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## EFFICIENT PREPARATION OF A VERSATILE CHIRAL SYNTHON FOR 1,2-DIAMINES VIA THE Fe(III)-CATALYZED DIASTEREOSELECTIVE OXIDATION OF 2-IMIDAZOLONE AND ITS APPLICATION

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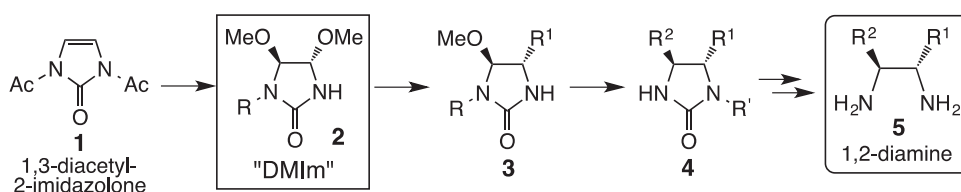
**Abstract** – The efficient and predominant preparation of (4*S*,5*S*)-4,5-dimethoxy-2-imidazolidinone (DMIm) was established *via* the Fe(III)-catalyzed diastereoselective oxidation of 1-[(1*S*,2*R*)-2-*exo*-alkoxyapocamphanecarbonyl]-2-imidazolone with aqueous H<sub>2</sub>O<sub>2</sub> up to 94% d.e., both of which were easily purified by column chromatography, followed by simple and convenient conversions. The obtained *N*-tosyl-(4*S*,5*S*)-DMIm proved to be a versatile chiral synthon for 1,2-diamines by the synthesis of (1*S*,2*S*)-1,2-diamino-1-(4-fluorophenyl)butane derivative, whose platinum complex showed potent antitumor activity.

The 1,2-diamine framework is an important component of a substantial number of compounds that are of biological and medicinal importance,<sup>1,2</sup> as well as for efficient chiral ligands for use in asymmetric reaction systems that include derivatives such as imidazolines and Schiff bases.<sup>3</sup> Hitherto, there have been a number of methodologies for the synthesis of chiral 1,2-diamines such as derivatization from amino acids, substitutional induction of nitrogen nucleophiles to haloalkanes, conjugate addition of nitrogen nucleophiles to nitroalkenes and aziridines, diamination of 1,2-diols, and the coupling reaction of imines. Most of these methodologies, however, are primarily for the construction of a specific side chain structure and/or a stereocenter.<sup>3</sup> Therefore, a versatile method for the chiral syntheses of various types of C<sub>2</sub>-symmetric and unsymmetric 1,2-diamines is still needed.

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\* Dedicated to Professor Dr. Isao Kuwajima on the occasion of his 77th birthday

We previously reported that both enantiomers of optically active *trans*-4,5-dimethoxy-2-imidazolidinone (DMIm, **2**) were available from the 5-membered heterocycle, 1,3-diacetyl-2-imidazolone (**1**), which functions as a versatile chiral synthon for the construction of various types of chiral 1,2-diamines (**5**), including the stepwise and stereospecific conversion of two hemiaminal ether moieties to other substituents followed by ring-cleavage (Scheme 1).<sup>4</sup>



Recently, we discovered an alternative and effective method for the preparation of both enantiomers of DMIm using the Fe(III) (FeCl(dipic)(H<sub>2</sub>O)<sub>2</sub>)-catalyzed oxidation of achiral 2-imidazolone by H<sub>2</sub>O<sub>2</sub>-urea followed by the optical resolution of the *N*-arylsulfonyl derivatives using (1*S*,2*R*)-2-*exo*-methoxyapocamphanecarboxylic acid (MAC acid).<sup>5,6</sup> This synthetic methodology avoided the use of bromine, which is harmful and difficult to handle, and presented a more practical and facile pathway to optical resolution compared with the previous one.

Although the preparation of both enantiomers of DMIm is useful for the construction of chemical libraries in the field of medicinal chemistry, a predominant supply of one of the enantiomers of DMIm would also be desirable for a versatile preparation of chiral 1,2-diamines with a particular configuration.

