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Graphical Abstract

Straightforward synthesis of 4,5-bifunctionalized 1,2-oxazinanes via Lewis acid promoted regio- and stereo-selective nucleophilic ring-opening of 3,6-dihydro-1,2-oxazine oxides

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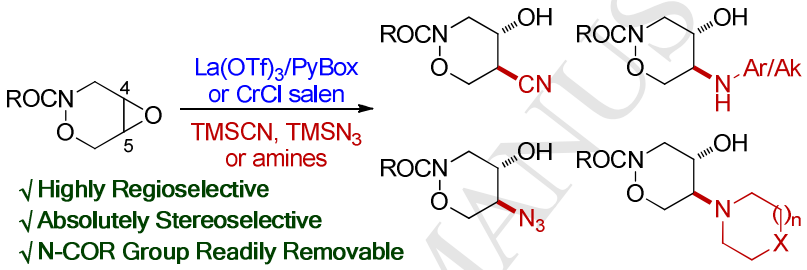

Lewis acid catalysis enabled highly selective ring-opening of 3,6-dihydro-1,2-oxazine oxide with nucleophiles gives rise to valuable functionalized 1,2-oxazinanes with readily removable *N*-COR group.

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Straightforward synthesis of 4,5-bifunctionalized 1,2-oxazinanes via Lewis acid promoted regio- and stereo-selective nucleophilic ring-opening of 3,6-dihydro-1,2-oxazine oxides

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Regioselective cyanide addition to epoxide

ABSTRACT

Functionalized 1,2-oxazinanes are interesting and valuable heterocycles with potential applications in synthetic and medicinal chemistry. A straightforward strategy for quick access to unprecedented *trans*-4-hydroxyl-5-azido/cyano/amino 1,2-oxazinanes are developed: *N-COR* 3,6-dihydro- 1,2-oxazine oxides are prepared with ease from related dihydro- 1,2-oxazines and opened by nucleophiles $TMSN_3$, TMSCN and aryl/alkyl amines. Appropriate Lewis acid catalysts are found playing a vital role for both reaction rate and regioselectivity. The *N-COR* group can be removed under mild conditions to provide highly desirable NH 1,2-oxazinanes inaccessible via previous methods.

1. Introduction

1,2-oxazinane or alternative tetrahydro 1,2-oxazine is a class of unique six-membered heterocycles containing an endocyclic N-O moiety which can be found in several bioactive natural products and synthetic molecules,[1] as exampled by **FR900482**,[2] **FR66979**[3] and their derivatives **FK973**,[4] **FK317**[5] (not shown), **Phyllantidine**,[6] **Alsmaphorazine A/B**[7] (Figure 1). It is also a useful intermediate in synthesis particularly for 1,4-amino alcohols.[8]

Recently, the synthesis of 1,2-oxazinane attracted considerable attention and several elegant methods have been developed. Roughly, these methods fall in two categories, namely (formal)/[3+3] cycloadditions of nitrones **1** with a 3-carbon synthon **2**, **4** or **6** (Scheme 1a) and amine catalyzed aldehyde α-oxyamination-cyclization casacade with nitroso compounds (Scheme 1b). Archambeau[9] and Rawal[10] groups disclosed conditions that promoted [3+3] cycloaddition of nitrone **1** with oxyallyl cations in situ generated from cyclic/acyclic α-tosyloxy ketones **2**, achieving functionalized 1,2-oxazinanes **3**. Since reported by Kerr et al in 2003,[11] Lewis acid promoted [3+3] cycloaddition reaction of nitrones **1** with cyclopropanes **4** has been advanced greatly,[12] especially in Sibi[13] and Tang[14] laboratories with respect to asymmetric catalytic version that give rise to enantiomerically pure poly-substituted 1,2-oxazinanes **5**. Doyle and co-workers developed transition metal catalyzed formal [3+3] cycloadditions of enoldiazo compounds **6** with nitrones to generate multiple substituted 3,6-dihydro-1,2-ozaxines **7** which can be converted into related 1,2-oxazinanes readily.[15] As pioneered by Yamamoto group,[16] domino reactions enabled by enamine catalysis also provide facile accesses to 1,2-oxazinanes. Enantiomeric pure 1,2-oxazanes **10** were synthesized efficiently in Zhong's laboratory through *L*-proline catalyzed reaction of enals **9** with nitroso arenes **8**.[17] Baidya and colleagues were able to convert dial **11** and nitroso compounds **8** into optically pure oxazinanes **12** in one pot by using L-proline as enamine catalyst.[18] A dual-organocatalyst-promoted asymmetric cascade devised by Sun and Lin group realized rapid construction of densely functionalized 1,2-oxazinanes **16** via sequential assembling of **8** with aliphatic aldehydes **13**, enals **14**, aryl amines **15**.[19] Additionally, several other elegant yet related methods appeared in the literature include Yu's catalytic asymmetric intramolecular aza-Michael addition approach,[20] Albrecht's domino aza-Michael/Michael addition approach,[21] and Pagenkopf's [4+2] cycloaddition of donor–acceptor cyclobutanes with nitrosoarenes.[22]

However, these methods still suffer from imperfections such as narrow substrate scope and limited product substitution patterns, especially removal of the unavoidable aryl or alkyl group from Nitrogen would encounter extraordinary difficulties.

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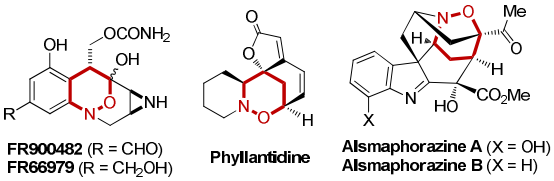
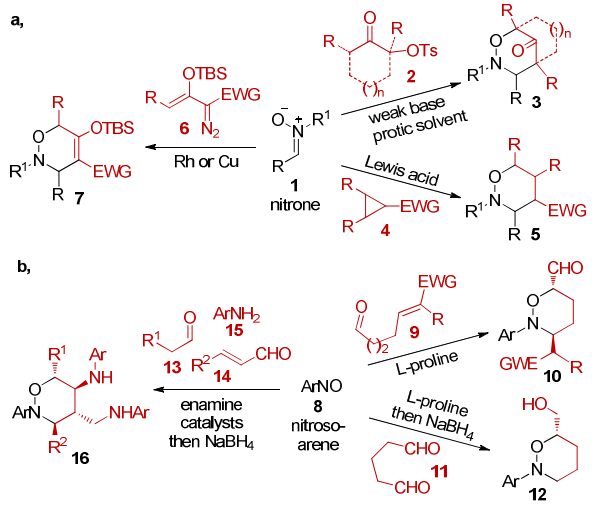
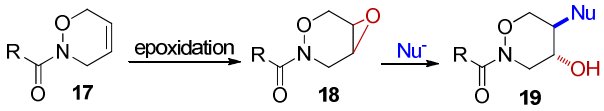


Figure 1. Examples of natural and synthetic products containing 1,2-oxazinane



Scheme 2. Recent progress in 1,2-oxazinane synthesis by using nitrone and nitrosoarene



Scheme 3. Proposed strategy for functionalized 1,2-ozaxinane synthesis from 3,6-dihydro-1,2-oxazine

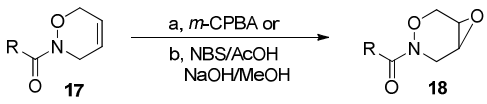
Therefore complementary strategy that can provide novel 1,2-oxazinanes in efficient manner is highly demanded. We envisioned that simple *N*-COR dihydro-1,2-oxazine like **17**, readily obtained from [4 + 2] cycloaddition of acyl nitroso compound with diene,[23] could serve as a facile starting point for this purpose as alkene group can participate in diverse chemical transformations. One straightforward approach is epoxidation of **17** followed by epoxide-opening using diverse nucleophiles to afford 4,5-difunctionalized 1,2-oxazinanes **19**. Based on above analysis, we initiated a research program at this direction and report our preliminary results herein.

2. Results and discussion

2.1. Synthesis of N-COR-1,2-oxazine oxide

Our research began with the synthesis of *N*-COR 3,6-dihydro-1,2-oxazine oxides **18**. Treatment of 3,6-dihydro-1,2-oxazine **17a** with *m*-CPBA afforded **18a** in 56% yield. Alternatively, bromoacetoxylation with NBS/AcOH and subsequent deacetylation-cyclization with NaOH in MeOH can provide the same epoxide in a higher overall yield of 78% (Scheme 3). Several homologues **18b-d** can also be made conveniently through this two-step protocol. The bromoacetoxylation intermediate of **17c** was isolated and NMR analysis demonstrated it was a *ca.* 1/1 regioisomeric mixture of two *trans*-1,2-bromoacetates, indicating that the C-C double bond in **17** is almost imperceptibly biased in stereo-electronical nature for the bromoacetoxylation.

