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Studies on the Lewis acid catalyzed synthesis of isoxazolidin-3-ones

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The reaction of α, β-epoxy esters with *N*-alkyl-1-phenylmethanimine oxides in the presence of a Lewis acid was explored in this study. A substrate sustained-release strategy was successfully employed to overcome the inherent conflict between substrate activation and catalyst poisoning, allowing for the efficient synthesis of a variety of substituted isoxazolidin-3-ones. The reaction employs inexpensive and readily available starting materials, proceeds under mild conditions, and demonstrates broad substrate compatibility. Moreover, when chiral epoxy substrates were used, the products were obtained with high retention of enantiomeric purity.

1. Introduction

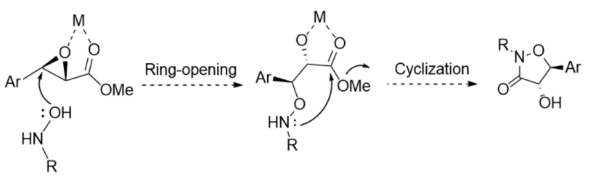
Isoxazolidin-3-ones represent a class of highly important heterocyclic compounds present in numerous bioactive molecules. Many isoxazolidin-3-ones and their analogues exhibit diverse biological activities, including antibacterial,[1,2] antitumor,[3] analgesic,[4] and sedative-hypnotic effects.[5,6]

Reports on the synthesis of isoxazolidin-3-ones remain relatively limited.[7–9] One documented method involves the synthesis of isoxazolidin-3-one with high yield *via* ring-opening of epoxy carboxylates with *N*-alkyl hydroxylamines.[10] In this approach, *tert*-butanol was used as the solvent, and an excess of potassium *tert*-butoxide was employed as an additive to facilitate the reaction. However, this method presents several drawbacks: *tert*-butanol has a high melting point and tends to solidify; potassium *tert*-butoxide is corrosive, hygroscopic, unstable, and exhibits poor solubility, leading to non-uniform stirring and poor operability. Likely due to these reasons, the reproducibility of the reaction yield in repeated experiments is also highly inconsistent. Therefore, developing efficient and reliable synthetic methods remains highly valuable.

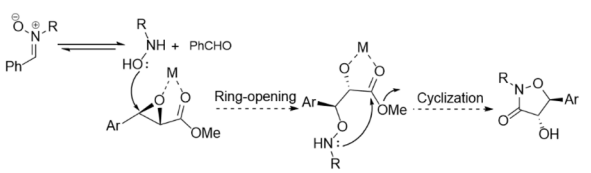
The effective catalysis of α, β-epoxy esters ring-opening reactions by Lewis acids has been extensively documented.[11,12] We envisioned activating α, β-epoxy esters substrates with a Lewis acid catalyst, followed by regioselective ring-opening with *N*-alkylhydroxylamines as nucleophiles and subsequent intramolecular cyclization to afford isoxazolidin-3-ones (Scheme 1).

However, preliminary experiments indicated that the desired products were not formed when various common Lewis acids, including indium bromide, aluminum chloride, and scandium trifluoromethanesulfonate, were employed as catalysts. We reasoned that this was likely due to the α-effect of *N*-alkyl hydroxylamines, which enhances their coordination ability,[13] causing them to preferentially bind to Lewis acids[14] and leading to catalyst deactivation. This inactivation prevented the catalytic reaction from proceeding. Thus, a key challenge in this study is to activate the α, β-epoxy esters with a Lewis acid while avoiding catalyst poisoning.

In exploratory experiments, we observed that *N*-methyl-1-phenylmethylimine oxide can undergo hydrolysis in solution to yield trace amounts of benzaldehyde and *N*-methylhydroxylamine, a process we hypothesized to be reversible. The *N*-methyl-1-phenylmethylimine oxide compound is simple and easy to synthesize: it can be prepared simply by mixing benzaldehyde with *N*-methylhydroxylamine in the presence of sodium bicarbonate and anhydrous magnesium sulfate, followed by stirring at room temperature for 5 h. We proposed that isoxazolidinone could be synthesized by using this compound



Scheme 1 Possible synthetic route to isoxazolidin-3-ones.



Scheme 2 Catalytic reaction based on sustained-release strategy.