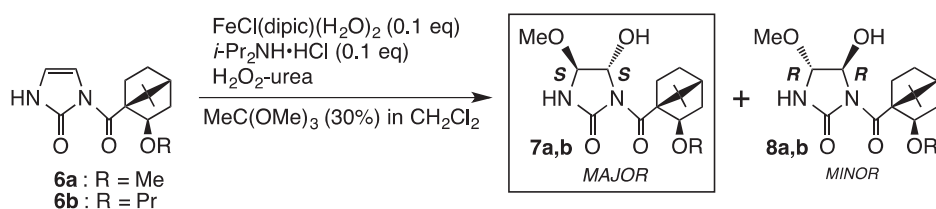
In our previous work, attempts to prepare chiral DMIm by diastereomeric addition to chiral 2-imidazolones were insufficient, because of the low regioselectivity of the addition reactions. Recent results concerning the Fe(III)-catalyzed oxidation of 2-imidazolone by H<sub>2</sub>O<sub>2</sub> motivated us to apply this methodology in a diastereoselective manner for the practical synthesis of chiral DMIm.

Herein, we report an efficient method for the predominant preparation of (4*S*,5*S*)-4,5-dimethoxy-2-imidazolidinone ((4*S*,5*S*)-DMIm) *via* the Fe(III)-catalyzed diastereoselective oxidation of 1-[(1*S*,2*R*)-2-*exo*-methoxyapocamphanecarbonyl] (MAC)- and 1-[(1*S*,2*R*)-2-*exo*-propoxyapocamphanecarbonyl] (PAC)-2-imidazolone with aqueous H<sub>2</sub>O<sub>2</sub> or H<sub>2</sub>O<sub>2</sub>-urea followed by simple conversions. A biologically interesting synthetic application of (4*S*,5*S*)-DMIm for chiral 1,2-diamine is also described.

We first examined the reactivity and diastereoselectivity of the Fe(III) complex-catalyzed oxidation of chiral 2-imidazolone, 1-[(1*S*,2*R*)-2-*exo*-methoxyapocamphanecarbonyl]-2-imidazolone (**6a**) (Table 1, entries 1-6). Under the same reaction conditions detailed in a previous report,<sup>5</sup> a 70% yield of the diastereomeric mixture of *trans*-4-methoxy-5-hydroxy-2-imidazolidinone (**7a** and **8a**) was obtained with moderate diastereoselectivity (entry 1). Based on the monitoring of the reaction mixture via TLC, we

decided that the addition of H<sub>2</sub>O<sub>2</sub>-urea should be divided. With three additions, each of a 0.5 equivalent, a slightly higher chemical yield was achieved (76%; entry 2). The higher concentration led to a much faster reaction with a slight decrease in diastereoselectivities (entries 3 and 4). Further addition of H<sub>2</sub>O<sub>2</sub>-urea (0.5 eq; total 2 eq) resulted in an 82% yield (entry 5). Lower reaction temperatures such as 0 °C retarded the reaction, given an acceptable reaction time, and resulted in an 80% yield with a 52% d.e. (entry 6). PAC-2-imidazolone had a bulkier *n*-propoxy moiety compared with the methoxy group in the chiral auxiliary, and showed a lower reactivity that resulted in a 27% yield and a d.e. value similar to that of MAC-2-imidazolone (entry 7).

**Table 1.** The Fe(III)-catalyzed oxidation of 1-[(1*S*,2*R*)-2-*exo*-alkoxyapocamphanecarbonyl]-2-imidazolone by hydrogen peroxide in the presence of MeC(OMe)<sub>3</sub>



Entry	R	Conc. (M) <sup>b</sup>	eq. of H <sub>2</sub> O <sub>2</sub> -urea	Temp (°C)	Method <sup>c</sup>	Time (h)	Yield (%) <sup>d</sup>	%d.e. <sup>e</sup>
1	Me	0.05	1.5	25	A	3	70	49
2	Me	0.05	1.5	25	B	2.5	76	50
3	Me	0.1	1.5	25	B	2	77	46
4	Me	0.2	1.5	25	C	1	77	42
5	Me	0.2	2	25	C	1.3	82	45
6	Me	0.2	2	0	B	3.5	80	52
7	Pr	0.2	2	0	B	5	27 <sup>f</sup>	51

a) Reactions were carried out in the mixture of trimethyl orthoacetate (1.6 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3.7 mL) with **6a/b** (0.265 mmol), FeCl(dipic)(H<sub>2</sub>O)<sub>2</sub> (7.7 mg, 0.1 eq), *i*-Pr<sub>2</sub>NH·HCl (3.6 mg, 0.1 eq) and H<sub>2</sub>O<sub>2</sub>-urea (37.4 mg, 1.5 eq) at 25 °C except for other designated conditions. For detail, see ref. 7.