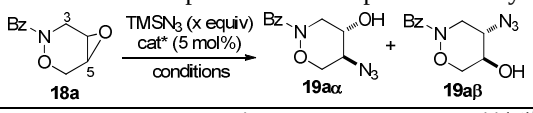
2.2. Azidolysis of the N-COR-1,2-oxazine oxide



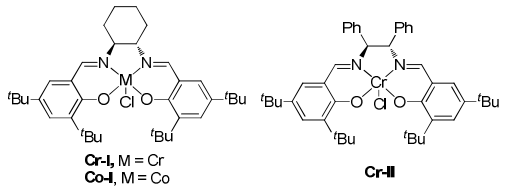
R: Ph (**17a/18a**), 4-MeOPh (**17b/18b**), 2-BrPh (**17c/18c**), 4-ClPh (**17d/18d**), 4-CNPh (**17e/18e**), 4-NO_2Ph (**17f/18f**), BnO (**17g/18g**), ^{t}BuO (**17h/18h**)

Scheme 1. Preparation of *N*-COR 1,2-oxazinane epoxide

Table 1. Conditions optimization for epoxide azidolysis[a]



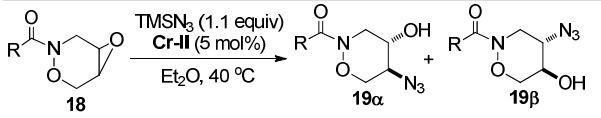
entry	x equiv	cat*	conditions Solv	T (°C)	time	Yield (%)[b] (α/β)[c]
1	1.1	**Cr-I**	DCM	40	3 d	12 (-)
2	1.1	**Cr-I**	THF	60	3 d	36 (-)
3	1.1	**Cr-I**	Et_2O	40	3 d	85 (3.1/1)
4	2.0	**Cr-I**	Et_2O	40	3 d	94 (3.6/1)
5	2.0	**Cr-I**	$^iPr_2O$	40	4 d	87 (2.8/1)
6	2.0	**Cr-I**	$^iPr_2O$	80	12 h	98 (2.1/1)
7	2.0	**Cr-I**	MTBE	80	12 h	94 (3.0/1)
8	2.0	**Cr-I**	DME	80	24 h	70 (2.5/1)
9	1.1	**Co-I**	Et_2O	40	3 d	45 (-)
10	1.1	**Cr-II**	Et_2O	40	3 d	80 (8.4/1)
11	2.0	**Cr-II**	Et_2O	40	3 d	88 (8.0/1)



[a]Conditions: **18a** (60.7 mg, 0.3 mmol), $TMSN_3$ (1.1 or 2.0 equiv), cat* (15.0 μmol), dry solvent (1.0 mL), 40 °C - 80 °C, N_2, in Schlenk flask, then $^nBu_4NF$ (0.45 mmol). [b]Isolated yield. [c]NMR ratio.

With the establishment of a robust protocol for the preparation of epoxide substrates, we set out to explore the azidolysis of the epoxide. Initial studies showed that NaN_3 was not a competent reagent to open up epoxide **18a** in MeOH/H_2O (v/v 8/1); the $TMSN_3/BF_3{\cdot}Et_2O$ combination in CH_2Cl_2 (DCM) decomposed the oxazine oxide substrate completely to a non-productive mixture, showing a quite different reactivity in comparison with its carbon congener cyclohexene oxide.[24] Finally, chromium salen-Cr(III) complex **Cr-I** was identified as an effective Lewis acid to promote this azidolysis with $TMSN_3$ (Table 1). Although the **Cr-I** (5 mol%) catalyzed reaction was very slow in DCM and tetrahydrofuran (THF), it did proceed smoothly in dry ether at 40 °C and completed in 3 days to give **19a** in 85% yield as an α/β 3.1/1 regio isomeric mixture (Table1 entries 1, 2 vs entry 3). **19aα** arises from the nucleophilic backside attack of azide anion at C5 while **19aβ** from the attack at C4. Increasing the amount of $TMSN_3$ from 1.1 equiv to 2.0 equiv resulted in a slightly improved yield with a similar α/β ratio (entry 4: 94% yield, 3.6/1). Isopropyl ether ($^iPr_2O$) worked equally well as a solvent (entry 5: 87% yield, α/β 2.8/1) and enhancement of the temperature to 80 °C accelerated this epoxide-opening process immensely that finished up in less than 12 h giving an increased yield albeit in conjunction with a decreased regioselectivity (entry 6: 98% yield, α/β 2.1/1). Methyl *tert*-butyl ether (MTBE)

Table 2. The electronic effects of the *N*-acyl group[a]



entry	R	time	product	yield (%)[b] (α/β)[c]
1	Ph	3 d	**19a**	80 (8.4/1)
2	4-MeOPh	3 d	**19b**	93 (1/0)
3	2-BrPh	6 d	**19c**	90 (6.1/1)
4	4-ClPh	5 d	**19d**	86 (7.7/1)
5	4-CNPh	6 d	**19e**	93 (6.7/1)
6	4-NO_2Ph	7 d	**19f**	66 (5.0/1)
7	BnO	3 d	**19g**	87 (8.5/1)
8	^{t}BuO	4 d	**19h**	72 (14.2/1)

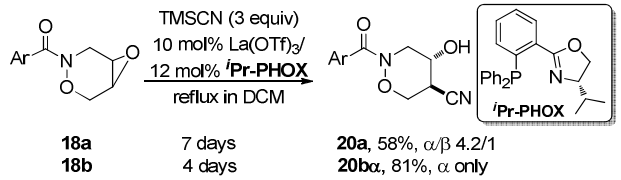
[a]Conditions: **18** (0.3 mmol), $TMSN_3$ (38 mg, 0.33 mmol), **Cr-II** (11.0 mg, 15.0 μmol), dry Et_2O (1.0 mL), 40 °C, N_2, in Schlenk flask, then ^{n}Bu_4NF (0.45 mmol). [b]Isolated yield. [c]NMR ratio.

showed comparable efficacy but dimethoxylethane (DME) turned out to be inferior in regards of reaction yield and selectivity (Entries 7 and 8). Using salen-Co(III) complex **Co-I** in place of **Cr-I** led to a drastic decrease in catalytic effectiveness (Entry 9), however complex **Cr-II,** carrying a more flexible non-cyclic diimine as the supporting ligand, improved the regioseletivity dramatically to α/β > 8.0/1 (entries 10 and 11).

With **Cr-II** as the Lewis acid catalyst, the electronic effects of the *N*-COR group were investigated by comparing the reaction outcomes of **18a-h** (Table 2). **18b** bearing electron-releasing *p*-methoxyl group delivered exclusively a single regio isomer **19b**α in 93% yield (entry 2). **18c-f** with electron withdrawing groups 2-Br, 4-Cl, 4-CN and 4-NO_2 afforded comparably high yields with the exception of the moderate yield of 66% for **19f**, whereas the α/β ratio dropped into the 5.0-7.7/1 range (entries 3-6). To our delight, epoxides **18g** and **18h** with the two most common amine protecting groups were also efficiently azidolysised with excellent regioselectivities under the catalytic effect of complex **Cr-II** (entries 7 and 8).

2.3. Cyanide addition to the N-acyl-1,2-oxazine oxide

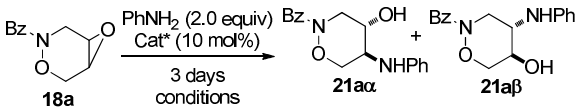
Cyanide addition to epoxides **18** was also intensively attempted and eventually the La(OTf)$_3$/iPr-PHOX combination was identified as a feasible catalysis system to realize this transformation by using TMSCN as the cyanide source. When carried out in the presence of 10 mol% La(OTf)$_3$ and 12 mol% ligand iPr-PHOX, the reaction of **18a** proceeded in a slow and selective manner to give an α/β 4.2/1 regio isomeric mixture of trans-adduct **20a** in 58% yield upon workup with TBAF. Surprisingly, it was found that **18b** is a better substrate than **18a** providing an exclusive α regioselectivity and an improved yield of 81% in a shortened reaction time (Scheme 4), but the underlying reasons keep elusive at present stage.



18a 7 days **20a**, 58%, α/β 4.2/1
18b 4 days **20b**α, 81%, α only

Scheme 4. Lewis acid catalyzed epoxide-opening with TMSCN

Table 3. Brief optimization of aniline addition to the epoxide[a]



entry	Cat*	Solv	T (°C)	Yield (%)[b] (α/β)[c]
1[d]	-	MTBE	80	67 (2.0:1)
2	**Cr-I**	MTBE	80	89 (3.0:1)
3[d]	**Cr-I**	MTBE	40	65 (4.1:1)
4	**Cr-I**	^{i}Pr_2O	40	80 (5.0:1)
5[d]	**Cr-I**	Et_2O	40	78 (5.7:1)
6[d,e]	**Cr-I**	DME	40	54 (9.3:1)
7	**Cr-II**	DME	40	81 (8.0:1)

