) in THF (40 mL) and H_2O (10 mL) was slowly added dropwise a 30% aqueous solution of H_2O_2 (3.5 mL, 34.14 mmol). To the resulting mixture was slowly added $LiOH{\cdot}H_2O$ (0.72 g, 17.07 mmol) in small portions at −10 to −5 °C. Once the addition was finished, the reaction was stirred at −5 °C for 1 h and 0 °C for 0.5 h. Two molars of aqueous Na_2SO_3 (18 mL) was then added dropwise slowly at 0–5 °C, and the mixture was stirred for 30 min. The alkaline mixture was extracted with chloroform (3 × 30 mL). The combined organic phases were concentrated and the residue was purified by flash chromatography (hexane/ethyl acetate = 1:1) to give Evans chiral auxiliary **1b** (1.19 g, recovery 74.1%). The aqueous phase (pH 11) was acidified to pH 2 with saturated aqueous $NaHSO_4$ before it was extracted with chloroform (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated to give epoxy acid **16** as a colorless oil, which could be used directly in the next step without further purification. The pure product (2.15 g, 71.6% yield) was obtained by flash chromatography (ethyl acetate): oil; $[\alpha]_D = -42.7$ (*c* 1.0, CH_2Cl_2); IR (neat): 3300–2800, 1705, 1503, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dt, $J_d = 6.8$, $J_t = 8.8$ Hz, 1H), 6.89–6.78 (m, 2H), 3.16 (d, $J = 4.8$ Hz, 1H), 3.02 (q, $J = 7.2$ Hz, 1H), 2.91 (d, $J = 4.8$ Hz, 1H), 1.19 (dd, $J = 7.2$, 0.8 Hz, 3H).

4.6.1. (2*R*,3*R*)-3-[3-(2,5-Difluorophenyl)-3,4-epoxy-2-methyl]-butanoic acid, 17. Following the previous procedure, the removal of Evans chiral auxiliary section from chlorohydrin imide **4d** was carried out with a 79.6% recovery of Evans auxiliary **1b** and epoxy acid **17** was obtained (73.8% yield): oil; $[\alpha]_D = -41.5$ (*c* 1.0, CH_2Cl_2); IR (neat): 3300–2800, 1711, 1487, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dt, $J_d = 6.8$, $J_t = 8.8$ Hz, 1H), 6.89–6.78 (m, 2H), 3.16 (d, $J = 4.8$ Hz, 1H), 3.02 (q, $J = 7.2$ Hz, 1H), 2.91 (d, $J = 4.8$ Hz, 1H), 1.19 (dd, $J = 7.2$, 0.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.51, 159.13, 157.52, 157.23, 155.61, 127.20, 127.15, 127.09, 127.04, 116.74, 116.67, 116.61, 116.58, 116.51, 116.45, 116.37, 116.34, 57.50, 51.85, 44.56, 12.33.

4.7. (2*R*,3*R*)-3-[3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-3-(1*H*-1,2,4-triazol-1-yl)]butanoic acid, 5a

To a cooled (0 °C) solution of sodium triazole (1.00 g, 10.98 mmol) in DMF (30 mL) was slowly added dropwise a solution of epoxy acid **16** obtained above (0.94 g, 4.12 mmol) in DMF (5 mL), and the mixture was heated to 60 °C for 3 h. The mixture was cooled to 0 °C, and 1 M HCl was then added until pH 3–4. The resulting mixture was extracted with ethyl acetate (5 × 20 mL) and the combined organic phases were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and then concentrated. Recrystallization (methanol) gave product **5a** as a white solid (1.09 g, 89.3% yield): mp 212–213 °C; $[\alpha]_D = -52.4$ (*c* 1.0, MeOH); IR (neat): 3350, 3107, 3000–2200, 1669, 1498, 1130 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.58 (s, 1H), 7.21–7.12 (m, 2H), 6.88–6.83 (m, 1H), 4.75 (d, $J = 14.4$ Hz, 1H), 4.68 (d, $J = 14.4$ Hz, 1H), 3.10 (q, $J = 7.2$ Hz, 1H), 0.84 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.32, 163.92, 163.76, 160.67, 160.62, 160.50, 160.46, 157.35, 157.19, 150.67, 145.19, 130.51, 130.43, 130.39, 130.31, 125.06, 125.01, 124.89, 124.84, 111.28, 111.24, 111.01, 110.97, 104.57, 104.20, 103.86, 76.04, 75.97, 56.41, 56.35, 45.46, 45.40, 12.97. Anal. Calcd for $C_{13}H_{13}F_2N_3O_3$: C, 52.53; H, 4.41; N, 14.14. Found: C, 52.69; H, 4.58; N, 14.11.