b) Concentration of substrate in the reaction system. Thus, volume of the solvents were changed.

c) Method A: H<sub>2</sub>O<sub>2</sub>-urea was added to the reaction mixture all at once; method B: 0.5 eq of H<sub>2</sub>O<sub>2</sub>-urea was added to the reaction mixture every 30 minutes; method C: 0.5 eq of H<sub>2</sub>O<sub>2</sub>-urea was added to the reaction mixture every 20 minutes;

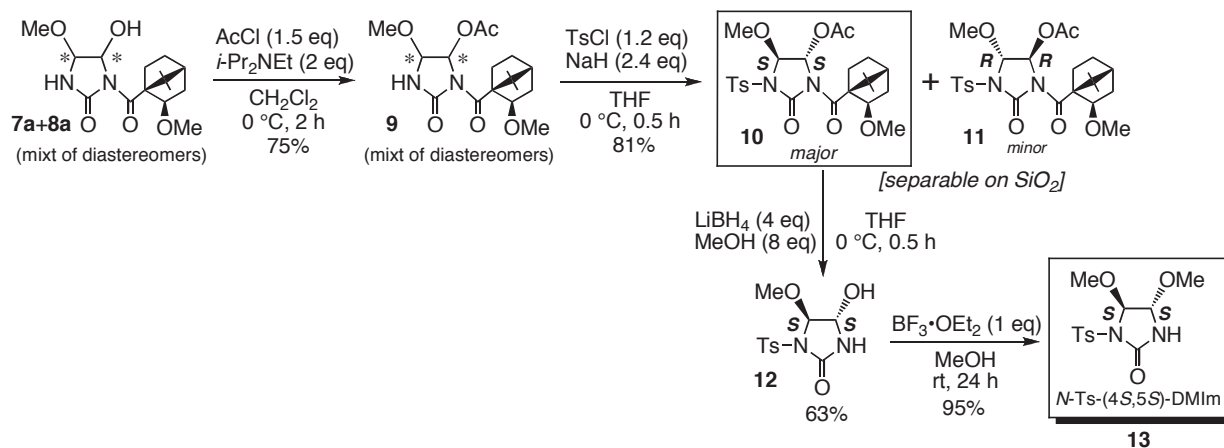
d) Isolated yields.

e) Determined by <sup>1</sup>H NMR.

f) 26% of starting material was recovered.

The obtained diastereomeric mixture of *trans*-4-methoxy-5-hydroxy-2-imidazolidinone (**7a+8a**; **7a/8a** = 76/24) was regioselectively acetylated, and the subsequent *N*-tosylation yielded a mixture of **10** and **11**, which was easily separable using SiO<sub>2</sub> chromatography. The MAC group of the major product **10** was

then reductively removed via a combination of  $\text{LiBH}_4$  and  $\text{MeOH}$  (1:2), and a 4-hydroxy group of **12** was smoothly converted to a methoxy moiety with a full retention of configuration to yield *N*-tosyl-(4*S*,5*S*)-DMIIm (**13**) (Scheme 2).



Scheme 2

We also tested a similar Fe(III)-catalyzed oxidation of chiral 2-imidazolones (**6a,b**) in the presence of *t*-BuOH, in place of  $\text{MeC}(\text{OMe})_3$  (Table 2). In accordance with Beller's procedure,<sup>8</sup> the treatment of a chiral 2-imidazolone with aqueous  $\text{H}_2\text{O}_2$  in the presence of a catalytic amount of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , dipicolinic acid, diisopropylamine, and powdered MS4A, and using a *t*-BuOH/ $\text{CH}_2\text{Cl}_2$  (1:1) mixture as a solvent, yielded *trans*-4-*tert*-butoxy-5-hydroxy-2-imidazolidinones (**14a/b**, **15a/b**), both of which were simply separated via  $\text{SiO}_2$  chromatography. The  $\text{FeCl}(\text{dipic})(\text{H}_2\text{O})_2$ -catalyzed oxidation of **6a** with aqueous  $\text{H}_2\text{O}_2$  gave results similar to those of the  $\text{FeCl}_3$ -catalyzed reaction (entries 1 and 3). The use of aqueous  $\text{H}_2\text{O}_2$  induced a higher diastereoselectivity compared with that induced by using  $\text{H}_2\text{O}_2$  urea as an oxidant, and a 94% d.e. was achieved when using 1-PAC-2-imidazolone (**6b**) as the substrate.<sup>11</sup>