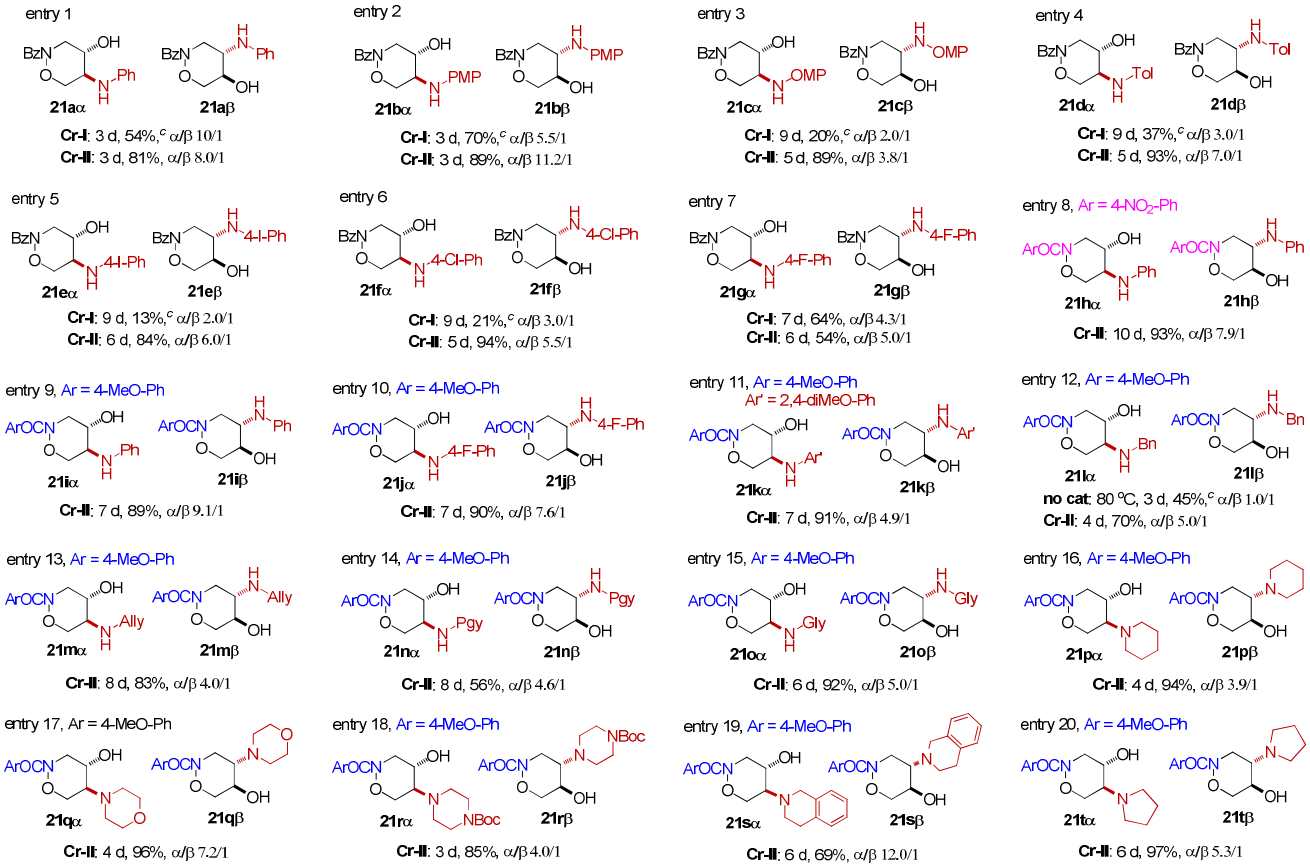
[a]Conditions: **18a** (0.3 mmol), $PhNH_2$ (56 mg, 0.6 mmol), Cat* (30.0 μmol), dry solvent (1.0 mL), 40 °C or 80 °C, 3 d, N_2, in Schlenk flask. [b]Isolated yield. [c]NMR ratio. [d]Epoxide detectable via TLC. [e]4 days instead.

2.4. Amine addition to the N-acyl-1,2-oxazine oxide

Next, we turned our attention to the highly valuable amine addition to 1,2-oxazinane epoxide **18** (Table 3), and quickly disclosed that the un-catalyzed reaction of **18a** with excess aniline (2 equiv) did occur in hot MTBE (80 °C) albeit slowly. After 3 days, an incomplete reaction mixture was observed from which **21a** was isolated in a form of **α/β** 2.0/1 inseparable isomeric mixture in 67% yield (entry 1). Catalytic amount of **Cr-I** improved the reaction rate and regioselectivity noticeably under the same conditions (entry 2, 89% yield, **α/β** 3.0/1). When the reaction was performed at 40 °C with MTBE, ^{i}Pr_2O or Et_2O as solvent, the ratio of two regioisomers increased to 4.1-5.7/1 favoring the C5 adduct **21aα** (entries 3-5). With DME as solvent, a further improvement of α/β ratio to 9.3/1 was obtained although accompanied with a slightly decreased reaction rate (entry 6). Finally, to our delight, the use of **Cr-II** as catalysis again showed superiority that remarkably accelerated the epoxide-opening process rendering the starting epoxide **18a** completely consumed in 3 d to give both a high yield and an excellent selectivity at the same time (entry 7: 81% yield, α/β 8/1).

Then, a series of substituted anilines were investigated as *N*-nucleophiles for this reaction using DME as reaction medium (Table 4). In most cases, the chromium salen complex **Cr-II** was superior to its congener **Cr-I** (entries 1-7). **Cr-II** was able to boost the reactions to completion in several days furnishing higher yields and α/β ratio, in contrast, the related reactions with **Cr-I** as catalyst normally proceeded much slower without full conversion even in longer time to afford corresponding cyclic trans vicinal amino alcohols **21a-21g** in inferior yield and selectivity. It seems that electronic donating group at the aniline benefits the reaction rate. The reaction of **18a** with *p*-methoxyl-aniline catalyzed by **Cr-II** finished 89% yield of **21b** in 3 days, while the same reaction with para-fluoride took 6 days to complete giving **21g** in only 54% yield (entry 2 vs 7); moreover, with stronger electron withdrawing 4-nitro-aniline, the reaction didn't take place at all in the presence of 10 mol% **Cr-I** (not shown). The decreased reaction rate and regioselectivity (5 d, **21cα/21cβ**: 5.0/1) for *o*-methoxyl-aniline ($OMPNH_2$) in comparison with those for its para congener $PMPNH_2$ might reflect the steric impact of nucleophile (entry 3 vs 2).

Table 4. Epoxide opening with aryl and alkyl amines[a, b]



[a]Conditions: **18a**, **18b** or **18f** (0.3 mmol), amine (0.6 mmol), **Cr-I or Cr-II** (30.0 μmol), dry solvent (1.0 mL), 40 °C or 80 °C, 3 d, N_2, in Schleck flask. [b]Isolated yield and NMR ratio were recorded. [c]Epoxide detectable via TLC.

In line with the trend previously observed for azidolysis with $TMSN_3$ (Table 2), epoxide **18f** was also less reactive than **18a** in **Cr-II** promoted reaction with aniline and took much longer time (10 d) to achieve a full conversion (entry 8 vs 1). Accordingly, **18b** led to a significant improvement in regioselectivity to α/β: 9.1/1 while a high yield of 1,2-amino alcohols **21i** was remained (entry 9). Alkylamines such as benzylamine ($BnNH_2$), allylamine ($AllyNH_2$) and propargylamine ($PgyNH_2$) are also feasible nucleophiles to open up the epoxide group under the promotion of chromium complex **Cr-II**, and the related adducts **21l-n** were collected with slight decline in yields and α/β ratio (entries 12-14). In the absence of **Cr-II** as catalyst, the same reaction of $BnNH_2$ with **18b** was slow even in 80 °C and delivered no regio discrimination, approving that the epoxide activating effect of the Lewis acidity tolerated stronger Lewis basicity of alkylamines as well (entry 12). Interestingly, less nucleophilic ethyl glycinate ($GlyNH_2$) reacted with **18b** more efficiently giving rise to **21o** in a 92% combined yield with a 5.0/1 regioselectivity (entry 15). *N*-heterocycles piperidine, morpholine, mono *N*-protected piperazine, tetrahydroisoquinoline and pyrrolidine all underwent this **Cr-II** catalyzed epoxide ring opening reaction with **18b** to provide biologically valuable alkaloids **21p-t** in high to excellent yields with good regioselectivities (entries 16-20).

In the absence of Cr-salen complex as catalyst, the dramatic decrease or totally disappearance of regioselectivity was observed for the amination of **18a** and **18b** with aniline and benzyl amine respectively, indicating that the C4 and C5 of the epoxide hold similar electronic properties, in line with previous postulation based on bromoacetoxylation of **17a**. One can imagine that, upon activation of the epoxide by a Lewis acid flanked by a big-sized ligand, the steric or/and electronic interactions between the *N*-substituent and the catalytic complex will define the transition-state conformation, leading to unsymmetrical activation of the two otherwise electronically symmetric C-O bonds and increased α/β ratio. Nevertheless, calculations will be benefit for insightful understanding of this catalytic reaction.

2.5. Structure determination

Our attempt to determine the structures of isomeric pairs of **19α/β**, **20α/β** and **21α/β** only by NMR analysis failed and therefore our efforts were turn to crystallography. Nice crystalline solids of **19aα** and **20bα** were obtained after several careful trials of crystallization operations. To our delight, treatment of **21iα** with triphosgene and pyridine in DCM produced solid oxazolidinone **22iα** from which single crystal was also grown with ease. X-ray diffraction experiments established

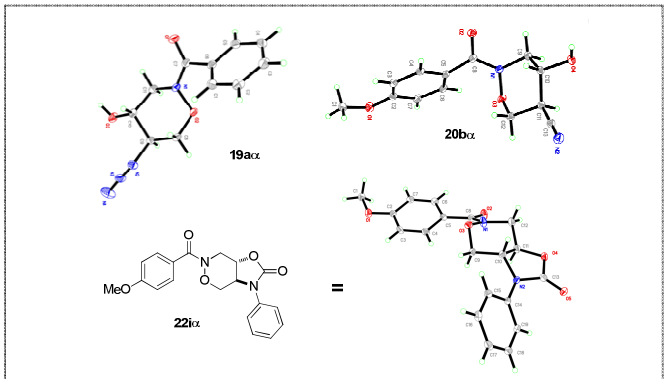
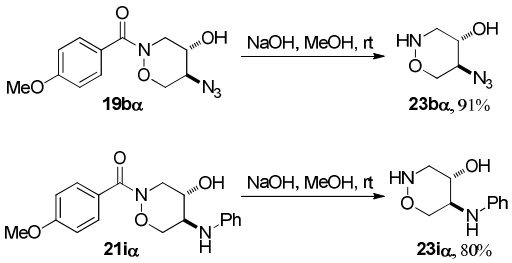


Figure 2. X-ray structures of **19aα**, **20bα** and **22iα**

the structures of the major isomers of ring opening reactions **19aα**, **20bα** and **21iα** to be the C5-adducts as shown in Figure 2. Consequently, the minor regioisomers were the corresponding C4-adducts as shown.