4.7.1. (2*R*,3*R*)-3-[3-(2,5-Difluorophenyl)-3-hydroxy-2-methyl-3-(1*H*-1,2,4-triazol-1-yl)]butanoic acid, 5b. Following the procedure described above, but using epoxy acid **17** as the reactant, **5b** was obtained as a white solid (1.08 g, 87.9% yield): mp 191–193 °C; $[\alpha]_D = -43.1$ (c 1.0, MeOH); IR (neat): 3416, 3200–2200, 1678, 1615, 1491, 1127 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.61 (s, 1H), 7.19–7.14 (m, 1H), 7.05–6.88 (m, 3H), 4.81 (d, $J = 14.4$ Hz, 1H), 4.73 (d, $J = 14.4$ Hz, 1H), 3.13 (q, $J = 7.2$ Hz, 1H), 0.84 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.78, 158.75, 157.17, 155.49, 153.9, 150.35, 144.90, 130.80, 130.75, 130.70, 130.65, 117.19, 117.13, 117.01, 116.95, 116.05, 115.99, 115.89, 115.83, 115.40, 115.37, 115.22, 115.20, 75.71, 75.67, 55.86, 55.84, 44.89, 44.87. Anal. Calcd for $C_{13}H_{13}F_2N_3O_3$: C, 52.53; H, 4.41; N, 14.14. Found: C, 52.62; H, 4.63; N, 14.07.

References

1. (a) Reformatskii, S. N. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1201; (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: London, 1996.
2. Bartroli, J.; Turmo, E.; Belloc, J.; Forn, J. *J. Org. Chem.* **1995**, *60*, 3000.
3. (a) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549; (b) Parrish, J. D.; Shelton, D. R.; Daniel, R. *Org. Lett.* **2003**, *5*, 3615; (c) Andrei, C.; Robert, A. *Tetrahedron Lett.* **2000**, *41*, 3039; (d) Shibata, I.; Suwa, H.; Sakakibara, H.; Baba, A. *Org. Lett.* **2002**, *4*, 301.
4. Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691.

5. Fukuzawa, S. I.; Matsuzawa, H.; Yoshimitsu, S. I. *J. Org. Chem.* **2000**, *65*, 1702.
6. Ojida, A.; Yamano, T.; Taya, N.; Tasaka, A. *Org. Lett.* **2002**, *4*, 3051.
7. Cozzi, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2951.
8. (a) Fromtling, R. A.; Castäner, J. *Drugs Future* **1997**, *22*, 326; (b) Naito, T.; Hata, K.; Tsuruoka, A. *Drugs Future* **1996**, *21*, 20; (c) Tasaka, A.; Kitazaki, T.; Tamura, N.; Tsuchimori, N.; Matsushita, Y.; Hayashi, R.; Okonogi, K.; Itoh, K. *Chem. Pharm. Bull.* **1997**, *45*, 321; (d) Umeda, I.; Yamazaki, T.; Ichihara, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 191.
9. Moriwake, T. *J. Org. Chem.* **1996**, *31*, 983.
10. Ocampo, R.; Dolbier, W. R.; Abboud, K. A.; Zuluaga, F. *J. Org. Chem.* **2002**, *67*, 72.
11. Ding, Y.; Zhao, G. *J. Chem. Soc., Chem. Commun.* **1992**, 941.
12. Inaba, S.-I.; Rieke, R. D. *Tetrahedron Lett.* **1985**, *26*, 155.
13. Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143.
14. Adrian, J. C., Jr.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett.* **1999**, *40*, 2457.
15. (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920; (b) Hooz, J.; kinke, S. *J. Am. Chem. Soc.* **1968**, *90*, 6891; (c) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.
16. Alexander, K.; Cook, S.; Gibson, C. L.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1538.