Optically pure (4*S*,5*S*)-*trans*-4-*tert*-butoxy-5-hydroxy-2-imidazolidinone (**14a**) was almost quantitatively converted to the corresponding (4*S*,5*S*)-*trans*-4-methoxy-5-hydroxy-2-imidazolidinone (**7a**), which led to *N*-tosyl-(4*S*,5*S*)-DMIIm (**13**) in the way similar to the reaction shown in Scheme 2 (Scheme 3).<sup>12</sup>

The versatility of the obtained *N*-tosyl-(4*S*,5*S*)-DMIIm (**13**) was demonstrated by the chiral synthesis of a (1*S*,2*S*)-1,2-diamino-1-(4-fluorophenyl)butane derivative (**21**) with a platinum complex (**22**) that showed potent antitumor activity<sup>13</sup> (Scheme 4). Thus, *N*-tosyl-(4*S*,5*S*)-DMIIm (**13**) was treated with 4-fluorophenylcuprate in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  at  $-30^\circ\text{C}$  for 3 hours, resulting in the regioselective replacement of the 4-methoxy moiety with a 4-fluorophenyl group with perfect retention of configuration and a 19% recovery of **13**. A subsequent 3-acetylation followed by the removal of the tosyl moiety under UV-irradiation in the presence of sodium cyanoborohydride and anisole<sup>5</sup> gave a 1-acetyl-4-methoxy derivative (**18**). A treatment of **18** with ethylcuprate in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  at  $-30^\circ\text{C}$  for 3 hours

**Table 2.** The Fe(III)-catalyzed oxidation of 1-[(1*S*,2*R*)-2-*exo*-alkoxyapocamphanecarbonyl]-2-imidazolone by hydrogen peroxide in the presence of *t*-BuOH<sup>a)</sup>

$\text{Fe(III) (0.1 eq)}$   
 $\text{H}_2\text{O}_2 \text{ (2 eq)}$   
 $t\text{-BuOH (50\% in CH}_2\text{Cl}_2)$   
 $0\text{ }^\circ\text{C, 1.5 h}$

$\text{6a : R = Me}$   
 $\text{6b : R = Pr}$

$\text{14a,b}$  (major) +  $\text{15a,b}$  (minor)  
*[separable on SiO<sub>2</sub>]*

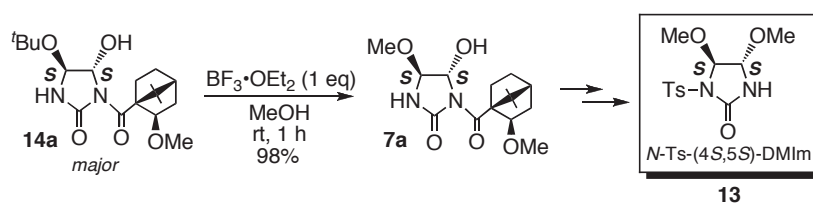
Entry	R	Fe(III) complex	H <sub>2</sub> O <sub>2</sub>	Yield (%) <sup>c)</sup>	%d.e. <sup>d)</sup>
1 <sup>b)</sup>	Me	FeCl <sub>3</sub> ·6H <sub>2</sub> O (0.1) dipicolinic acid (0.1) <i>i</i> -Pr <sub>2</sub> NH (0.2)	30% H <sub>2</sub> O <sub>2</sub> aq	84	63
2 <sup>b)</sup>	Pr	FeCl <sub>3</sub> ·6H <sub>2</sub> O (0.1) dipicolinic acid (0.1) <i>i</i> -Pr <sub>2</sub> NH (0.2)	30% H <sub>2</sub> O <sub>2</sub> aq	74	94
3 <sup>b)</sup>	Me	FeCl(dipic)(H <sub>2</sub> O) <sub>2</sub> (0.1) <i>i</i> -Pr <sub>2</sub> NH·HCl (0.1)	30% H <sub>2</sub> O <sub>2</sub> aq	88	63
4	Me	FeCl(dipic)(H <sub>2</sub> O) <sub>2</sub> (0.1) <i>i</i> -Pr <sub>2</sub> NH·HCl (0.1)	H <sub>2</sub> O <sub>2</sub> -urea	85	56
5	Pr	FeCl(dipic)(H <sub>2</sub> O) <sub>2</sub> (0.1) <i>i</i> -Pr <sub>2</sub> NH·HCl (0.1)	H <sub>2</sub> O <sub>2</sub> -urea	35	78