2.6. Removal of the N-protecting group

Removal of the 4-methoxybenzoyl *N*-protecting group in these products would give rise to valuable small *N*-heterocycles ready for further derivatization. For this purpose, **19bα** and **21iα** were selected for examples and treated with NaOH in MeOH, the hydrolysis of the amide bond proceeded smoothly in room temperature and 4-hydoxyl-5-azido-1,2-oxazinane **23bα** and 4-hydoxyl-5-phenylamino-1,2-oxazinane **23iα** were achieved respectively in high yields (Scheme 5).



Scheme 5. Showcases of *N*-aroyl deprotection

3. Conclusions

In summary, a fast entry toward valuable *trans*-4-hydroxyl-5-azido/cyano/amino 1,2-oxazinanes have been developed that features an efficient epoxidation of readily accessible *N-COR* 3,6-dihydro-1,2-oxazines and a subsequent epoxide ring-opening with nucleophiles $TMSN_3$, TMSCN and amines. Appropriate Lewis acid catalysts are critical for these regioselective processes. For azide and cyanide addition, salen-Cr(III) complex and $La(OTf)_3$/^{i}Pr-PHOX are essential for the reactions to occur respectively. For the aminolysis of the 3,6-dihydro-1,2-oxazine oxides with aryl and alkyl anines, salen-Cr(III) complexes as catalysts, particularly **Cr-II**, improve the transformation remarkably in two aspects: increasing the reaction rate by a large margin that enables a much milder reaction temperature possible, and raising the α regioselectivity to a level that renders the method synthetically useful. The removal of the *N-a*royl protection group is achieved with efficiency to release the corresponding free 1,2-oxazinanes, potentially useful *N*-heterocycle building blocks in medicinal chemistry.

4. Experimental section

4.1. General information

NMR spectra were recorded using Bruker AV-300 / AV-400 spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets), coupling constants (Hz) and integration. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator and/or by exposure to phosphormolybdic acid/alkalinity potassium permanganate/ninhydrine followed by brief heating with a heat gun. Liquid chromatography (flash chromatography) was performed on 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under nitrogen or argon with anhydrous solvents in oven-dried glassware, unless otherwise noted. All reagents were commercially obtained and, where appropriate, purified prior to use.

4.2. Azidolysis

4.2.1. Procedure

To a 10 mL sealed tube equipped with a stir bar were added **Cr-II** (11.0 mg, 15.0 μmol), **18** (0.3 mmol), $TMSN_3$ (38.0 mg, 0.33 mmol) and anhydrous Et_2O (1.0 mL). Then the solution was evacuated and refilled with N_2 three times and stirred for 3 - 7 days at 40 °C. When completed as indicated by TLC, the reaction mixture was concentrated in vacuo. TBAF (0.45mL, 1.0 M, 0.45mmol) was added and the reaction mixture was stirred for 5 min. The solution was diluted with ethyl acetate (10.0 mL) and extracted with ethyl acetate (3 x 50.0 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Purification via flash column chromatography with silica gel (eluting with PE/EA = 2/1 (v/v)) yielded **19α** and **19β**

*4.2.2. Characterization of **19***

*4.2.2.1 **19aα** and **19aβ***

Inseparable mixture, white waxy solid (total 59.1 mg, 80% yield); m.p. 90-91 °C. The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 8.4 : 1. **19aα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 4.34 (d, *J* = 13.9 Hz, 1H), 4.21 – 4.13 (m, 1H), 3.94 – 3.86 (m, 1H), 3.77– 3.54 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.77, 132.59, 131.61, 128.89, 128.22, 71.29, 67.16, 60.28, 47.96. **19aβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 4.50 (d, *J* = 9.52 Hz, 1H), 4.21 – 4.13 (m, 1H), 3.94 – 3.86 (m, 1H), 3.77 – 3.54 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.77, 132.59, 131.61, 128.89, 128.22, 71.29, 67.16, 60.28, 47.96. HRMS (ESI) *m/z* Calculated for $C_{11}H_{13}N_4O_4^+[M + H]^+$ 249.0982, found 249.0976.

*4.2.2.2 **19bα***

Yellow oil (α only,78.0mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.35 (d, *J* = 12.1 Hz, 1H), 4.16 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.94 – 3.88 (m, 1H), 3.85 (s, 3H), 3.74 – 3.55 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.70, 162.45, 131.47, 124.41, 113.47, 71.24, 67.33, 60.42, 55.53, 48.04. HRMS (ESI) *m/z* Calculated for $C_{12}H_{15}N_4O_4^+[M + H]^+$ 279.1088, found 279.1083.

*4.2.2.3 **19cα** and **19cβ***

Inseparable mixture, yellow oil (total 88.4 mg, 90% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 6.1 : 1. **19cα**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 1H), 7.40 – 7.26 (m, 3H), 4.36 (d, *J* = 13.1 Hz, 1H), 4.18 – 4.05 (m, 1H), 3.98 – 3.72 (m, 2H), 3.69 – 3.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.13, 136.37, 132.96, 131.02, 127.96, 127.37, 119.04, 71.60, 66.90, 60.03, 46.60. **19cβ**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 1H), 7.40 – 7.26 (m, 3H), 4.54 (d, *J* = 15.2 Hz, 1H), 4.18 – 4.05 (m, 1H), 3.98 – 3.72 (m, 2H), 3.69 – 3.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.13, 136.37, 132.96, 131.02, 127.96, 127.37, 119.04, 71.60, 66.90, 60.03, 46.60. HRMS (ESI) *m/z* Calculated for $C_{11}H_{11}BrN_4NaO_3^+[M + Na]^+$ 348.9907, 350.9886, found 348.9909, 350.9890.

*4.2.2.4 **19dα** and **19dβ***

Inseparable mixture, yellow oil (total 73.1 mg, 86% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 7.7 : 1. **19dα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66

– 7.61 (m, 2H), 7.43 – 7.35 (m, 2H), 4.37 – 4.28 (m, 1H), 4.16 (dd, *J* = 11.6, 3.5 Hz, 1H), 3.99 – 3.82 (m, 2H), 3.78 – 3.69 (m, 1H), 3.69 – 3.62 (m, 1H), 3.61 – 3.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.50, 137.81, 130.66, 130.44, 128.43, 71.32, 66.89, 59.99, 47.68. **19dβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 2H), 7.43 – 7.35 (m, 2H), 4.53 – 4.43 (m, 1H), 4.08 (dd, *J* = 11.5, 3.9 Hz, 1H), 3.99 – 3.82 (m, 2H), 3.78 – 3.69 (m, 1H), 3.69 – 3.62 (m, 1H), 3.61 – 3.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.50, 137.81, 130.66, 130.44, 128.43, 71.32, 66.89, 59.99, 47.68. HRMS (ESI) *m/z* Calculated for $C_{11}H_{11}ClN_4NaO_3^+$[M + Na]$^+$ 305.0412, found 305.0411.

4.2.2.5 ***19eα*** *and* ***19eβ***

Inseparable mixture, yellow oil (total 69.0mg, 93% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 6.7 : 1. **19eα**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.67 (m, 4H), 4.30 (d, *J* = 13.2 Hz, 1H), 4.16 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.98 – 3.85 (m, 1H), 3.80 – 3.70 (m, 1H), 3.70 – 3.62 (m, 1H), 3.62 – 3.52 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.37, 136.84, 132.02, 129.37, 118.07, 114.81, 71.48, 66.65, 59.84, 47.51. **19eβ**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.67 (m, 4H), 4.46 (d, *J* = 9.6 Hz, 1H), 4.07 (dd, *J* = 12.2, 3.0 Hz, 1H), 3.98 – 3.85 (m, 1H), 3.80 – 3.70 (m, 1H), 3.70 – 3.62 (m, 1H), 3.62 – 3.52 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.37, 136.84, 132.02, 129.37, 118.07, 114.81, 71.48, 66.65, 59.84, 47.51. HRMS (ESI) *m/z* Calculated for $C_{12}H_{11}ClN_5NaO_3^+$[M + Na]$^+$ 296.0754, found 296.0752.

4.2.2.6 ***19fα*** *and* ***19fβ***

Inseparable mixture, yellow oil (total 75.2 mg, 66% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 5.0 : 1. **19fα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.7 Hz, 2H), 7.83 (d, *J* = 8.6 Hz, 2H), 4.32 (d, *J* = 12.9 Hz, 1H), 4.18 (d, *J* = 9.3Hz1H), 4.04 – 3.90 (m, 1H), 3.89 – 3.77 (m, 1H), 3.76 – 3.64 (m, 1H), 3.64 – 3.55 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.32, 149.41, 138.55, 129.94, 123.44, 71.55, 66.81, 59.89, 47.41. **19fβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.7 Hz, 2H), 7.83 (d, *J* = 8.6 Hz, 2H), 4.47 (d, *J* = 11.6Hz, 1H), 4.10 (d, *J* = 12.3Hz 1H), 4.04 – 3.90 (m, 1H), 3.89 – 3.77 (m, 1H), 3.76 – 3.64 (m, 1H), 3.64 – 3.55 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.32, 149.41, 138.55, 129.94, 123.44, 71.55, 66.81, 59.89, 47.41. HRMS (ESI) *m/z* Calculated for $C_{11}H_{11}N_5NaO_5^+$[M + Na]$^+$ 316.0652, found 316.0651.