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as a sustained-releasing source of *N*-alkyl hydroxylamines *via* hydrolysis, allowing them to react with α, β-epoxy esters (Scheme 2). Since only trace amounts of *N*-alkylhydroxylamines are present in the solution, their impact on the Lewis acid can be minimized, thereby preserving its catalytic activity. However, an alternative pathway is also possible, in which the imine oxides could react directly with the α, β-epoxy esters substrate to form six-membered ring compounds. Therefore, the proposed approach remains challenging.

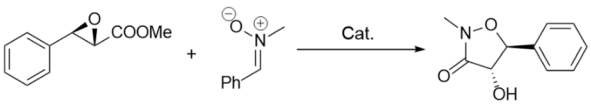
If successfully implemented, this substrate sustained-release strategy could resolve the conflict between Lewis acid activation and catalyst poisoning. Herein, we report a Lewis acid-catalyzed reaction of α, β-epoxy esters with *N*-alkyl-1-phenylmethylimine oxides for the synthesis of 4-hydroxy-2-alkyl-5-arylisoxazolidin-3-ones.

2. Results and discussion

Initial screening of various Lewis acid catalysts and reaction conditions was performed using the reaction between methyl 3-phenyloxirane-2-carboxylate and *N*-methyl-1-phenylmethylimine oxide as a model system (Table 1).

Initially, the reaction conducted in dichloromethane (DCM) without any catalyst failed to yield the desired product (Table 1, entries 1–2). Subsequent attempts using Brønsted acid catalysts also proved ineffective, with no detectable product formation. Screening of various Lewis acid catalysts revealed that $AlCl_3$, $FeCl_3$, $ZnCl_2$, and $Bi(OTf)_3$ could all promote the reaction to afford the target product, albeit with low yields (Table 1, entries 3–6). These preliminary results validated the feasibility of our proposed catalytic strategy. Further optimization efforts identified $Yb(OTf)_3$ and $Zn(OTf)_2$ as more efficient catalysts, delivering improved yields. Intriguingly, when $InBr_3$ or $InCl_3$ was employed in DCM, the reaction exhibited negligible productivity. However, switching the solvent to acetonitrile (CH_3CN) resulted in a remarkable enhancement in yield for both indium-based catalysts (Table 1, entries 11–14). We tried to use CH_3CN as solvent and $Yb(OTf)_3$ or $Zn(OTf)_2$ as catalysts, expecting to further improve the reaction yield. The results showed that the yields did improve slightly after changing the solvent, but still not as good as the yield with $InBr_3$ as the catalyst (Table 1, entries 15–16). Then $InBr_3$ was chosen as the catalyst, and the reaction solvents were further screened (Table 1, entries 17–20), and it was found that tetrahydrofuran (THF), *N*,*N*-

Table 1 Screening of catalysts and reaction conditions[a]



Entry	Catalysts	Equivalent	Solvents	Temp. [°C]	Time [h]	Yield[b] [%]
1	—	—	DCM	25	12	0
2	TfOH	0.5	DCM	25	12	0
3	$AlCl_3$	0.1	DCM	25	12	3
4	$FeCl_3$	0.1	DCM	25	12	Trace
5	$ZnCl_2$	0.1	DCM	25	12	Trace
6	$Bi(OTf)_3$	0.1	DCM	25	12	7
7	$In(OTf)_3$	0.1	DCM	25	12	21
8	$Sc(OTf)_3$	0.1	DCM	25	12	23
9	$Yb(OTf)_3$	0.1	DCM	25	12	39
10	$Zn(OTf)_2$	0.1	DCM	25	12	45
11	$InBr_3$	0.1	DCM	25	12	6
12	$InCl_3$	0.1	DCM	25	12	Trace
13	$InBr_3$	0.1	CH_3CN	25	12	67
14	$InCl_3$	0.1	CH_3CN	25	12	38
15	$Yb(OTf)_3$	0.1	CH_3CN	25	12	47
16	$Zn(OTf)_2$	0.1	CH_3CN	25	12	52
17	$InBr_3$	0.1	THF	25	12	19
18	$InBr_3$	0.1	DCE	25	12	44
19	$InBr_3$	0.1	DMF	25	12	11
20	$InBr_3$	0.1	Toluene	25	12	Trace
21	$InCl_3$	0.1	CH_3CN	50	8	75
22	$Zn(OTf)_2$	0.1	CH_3CN	50	8	87
23	$InBr_3$	0.1	CH_3CN	50	8	93
24[c]	$InBr_3$	0.1	CH_3CN	50	8	20
25	$InBr_3$	0.05	CH_3CN	50	8	66