a) For reaction conditions, see ref. 9.

b) MS4A (powdered) was added to the reaction mixture.<sup>10)</sup>

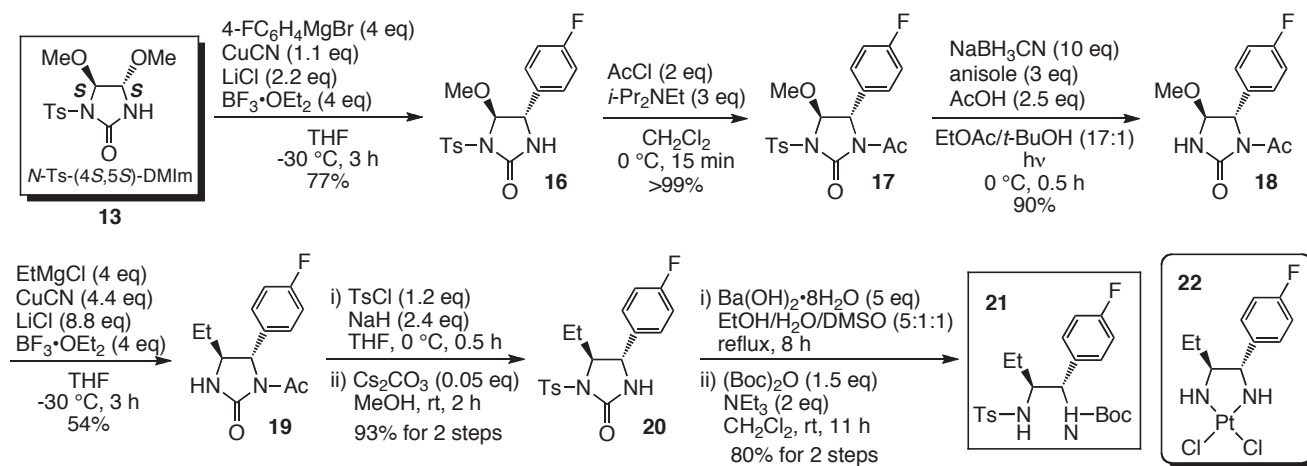
c) Isolated yields.

d) Determined by <sup>1</sup>H NMR.



**Scheme 3**

gave a 54% yield of *trans*-4-ethyl-5-(4-fluorophenyl)-2-imidazolidinone (**19**), accompanied by a *cis*-adduct (9%)<sup>14</sup> and the recovered **18** (26%). Smooth tosylation and deacetylation followed by hydrolytic ring-opening with Ba(OH)<sub>2</sub>·8H<sub>2</sub>O in a mixture of EtOH, H<sub>2</sub>O and DMSO (5:1:1), with subsequent *N*-Boc protection, afforded the (3*S*,4*S*)-*N,N'*-diprotected diamine **21** in an 80% yield in 2 steps, and both of the protecting groups could be easily removed under acidic condition (TFA for the Boc group) and reductive condition (sodium naphthalenide for tosyl group), respectively.