4.2.2.7 ***19gα*** *and* ***19gβ***

Inseparable mixture, yellow oil (total 72.6 mg, 87% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 8.5 : 1. **19gα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 1H), 5.12 (s, 1H), 4.17 (dd, *J* = 11.7, 3.8 Hz, 1H), 4.03 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.70 – 3.54 (m, 1H), 3.54 – 3.46 (m, 1H), 3.44 – 3.32 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.76, 135.51, 128.69, 128.56, 128.20, 70.24, 68.32, 67.16, 60.51, 49.78. **19gβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 1H), 5.12 (s, 1H), 4.27 (dd, *J* = 12.1, 5.0 Hz, 1H), 4.03 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.70 – 3.54 (m, 1H), 3.54 – 3.46 (m, 1H), 3.44 – 3.32 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.76, 135.51, 128.69, 128.56, 128.20, 70.24, 68.32, 67.16, 60.51, 49.78. HRMS (ESI) *m/z* Calculated for $C_{12}H_{14}$ $NaN_4O_4^+$[M + Na]$^+$ 301.0907, found 301.0906.

4.2.2.8 ***19hα*** *and* ***19hβ***

Inseparable mixture, yellow oil (total 53.0 mg, 72% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 14.2 : 1. **19hα**: ^{1}H NMR (400 MHz, $CDCl_3$) 4.20 (dd, *J* = 11.0, 3.2 Hz, 1H), 4.05 (dd, *J* = 13.6, 3.9 Hz, 1H), 3.76 - 3.66 (m, 1H), 3.66 – 3.53 (m, 2H), 3.47 (s, 1H), 3.39 - 3.28 (m, 1H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.17, 82.74, 69.88, 67.59, 60.94, 50.09, 28.29. **19hβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (dd, *J* = 11.8, 4.0 Hz, 1H), 4.05 (dd, *J* = 13.6, 3.9 Hz, 1H), 3.76 - 3.66 (m, 1H), 3.66 – 3.53 (m, 2H), 3.47 (s, 1H), 3.39 - 3.28 (m, 1H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.17, 82.74, 69.88, 67.59, 60.94, 50.09, 28.29. HRMS (ESI) *m/z* Calculated for $C_9H_{16}N_4NaO_4^+$ [M + Na]$^+$ 267.1064, found 267.1069.

4.3. Cyanide addition

4.3.1. Procedure

To a 10 mL sealed tube equipped with a stir bar were added La(OTf)$_3$ (17.6 mg, 30.0 μmol), ^{i}Pr-PHOX (13.4 mg, 36.0 μmol), **18** (0.3 mmol), TMSCN (89.3 mg, 0.9 mmol) and anhydrous DCM (1.0 mL). Then the solution was evacuated and refilled with N_2 three times and stirred for 4 - 7 days at reflux. When completed as indicated by TLC, the reaction mixture was concentrated in vacuo. TBAF (0.45 mL, 1.0 M, 0.45mmol) and THF (1.0 mL) was added and the reaction mixture was stirred for 5 min. The solution was diluted with ethyl acetate (10.0 mL) and extracted with ethyl acetate (3 x 50.0 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Purification via flash column chromatography with silica gel (eluting with PE/EA = 2/1 (v/v)) yielded **20α** and **20β**

4.3.2. Characterization of ***20***

4.3.2.1 ***20aα*** *and* ***20aβ***

Inseparable mixture, white solid (total 40.7 mg, 58% yield); m.p. 98-99 ^{o}C. The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 4.2 : 1. **20aα:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 2H), 7.58 – 7.47 (m, 1H), 7.48 – 7.38 (m, 2H), 4.30 (dd, J = 11.7, 3.5 Hz, 1H),4.26 – 4.09 (m, 2H), 3.97 – 3.85 (m, 2H), 3.01 – 2.89 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.99, 132.26, 131.86, 128.88, 128.34, 117.45, 69.08, 64.38, 48.55, 34.27. **20aβ**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 2H), 7.58 – 7.47 (m, 1H), 7.48 – 7.38 (m, 2H),4.53 (dd, J = 13.7, 3.9 Hz, 1H). 4.26 – 4.09 (m, 2H), 3.85 – 3.75 (m, 1H), 3.62 – 3.53 (m, 1H),3.01 – 2.89 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.99, 132.26, 131.97, 128.95, 128.34, 117.45, 74.33, 65.51, 48.55, 33.48. HRMS (ESI) *m/z* Calculated for $C_{14}H_{15}NNaO_2^+$[M + Na]$^+$ 255.0740, found 255.0735.

4.3.2.2 ***20bα***

White solid (α only, 63.7 mg, 81%); m.p. 132-133 ^{o}C. ^{1}H NMR (400 MHz, DMSO) δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 5.94 (s, 1H), 4.33 (dd, *J* = 13.4, 3.8 Hz, 1H), 4.05 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.96 (td, *J* = 7.6, 3.9 Hz, 1H), 3.83 – 3.71 (m, 4H), 3.52 (dd, *J* = 11.3, 7.5 Hz, 1H), 3.05 (td, *J* = 8.1, 4.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 168.70, 161.66, 130.75, 124.52, 118.99, 113.41, 74.05, 64.28, 55.34, 42.82, 32.68. HRMS (ESI) *m/z* Calculated for $C_{13}H_{14}N_2NaO_4^+$ [M +Na]$^+$ 285.0846, found 285.0846.

4.4. Amine addition

4.4.1. Procedure

To a 10 mL sealed tube equipped with a stir bar were added **Cr-II** (22.0mg, 30.0 μmol), **18** (0.3 mmol), amine (0.6 mmol)

and anhydrous DME (1.0 mL). Then the solution was evacuated and refilled with N_2 three times and stirred for 3 - 10 days at 40 ^oC. When completed as indicated by TLC, the reaction mixture was concentrated in vacuo. The reaction mixture was purified via flash column chromatography with silica gel (eluting with PE/EA = 2/1 (v/v)) to yield **21α** and **21β**

*4.4.2. Characterization of **21***

*4.4.2.1 **21aα** and **21aβ***

Inseparable mixture, yellow viscous liquid (total 72.0 mg, 81% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 8.0 : 1. **21aα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, *J* = 9.3 Hz, 2H), 7.48 (t, *J* = 7.0 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 2H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 2H), 4.40 (d, *J* = 10.0 Hz, 1H), 4.25 – 4.08 (m, 1H), 4.05 – 3.87 (m, 2H), 3.68 – 3.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.79, 146.14, 133.01, 131.38, 129.68, 128.79, 128.18, 118.61, 113.40, 72.95, 65.76, 53.15, 47.96. **21aβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, *J* = 9.3 Hz, 2H), 7.48 (t, *J* = 7.0 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 2H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 2H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.25 – 4.08 (m, 1H), 4.05 – 3.87 (m, 2H), 3.68 – 3.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.79, 146.14, 133.01, 131.52, 129.68, 128.94, 128.18, 118.94, 113.76, 74.50, 67.56, 54.06, 47.96. HRMS (ESI) *m/z* Calculated for $C_{17}H_{19}N_2O_3^+[M + H]^+$ 299.1390, found 299.1386.

*4.4.2.2 **21bα** and **21bβ***

Inseparable mixture, yellow viscous liquid (total 87.4 mg, 89% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 11.2 : 1. **21bα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 1H), 7.53 – 7.43 (m, 1H), 7.43 – 7.34 (m, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 4.35 (d, *J* = 9.1 Hz, 1H), 4.27 – 4.17 (m, 1H), 3.94 – 3.83 (m, 1H), 3.73 (s, 2H), 3.63 – 3.55 (m, 1H), 3.52 – 3.46 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.59, 152.95, 140.06, 133.03, 131.31, 128.74, 128.14, 115.22, 115.19, 73.05, 66.01, 55.85, 54.51, 48.06. **21aβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 1H), 7.53 – 7.43 (m, 1H), 7.43 – 7.34 (m, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.27 – 4.17 (m, 1H), 3.94 – 3.83 (m, 1H), 3.73 (s, 2H), 3.63 – 3.55 (m, 1H), 3.52 – 3.46 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.59, 153.18, 139.89, 132.87, 131.43, 128.87, 128.14, 115.62, 115.55, 74.50, 67.80, 55.85, 55.19, 48.06. HRMS (ESI) *m/z* Calculated for $C_{18}H_{21}N_2O_4^+[M + H]^+$ 329.1496, found 329.1492.

*4.4.2.3 **21cα** and **21cβ***

Inseparable mixture, yellow viscous liquid (total 88.4 mg, 89% yield). The area of methyl peak of methoxyl group in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β= 3.8 : 1. **21cα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.2 Hz, 2H), 7.52 – 7.44 (m, 1H), 7.44 - 7.37 (m, 2H), 6.88 – 6.82 (m, 1H), 6.81 – 6.76 (m, 1H), 6.76 – 6.71 (m, 1H), 6.70 – 6.65 (m, 1H), 4.60 (s, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.17 (d, *J* = 12.3 Hz, 1H), 4.05 – 3.90 (m, 2H), 3.83 (s,3H), 3.72 – 3.64 (m, 1H), 3.59 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.49, 146.92, 135.95, 133.06, 131.18, 128.67, 128.06, 121.34, 117.54, 110.27, 109.85, 72.87, 65.45, 55.42, 52.59, 47.85. **21cβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.2 Hz, 2H), 7.52 – 7.44 (m, 1H), 7.44 - 7.37 (m, 2H), 6.88 – 6.82 (m, 1H), 6.81 – 6.76 (m, 1H), 6.76 – 6.71 (m, 1H), 6.70 – 6.65 (m, 1H), 4.60 (s, 1H), 4.43 (d, *J* = 11.1 Hz, 1H), 4.17 (d, *J* = 12.3 Hz, 1H), 4.05 – 3.90 (m, 2H), 3.84 (s,3H), 3.72 – 3.64 (m, 1H), 3.59 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.49, 147.07, 136.04, 132.91, 131.29, 128.74, 128.06, 121.45, 117.79, 110.53, 109.85, 74.35, 67.60, 55.48, 53.46, 47.85. HRMS (ESI) *m/z* Calculated for $C_{18}H_{20}N_2NaO_4^+[M + Na]^+$ 351.1315, found 351.1312.

*4.4.2.4 **21dα** and **21dβ***

Inseparable mixture, yellow viscous liquid (total 87.0 mg, 93% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 7.0 : 1. **21dα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 2H), 7.51 – 7.45 (m, 1H), 7.43 – 7.37 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.66 – 6.54 (m, 2H), 4.38 (d, *J* = 9.2 Hz, 1H), 4.26 – 4.11 (m, 1H), 3.98 – 3.82 (m, 2H), 3.81 – 3.65 (m, 2H), 3.64 – 3.58 (m, 1H), 3.58 – 3.53 (m, 1H), 2.24 (s,3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.66, 143.78, 133.05, 131.32, 130.11, 128.76, 128.15, 113.69, 73.00, 65.87, 53.64, 48.04, 20.46. **21dβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 2H), 7.51 – 7.45 (m, 1H), 7.43 – 7.37 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.66 – 6.54 (m, 2H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.26 – 4.11 (m, 1H), 3.98 – 3.82 (m, 2H), 3.81 – 3.65 (m, 2H), 3.64 – 3.58 (m, 1H), 3.58 – 3.53 (m, 1H), 2.24 (s,3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.66, 143.78, 132.90, 131.44, 130.11, 128.89, 127.94, 114.01, 74.48, 67.67, 54.42, 48.04, 20.46. HRMS (ESI) *m/z* Calculated for $C_{18}H_{20}N_2NaO_3^+[M + Na]^+$ 335.1366, found 335.1376.

*4.4.2.5 **21eα** and **21eβ***

Inseparable mixture, yellow viscous liquid (total 106.0 mg, 84% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 6.0 : 1. **21eα**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.79 (t, *J* = 8.4 Hz, 2H), 7.53 – 7.44 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 4H), 6.39 (d, *J* = 8.6 Hz, 2H), 4.36 (d, *J* = 10.0 Hz, 1H), 4.24 – 4.05 (m, 2H), 3.99 – 3.79 (m, 2H), 3.69 – 3.54 (m, 1H), 3.54 – 3.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.58, 145.94, 138.10, 132.79, 131.45, 128.64, 128.21, 115.33, 78.91, 72.66, 65.27, 52.77, 47.96. **21eβ**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.79 (t, *J* = 8.4 Hz, 2H), 7.53 – 7.44 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 4H), 6.39 (d, *J* = 8.6 Hz, 2H), 4.46 (d,*J* = 9.1 Hz, 1H), 4.24 – 4.05 (m, 2H), 3.99 – 3.79 (m, 2H), 3.69 – 3.54 (m, 1H), 3.54 – 3.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.58, 146.14, 138.10, 132.54, 131.62, 128.83, 128.21, 115.50, 79.11, 74.39, 67.13, 53.50, 46.49. HRMS (ESI) *m/z* Calculated for $C_{17}H_{17}IN_2NaO_3^+[M + Na]^+$ 447.0176, found 447.0182.

*4.4.2.6 **21fα** and **21fβ***

Inseparable mixture, yellow viscous liquid (total 94.0 mg, 94% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 5.5 : 1. **21fα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.59 m, 2H), 7.72 – 7.59 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.60 – 6.47 (m, 2H), 4.37 (d,*J* = 10.4 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.99 – 3.77 (m, 2H), 3.70 – 3.55 (m, 1H), 3.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.56, 144.89, 132.81, 131.43, 129.37, 128.63, 128.20, 122.74, 114.25, 72.73, 65.35, 53.07, 47.92. **21fβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.59 m, 2H), 7.72 – 7.59 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.60 – 6.47 (m, 2H), 4.37 (d, *J* = 10.4 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.99 – 3.77 (m, 2H), 3.70 – 3.55 (m, 1H), 3.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.82, 145.09, 132.58, 131.59, 129.37, 128.81, 128.20, 122.86, 114.42, 74.40, 67.21, 53.77, 47.92. HRMS (ESI) *m/z* Calculated for $C_{17}H_{17}ClN_2NaO_3^+[M + Na]^+$ 355.0820, found 355.0826.

*4.4.2.7 **21gα** and **21gβ***

Inseparable mixture, yellow viscous liquid (total 51.0 mg, 54% yield). The area of one alkyl-H peak on the 1,2-oxazinane

ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 5.0 : 1. **21gα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.61 (m, 2H), 7.54 – 7.44 (m, 1H), 7.44 – 7.35 (m, 2H), 6.93 – 6.80 (m, 2H), 6.65 – 6.51 (m, 2H), 4.37 (d, *J* = 9.2 Hz, 1H), 4.26 – 4.12 (m, 1H), 4.04 – 3.80 (m 2H), 3.69 – 3.58 (m, 1H), 3.53 – 3.47 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.68, 156.28 (d, *J* = 236.3 Hz), 142.56 (d, *J* = 1.9 Hz), 132.94, 131.41, 128.72, 128.19, 116.06 (d, *J* = 22.4 Hz), 114.36 (d, *J* = 7.4 Hz), 72.94, 65.72, 53.86, 48.04. **21gβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.61 (m, 2H), 7.54 – 7.44 (m, 1H), 7.44 – 7.35 (m, 2H), 6.93 – 6.80 (m, 2H), 6.65 – 6.51 (m, 2H), 4.54 (d, *J* = 9.1 Hz, 1H), 4.26 – 4.12 (m, 1H), 4.04 – 3.80 (m 2H), 3.69 – 3.58 (m, 1H), 3.53 – 3.47 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.68, 156.28 (d, *J* = 236.3 Hz), 142.56 (d, *J* = 1.9 Hz), 132.74, 131.55, 128.88, 128.19, 116.06 (d, *J* = 22.4 Hz), 114.55 (d, *J* = 7.6 Hz), 74.48, 67.58, 54.52, 48.04. HRMS (ESI) *m/z* Calculated for $C_{17}H_{18}FN_2O_3^+[M + H]^+$ 317.1296, found 317.1293.

4.4.2.8 ***21hα*** *and* ***21hβ***

Inseparable mixture, yellow viscous liquid (total 97.0 mg, 93% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 7.9 : 1. **21hα**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.17 (t, *J* = 7.7 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 7.9 Hz, 2H), 4.39 (d, *J* = 9.6 Hz, 1H), 4.26 – 4.12 (m, 1H), 4.07 – 3.93 (m, 2H), 3.71 – 3.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.09, 149.10, 145.97, 138.97, 129.68, 129.65, 123.31, 118.64, 113.22, 73.24, 65.27, 52.71, 47.38. **21hβ**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.17 (t, *J* = 7.7 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 7.9 Hz, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.26 – 4.12 (m, 1H), 4.07 – 3.93 (m, 2H), 3.71 – 3.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.09, 149.21, 146.20, 138.63, 129.89, 129.26, 123.31, 118.87, 113.49, 73.24, 67.37, 53.64, 47.38. HRMS (ESI) *m/z* Calculated for $C_{17}H_{17}N_3NaO_5^+[M + H]^+$ 366.1060, found 366.1059.

4.4.2.9 ***21iα*** *and* ***21iβ***

Inseparable mixture, yellow viscous liquid (total 88.0 mg, 89 % yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 9.1 : 1. **21iα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.16 (t, *J* = 7.8 Hz, 2H), 6.93 – 6.85 (m, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.78 – 6.59 (m, 2H), 4.39 (d, *J* = 7.8 Hz,1H), 4.26 – 4.16 (m, 1H), 4.13 – 3.98 (m, 1H), 3.97 – 3.87 (m, 2H), 3.84 – 3.81 (m, 3H), 3.65 – 3.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.33, 162.15, 146.33, 131.21, 129.59, 124.80, 118.38, 113.39, 113.32, 72.86, 65.82, 55.43, 53.27, 48.15. **21iβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H), 7.16 (t, *J* = 7.8 Hz, 2H), 6.93 – 6.85 (m, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.78 – 6.59 (m, 2H), 4.39 (d, *J* = 7.8 Hz,1H), 4.26 – 4.16 (m, 1H), 4.13 – 3.98 (m, 1H), 3.97 – 3.87 (m, 2H), 3.84 – 3.81 (m, 3H), 3.65 – 3.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.54, 162.25, 146.43, 131.34, 129.59, 124.69, 118.51, 113.52, 113.32, 74.40, 67.45, 55.43, 53.81, 46.71. HRMS (ESI) *m/z* Calculated for $C_{18}H_{20}N_2NaO_4^+[M + Na]^+$ 351.1315, found 351.1322.