Scheme 4

In conclusion, we established an efficient method for the predominant preparation of (4*S*,5*S*)-4,5-dimethoxy-2-imidazolidinone (DMIm) via the Fe(III)-catalyzed diastereoselective oxidation of chiral 2-imidazolone, 1-[(1*S*,2*R*)-2-*exo*-alkoxyapocamphanecarbonyl]-2-imidazolone, by aqueous H<sub>2</sub>O<sub>2</sub> up to 94% d.e., with facile purification accomplished via column chromatography, followed by simple and convenient conversions. The obtained *N*-tosyl-(4*S*,5*S*)-DMIm (**13**) proved to be a versatile chiral synthon for 1,2-diamines; the synthesis of a (1*S*,2*S*)-1,2-diamino-1-(4-fluorophenyl)butane derivative (**21**) had a platinum complex that showed potent antitumor activity. Mechanistic studies for the Fe(III)-catalyzed oxidation of 2-imidazolone and further synthetic application using chiral DMIm are underway.

## ACKNOWLEDGEMENTS

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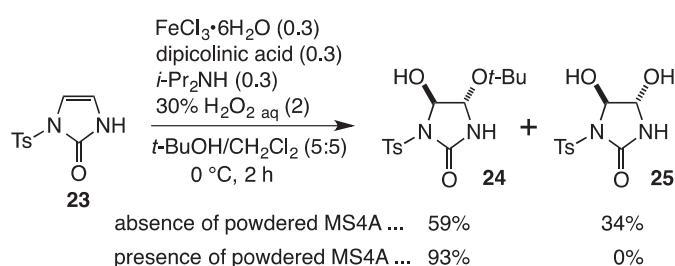
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  7. General procedure for the FeCl(dipic)(H<sub>2</sub>O)<sub>2</sub>-catalyzed oxidation of 1-[(1*S*,2*R*)-2-*exo*-alkoxyapocamphanecarbonyl]-2-imidazolone by hydrogen peroxide in the presence of MeC(OMe)<sub>3</sub>: The mixture of FeCl(dipic)(H<sub>2</sub>O)<sub>2</sub> (7.7 mg, 0.1 eq; the granule was pulverized by microspatula) and *i*-Pr<sub>2</sub>NH•HCl (3.6 mg, 0.1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (2.3 mL) was stirred at 25 °C for 30 min and 2-imidazolone (0.2648 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.4 mL) was added to the mixture. After pouring MeC(OMe)<sub>3</sub> (1.6 mL) into the mixture at 0 °C was added H<sub>2</sub>O<sub>2</sub>-urea (37.4 mg, 1.5 eq) at once with stirring at 25 °C. After the consumption of 2-imidazolone (monitored by TLC), the reaction mixture was passed through a SiO<sub>2</sub> pad to remove the iron species and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on SiO<sub>2</sub> (hexane/EtOAc; 9/1 to 5/5) to yield the 4-methoxy-5-hydroxy-2-imidazolidinones.
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  9. General procedure for the Fe(III)-catalyzed oxidation of 1-[(1*S*,2*R*)-2-*exo*-alkoxyapocamphanecarbonyl]-2-imidazolone by hydrogen peroxide in the presence of *t*-BuOH (Table 2, entries 1 and 2): To a suspension of FeCl<sub>3</sub>•6H<sub>2</sub>O (10.2 mg, 0.1 eq) and dipicolinic acid (6.3 mg, 0.1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and *t*-BuOH (0.5 mL) was added *i*-Pr<sub>2</sub>NH (10.7 μL, 0.2 eq) and the suspension was stirred at 25 °C for 30 min. After the addition of 1-[(1*S*,2*R*)-2-*exo*-alkoxyapocamphanecarbonyl]-2-imidazolone (**6a,b**) (0.38 mmol), powdered molecular sieves 4A (378 mg), CH<sub>2</sub>Cl<sub>2</sub> (2.9 mL) and *t*-BuOH (2.9 mL) to the catalyst mixture with stirring for 10 min at 25 °C, an aqueous H<sub>2</sub>O<sub>2</sub> solution (30%; 77.4 μL, 2 eq) in *t*-BuOH (0.7 mL) was added to the reaction mixture over 1 h using a syringe pump at 0 °C followed by stirring for 30 min at 0 °C. After the consumption of 2-imidazolone (monitored by TLC), the reaction mixture was passed through a SiO<sub>2</sub> pad (EtOAc as eluent) to quench the reaction and the eluent was then evaporated *in vacuo* followed by flash column