4.4.2.10 ***21jα*** *and* ***21jβ***

Inseparable mixture, yellow viscous liquid (total 93.0 mg, 90% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 7.6 : 1. **21jα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.65 (m, 2H), 6.92 – 6.80 (m, 4H), 6.65 – 6.52 (m, 2H), 4.36 (dd, *J* = 8.5, 1.8 Hz 1H), 4.25 – 4.15 (m, 1H), 3.96 – 3.85 (m, 2H), 3.85 – 3.79 (m, 3H), 3.69 – 3.55 (m, 1H), 3.54 – 3.45 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.38, 162.21, 156.27 (d, *J* = 236.2 Hz), 142.60 (d, *J* = 2.0 Hz), 131.22, 124.71, 116.03 (d, *J* = 22.4 Hz), 114.41 (d, *J* = 7.4 Hz), 113.42, 72.85, 65.85, 55.44, 54.05, 48.14. **21jβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.65 (m, 2H), 6.92 – 6.80 (m, 4H), 6.65 – 6.52 (m, 2H), 4.52 (d, *J* = 7.3 Hz 1H), 4.25 – 4.15 (m, 1H), 3.96 – 3.85 (m, 2H), 3.85 – 3.79 (m, 3H), 3.69 – 3.55 (m, 1H), 3.54 – 3.45 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.38, 162.21, 156.27 (d, *J* = 236.2 Hz), 142.60 (d, *J* = 2.0 Hz), 131.37, 124.71, 116.03 (d, *J* = 22.4 Hz), 114.63 (d, *J* = 7.5 Hz), 113.42, 74.41, 65.85, 55.44, 54.05, 48.14. HRMS (ESI) *m/z* Calculated for $C_{18}H_{19}FN_2NaO_4^+[M + Na]^+$ 369.1221, found 369.1230.

4.4.2.11 ***21kα*** *and* ***21kβ***

Inseparable mixture, yellow viscous liquid (total 106.0 mg, 91% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 4.9 : 1. **21kα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 2H), 6.92 – 8.65 (m, 2H), 6.61 (d,*J* = 8.6 Hz, 1H), 6.47– 6.42 (m, 1H), 6.41 – 6.34 (m, 1H), 4.35 (dd, *J* = 11.4, 2.6 Hz,1H), 4.28 – 4.15 (m, 1H), 3.94 – 3.84 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.64 – 3.58 (m, 1H), 3.3 – 3.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.33, 162.07, 152.84, 148.49, 131.23, 130.04, 124.97, 113.31, 111.84, 104.10, 99.47, 73.03, 66.19, 55.83, 55.57, 55.41, 54.24, 48.06. **21kβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 2H), 6.92 – 8.65 (m, 2H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.47– 6.42 (m, 1H), 6.41 – 6.34 (m, 1H), 4.61 (d, *J* =10.5, 1H), 4.28 – 4.15 (m, 1H), 3.94 – 3.84 (m, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.64 – 3.58 (m, 1H), 3.3 – 3.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.18, 162.13, 153.07, 148.69, 131.23, 129.97, 124.93, 113.31, 112.23, 104.18, 99.47, 74.38, 68.27, 55.83, 55.60, 55.41, 54.83, 47.05. HRMS (ESI) *m/z* Calculated for $C_{20}H_{25}N_2O_6^+[M + H]^+$ 389.1707, found 389.1707.

4.4.2.12 ***21lα*** *and* ***21lβ***

Inseparable mixture, yellow viscous liquid (total 72.0mg, 70% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 5.0 : 1. **21lα**:^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.7 Hz, 2H), 7.33 – 7.17 (m, 5H), 6.89 – 6.80 (m, 2H), 4.41 (d, *J* = 12.7 Hz, 1H), 4.17 – 3.99 (m, 1H), 3.84 – 3.70 (m, 5H), 3.70 – 3.62 (m, 1H), 3.49 – 3.29 (m, 2H), 2.86 – 2.78 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.02, 162.08, 139.89, 131.25, 128.71, 128.13, 127.43, 124.92, 113.32, 73.51, 67.79, 58.65, 55.46, 51.73, 48.68. **21lβ**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.7 Hz, 2H), 7.33 – 7.17 (m, 5H), 6.89 – 6.80 (m, 2H), 4.62 (d, *J* = 13.2 Hz, 1H), 4.17 – 3.99 (m, 1H), 3.84 – 3.70 (m, 5H), 3.70 – 3.62 (m, 1H), 3.49 – 3.29 (m, 2H), 2.86 – 2.78 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.63, 162.08, 139.76, 131.16, 128.71, 128.28, 127.43, 124.92, 113.32, 74.36, 68.92, 58.09, 55.46, 51.19, 48.68. HRMS (ESI) *m/z* Calculated for $C_{19}H_{22}N_2NaO_4^+$ $[M + Na]^+$ 365.1472, found 365.1467.

4.4.2.13 ***21mα*** *and* ***21mβ***

Inseparable mixture, yellow viscous liquid (total 60.0mg, 83% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 4.0 : 1. **21mα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.88 – 5.75 (m, 1H), 5.23– 5.05 (m, 2H), 4.46 (d, *J* = 11.2 Hz, 1H), 4.23 – 4.03 (m, 1H), 3.81 (s, 3H), 3.68 (s, 1H), 3.54 – 3.33 (m, 2H), 3.33 – 3.05 (m, 2H), 2.99 – 2.69 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.89, 162.04, 136.43, 131.17, 124.88, 116.65, 113.29, 73.47, 67.57, 58.43, 55.40, 50.14, 48.77. **21mβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.88 – 5.75 (m, 1H), 5.23– 5.05 (m, 2H), 4.64 (d, *J* = 11.5 Hz, 1H),

4.23 – 4.03 (m, 1H), 3.81 (s, 3H), 3.68 (s, 1H), 3.54 – 3.33 (m, 2H), 3.33 – 3.05 (m, 2H), 2.99 – 2.69 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.54, 161.98, 136.43, 131.17, 125.04, 116.84, 113.29, 74.41, 68.74, 57.86, 55.40, 49.64, 48.77. HRMS (ESI) *m/z* Calculated for $C_{15}H_{21}N_2O_4^+$ $[M + H]^+$ 293.1496, found 293.1497.

4.4.2.14 ***21nα*** *and* ***21nβ***

Inseparable mixture, yellow viscous liquid (total 40.0mg, 56% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 4.6 : 1. **21nα**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.48 (dd, *J* = 13.1, 3.6 Hz, 1H), 4.25 (dd, *J* = 11.4, 4.1 Hz, 1H), 3.83 (s, 3H), 3.78 – 3.65 (m, 1H), 3.61 – 3.36 (m, 4H), 3.07 – 2.93 (m, 1H), 2.31 – 2.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.10, 162.15, 131.29, 124.86, 113.36, 81.76, 73.13, 72.40, 67.72, 58.02, 55.48, 48.67, 36.40. **21nβ**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.65 (dd, *J* = 13.1, 3.8 Hz, 1H), 4.21 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.83 (s, 3H), 3.78 – 3.65 (m, 1H), 3.61 – 3.36 (m, 4H), 3.07 – 2.93 (m, 1H), 2.31 – 2.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.10, 162.15, 131.20, 125.03, 113.36, 81.59, 74.24, 72.60, 68.69, 57.25, 55.48, 48.67, 36.06. HRMS (ESI) *m/z* Calculated for $C_{15}H_{19}N_2O_4^+$ $[M + H]^+$291.1339, found 291.1337.

4.4.2.15 ***21oα*** *and* ***21oβ***

Inseparable mixture, yellow viscous liquid (total 77.0mg, 92% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 5.0 : 1. **21oα**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.58 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.53 (d, *J* = 10.6 Hz, 1H), 4.23 – 4.04 (m, 3H), 3.82 (s, 3H), 3.73 – 3.62 (m, 1H), 3.57 – 3.26 (m, 4H), 2.79 – 2.67 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.28, 169.84, 162.04, 131.18, 124.97, 113.31, 73.34, 68.00, 61.37, 59.52, 55.43, 49.01, 48.47, 14.24. **21oβ**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.58 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.62 (d, *J* = 4.0 Hz, 1H), 4.23 – 4.04 (m, 3H), 3.82 (s, 3H), 3.73 – 3.62 (m, 1H), 3.57 – 3.26 (m, 4H), 2.79 – 2.67 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.28, 169.84, 162.04, 131.18, 124.97, 113.31, 73.34, 68.00, 61.37, 59.52, 55.43, 48.81, 48.47, 14.24. HRMS (ESI) *m/z* Calculated for $C_{16}H_{22}N_2NaO_6^+$ $[M + Na]^+$ 361.1370, found361.1364.

4.4.2.16 ***21pα*** *and* ***21pβ***

Inseparable mixture, yellow viscous liquid (total 75.0mg, 94% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 3.9 : 1. **21pα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.8 Hz, 2H), 6.82 – 6.73 (m, 2H), 4.68 (dd, *J* = 12.6, 4.8 Hz, 1H), 4.08 – 3.97 (m, 1H), 3.81 – 3.65 (m, 4H), 3.40 – 3.26 (m, 1H), 3.11 – 2.98 (m, 1H), 2.78 – 2.47 (m, 3H), 2.44 – 2.27 (m, 2H), 1.50 – 1.28 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.46, 162.05, 131.21, 125.19, 113.34, 69.74, 67.45, 63.61, 60.53, 55.49, 50.70, 26.80, 24.69, 21.19, 14.32. **21pβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.8 Hz, 2H), 6.82 – 6.73 (m, 2H), 4.58 (dd, *J* = 12.8, 4.2 Hz, 1H), 4.08 – 3.97 (m, 1H), 3.81 – 3.65 (m, 4H), 3.40 – 3.26 (m, 1H), 3.11 – 2.98 (m, 1H), 2.78 – 2.47 (m, 3H), 2.44 – 2.27 (m, 2H), 1.50 – 1.28 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.46, 162.05, 131.21, 125.19, 113.34, 75.39, 66.31, 64.41, 58.57, 55.49, 49.72, 26.74, 24.69, 21.19, 14.32. HRMS (ESI) *m/z* Calculated for $C_{17}H_{25}N_2NaO_4^+$[M + Na]$^+$ 321.1809, found 321.1806.