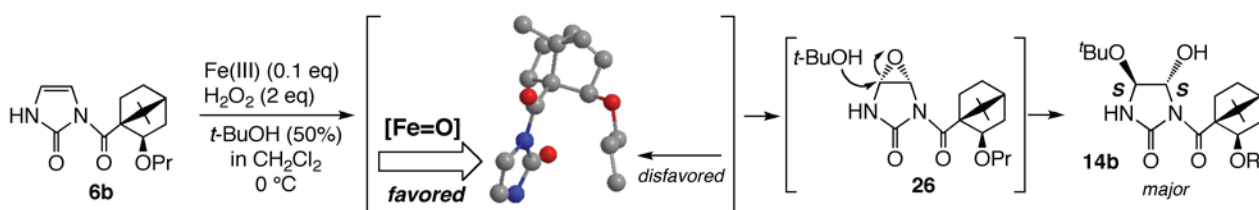
chromatography on silica gel ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ ; 95/5 to 85/15) to yield (4*S*,5*S*)-1-[(1*S*,2*R*)-2-*exo*-alkoxyapocamphanecarbonyl]-4-*tert*-butoxy-5-hydroxy-2-imidazolidinone (**14a,b**) predominantly, along with the corresponding (4*R*,5*R*)- isomer (**15a,b**).

10. From the preliminary finding as follows: the treatment of *N*-tosyl-2-imidazolone (**23**) with aqueous hydrogen peroxide solution (30%) in the presence of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , dipicolinic acid and diisopropylamine using a *t*-BuOH/ $\text{CH}_2\text{Cl}_2$  (1:1) mixture as a solvent yielded 4-*tert*-butoxy-5-hydroxy- (**24**) and 4,5-dihydroxy-2-imidazolidinone (**25**). The prior addition of powdered MS4A to the reaction mixture before the addition of 30%  $\text{H}_2\text{O}_2$  aq dramatically decreased the 4,5-dihydroxy adduct, and increased the 4-*tert*-butoxy-5-hydroxy-product (Scheme 5).



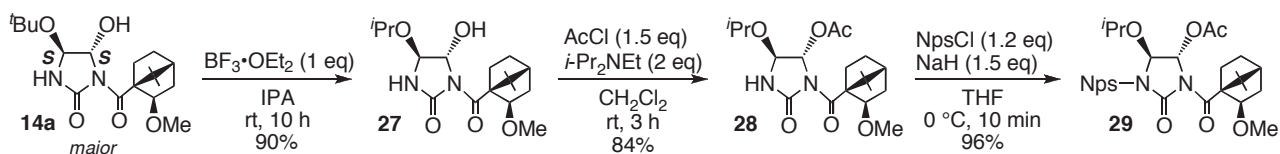
Scheme 5

11. The observed stereoselectivity is consistent with the postulation that iron oxide species approach from the less hindered face of 2-imidazolone to form epoxide **26** followed by the an anti-periplanar attack of alkoxy group to give the (4*S*,5*S*)-product predominantly (Scheme 6).



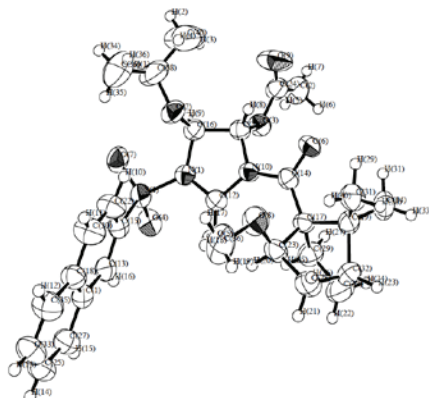
Scheme 6

12. Absolute configuration of **14a** was determined by the X-ray crystallographical analysis of compound **29**, derived from **14a** (Scheme 7), as depicted in Figure 1. The X-ray crystallographical data of **29** (CCDC number: 1016706) can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).



Scheme 7





**Figure 1.** ORTEP drawing of the compound **29**

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14. We speculate that the attack of ethylcuprate toward the acyliminium ion intermediate was not effectively controlled by the vicinal 4-fluorophenyl group to form *cis*-adduct as a minor product.