4.4.2.17 ***21qα*** *and* ***21qβ***

Inseparable mixture, yellow viscous liquid (total 77.0mg, 96% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 7.2 : 1. **21qα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.75 (dd, *J* = 12.8, 4.6 Hz, 1H), 4.15 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.91 – 3.81 (m, 4H), 3.76 – 3.64 (m, 6H), 3.27 – 3.19 (m, 1H), 2.96 (s, 1H), 2.84 – 2.75 (m, 2H), 2.72 – 2.65 (m, 1H), 2.57 – 2.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.52, 162.07, 131.20, 124.84, 113.29, 74.97, 69.56, 67.42, 66.11, 64.31, 63.66, 55.41, 49.89, 41.78. **21qβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.75 (dd, *J* = 12.8, 4.6 Hz, 1H), 4.15 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.91 – 3.81 (m, 4H), 3.76 – 3.64 (m, 6H), 3.27 – 3.19 (m, 1H), 2.96 (s, 1H), 2.84 – 2.75 (m, 2H), 2.72 – 2.65 (m, 1H), 2.57 – 2.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.81, 162.07, 131.16, 124.88, 113.29, 74.97, 69.56, 67.34, 65.29, 64.31, 63.66, 55.41, 49.26, 41.78. HRMS (ESI) *m/z* Calculated for $C_{16}H_{23}N_2HO_5^+$[M + H]$^+$ 323.1601, found 323.1601.

4.4.2.18 ***21rα*** *and* ***21rβ***

Inseparable mixture, yellow viscous liquid (total 90.3 mg, 85% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 4.0 : 1. **21rα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.7 Hz, 2H), 6.93 – 6.80 (m, 2H), 4.72 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.09 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.94 – 3.78 (m, 4H), 3.71 – 3.58 (m, 1H), 3.52 – 3.30 (m, 5H), 3.24 – 3.12 (m, 1H), 2.87 – 2.67 (m, 3H), 2.57 – 2.43 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.49, 162.04, 154.55, 131.14, 124.80, 113.26, 79.90, 74.98, 69.65, 66.15, 63.80, 55.37, 49.34, 44.37, 41.92, 28.39. **21rβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.7 Hz, 2H), 6.93 – 6.80 (m, 2H), 4.64 (dd, *J* = 12.9, 4.0 Hz, 1H), 4.14 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.94 – 3.78 (m, 4H), 3.71 – 3.58 (m, 1H), 3.52 – 3.30 (m, 5H), 3.24 – 3.12 (m, 1H), 2.87 – 2.67 (m, 3H), 2.57 – 2.43 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.80, 162.04, 154.60, 131.14, 124.80, 113.26, 79.97, 74.98, 69.65, 65.31, 64.44, 55.37, 49.34, 44.37, 41.92, 28.39. HRMS (ESI) *m/z* Calculated for $C_{21}H_{31}N_3NaO_6^+$[M + Na]$^+$ 444.2105, found 444.2104.

4.4.2.19 ***21sα*** *and* ***21sβ***

Inseparable mixture, yellow viscous liquid (total 63.6 mg, 69% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 12.0 : 1. **21sα**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.10 – 7.03 (m, 1H), 6.97 (d, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.65 (t, *J* = 7.3 Hz, 1H), 4.75 (dd, *J* = 13.0, 4.5 Hz, 1H), 4.19 – 4.04 (m, 2H), 4.04 – 3.97 (m, 1H), 3.84 (s, 3H), 3.77 – 3.69 (m, 1H), 3.43 – 3.32 (m, 2H), 3.16 – 3.09 (m, 1H), 2.75 (t, *J* = 6.3 Hz, 2H), 1.99 – 1.77 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.65, 162.21, 145.11, 131.35, 129.81, 127.36, 124.71, 123.89, 117.40, 113.38, 111.48, 70.21, 64.45, 59.56, 55.48, 49.63, 43.02, 28.13, 22.58. **21sβ**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.10 – 7.03 (m, 1H), 6.97 (d, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.65 (t, *J* = 7.3 Hz, 1H), 4.46 (d, *J* = 15.4 Hz, 1H), 4.19 – 4.04 (m, 2H), 4.04 – 3.97 (m, 1H), 3.84 (s, 3H), 3.77 – 3.69 (m, 1H), 3.43 – 3.32 (m, 2H), 3.16 – 3.09 (m, 1H), 2.75 (t, *J* = 6.3 Hz, 2H), 1.99 – 1.77 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.65, 162.21, 145.11, 131.41, 129.81, 127.36, 124.71, 123.89, 117.40, 113.38, 111.48, 70.21, 64.45, 59.56, 55.48, 49.63, 43.02, 28.13, 22.58. HRMS (ESI) *m/z* Calculated for $C_{21}H_{24}N_2NaO_5^+$ $[M + Na]^+$ 391.1628, found391.1632.

*4.4.2.20 **21tα** and **21tβ***

Inseparable mixture, yellow viscous liquid (total 74.0mg, 97% yield). The area of one alkyl-H peak on the 1,2-oxazinane ring in α isomer was compared with that in β isomer to derive a ^{1}H NMR ratio of α/β = 5.3 : 1.**21tα**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.7, 4.5 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.40 (dd, *J* = 13.1, 3.3 Hz, 1H), 4.18 (dd, *J* = 11.6, 3.3 Hz, 1H), 4.03 – 3.88 (m, 1H), 3.86 – 3.72 (m, 4H), 3.69 – 3.59 (m, 1H), 3.56 – 3.35 (m, 1H), 2.87 – 2.57 (m, 5H), 1.87 – 1.67 (m, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.15, 161.99, 131.16 (d, *J* = 8.0 Hz), 125.16, 113.28, 74.53, 70.16, 66.66, 65.62, 62.89, 55.43, 50.46, 49.66, 42.27, 23.58. **21tβ**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.7, 4.5 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.53 (dd, *J* = 13.2, 3.7 Hz, 1H), 4.18 (dd, *J* = 11.6, 3.3 Hz, 1H), 4.03 – 3.88 (m, 1H), 3.86 – 3.72 (m, 4H), 3.69 – 3.59 (m, 1H), 3.56 – 3.35 (m, 1H), 2.87 – 2.57 (m, 5H), 1.87 – 1.67 (m, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.69, 161.99, 131.16 (d, *J* = 8.0 Hz), 125.16, 113.28, 74.53, 70.16, 66.66, 65.62, 61.75, 55.43, 50.46, 48.47, 42.27, 23.66.HRMS (ESI) *m/z* Calculated for $C_{16}H_{23}N_2O_4^+$ $[M + H]^+$ 307.1652, found307.1647.

4.5. N-Acyl deprotection

4.5.1. Procedure

To a 10 mL sealed tube equipped with a stir bar were added **19bα** or **21iα** (0.55 mmol), NaOH (87.0 mg, 2.2 mmol) and anhydrous MeOH (1.0 mL). Then the solution was stirred for 36 hours at room temperature. When completed as indicated by TLC, The reaction mixture was concentrated under vacuum and purified via flash column chromatography with silica gel (eluting with DCM/MeOH = 50/1 (v/v)) to yield **23bα** or **23iα**.

*4.5.2. Characterization of **23***

*4.5.2.1. **23bα***

White solid (72.3 mg, 91% yield); m.p. 60-61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.70 (td, *J* = 7.3, 4.0 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.43 – 3.32 (m, 2H), 2.93 (dd, *J* = 12.7, 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.85, 67.32, 60.51, 51.86. HRMS (ESI) *m/z* Calculated for $C_4H_9N_4O_2^+$ $[M + H]^+$ 145.0720, found 145.0713.

*4.5.2.2. **23iα***

White solid (62.3 mg, 80% yield); m.p. 134-135 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.01 (t, *J* = 7.9 Hz, 2H), 6.59 (d, *J* = 7.8 Hz, 2H), 6.46 (t, *J* = 7.2 Hz, 1H), 6.36 – 6.29 (m, 1H), 5.48 (d, *J* = 7.4 Hz, 1H), 4.99 (s, 1H), 4.00 (dd, *J* = 11.3, 4.0 Hz, 1H), 3.49 – 3.41 (m, 1H), 3.26 (dd, *J* = 11.2, 8.3 Hz, 1H), 3.22 – 3.11 (m, 2H), 2.75 – 2.65 (m, 1H). ^{13}C NMR (75 MHz, DMSO) δ 153.47, 134.13, 120.79, 117.36, 76.21, 72.24, 59.89, 58.95. HRMS (ESI) *m/z* Calculated for $C_4H_9N_4O_2^+$ $[M + H]^+$ 145.0720, found 145.0727.

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Supplementary Material

Supplementary material including experimental details for substrate synthesis and characterizations, crystal data and structure refinement and copies of NMR spectra related to this article can be found online at https://doi.org/xxxxx.

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