[a] Reaction conditions: under a nitrogen atmosphere, (methyl (2*S*,3*R*)-3-phenyloxirane-2-carboxylate) (0.6 mmol), *N*-methyl-1-phenylmethanimine oxide (0.72 mmol) and catalyst were added to 1 mL solvent. The reactions were proceeded at room temperature for 12 hours or at 50 °C for 8 hours. [b] Yield determination: the crude reaction mixture was directly analyzed by ^{1}H NMR spectroscopy using dimethyl terephthalate as an internal standard. [c] The solvent was pre-dried by 4 Å molecular sieve for 48 h and 50 mg 4 Å molecular sieve was added into the reaction mixture.

dimethylformamide (DMF), and toluene were poor efficiency as solvents, and the reaction in 1,2-dichloroethane (DCE) achieved good yields, but CH_3CN is still the best solvent for the reaction.

Subsequent optimization revealed that elevating the reaction temperature to 50 °C significantly enhanced the catalytic efficiency for different catalysts (Table 1, entries 21–23). Under the optimized conditions, $InBr_3$ afforded the product in a remarkable yield of 93% (Table 1, entry 23), outperforming all other catalysts tested. Interestingly, when dry solvents were used, the reaction yield decreased significantly (Table 1, entry 24), indicating that trace amounts of water in the solvent are crucial for the reaction. Control experiments showed that when the water content in the solvent was 1% (vol%), the reaction gave high yields (>90%), but when the water content was extended to 2%, the yield dropped markedly (60%), which might be attributed to hydrolysis and deactivation of the catalyst caused by excess water. Reducing the $InBr_3$ loading to 0.05 equiv. resulted in a marked decline in yield (Table 1, entry 25), confirming the critical role of catalyst dosage. The reaction protocol was ultimately established as follows: $InBr_3$ (0.1 equiv.) in CH_3CN at 50 °C, achieving reproducible high yields while balancing catalytic activity and cost efficiency.

To broaden the substrate scope, a series of reactions between variously substituted chiral (2*S*, 3*R*)-methyl 3-phenyloxirane-2-carboxylates and *N*-alkyl-1-phenylmethanimine oxides were investigated (Table 2).

The corresponding isoxazolidin-3-ones were obtained in high yields (up to 94%). The reaction showed good tolerance toward *meta*- or *para*-substituents on the aromatic ring of the epoxy esters (Table 2, entries 3–10). In contrast, *ortho*-substituted substrates afforded lower yields (Table 2, entry 2), presumably due to steric hindrance. Electron-donating substituents, such as methyl groups, resulted in slightly lower yet still moderate yields (Table 2, entries 6–7). Strong electron-withdrawing substituents, including nitro, cyano, and trifluoromethyl groups, were well tolerated, consistently delivering excellent yields (Table 2, entries 8–10). Significantly, the use of chiral starting substrates led to products with well-retained enantiomeric purity. Furthermore, the absolute configuration of the isoxazolidin-3-one compounds was established as 4*S*,5*S* by comparison with the known configuration of the α,β-epoxy ester precursors. All products displayed substantial polarity differences from the benzaldehyde byproduct, facilitating straightforward purification. The benzaldehyde byproduct was recovered in over 80% yield in all cases.

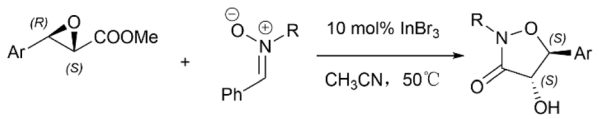
Scaling the model reaction from 0.6 mmol to 8 mmol maintained excellent reaction yields, conclusively demonstrating the practical applicability of this methodology.

The proposed reaction mechanism is illustrated in Scheme 3:

Indium bromide initially coordinates with α, β-epoxy esters, thereby activating the substrates. The *N*-alkylhydroxylamine, generated *via* hydrolysis of the imine oxide, undergoes nucleophilic ring-opening of the activated α, β-epoxy esters, followed by intramolecular cyclization to form the isoxazolidin-3-one products, while regenerating the indium bromide catalyst. The continuous consumption of hydroxylamine shifts the hydrolysis equilibrium of the imine oxide, thereby promoting the steady release of *N*-alkylhydroxylamine, which in turn sustains the catalytic reaction cycle.

To validate the proposed mechanism, *N*-methyl-1-phenylmethanimine oxide was stirred in CH_3CN for 3 hours. TLC analysis indicated the formation of benzaldehyde, which was further confirmed by faint signals in the ^1H NMR spectrum. These results suggest the occurrence of minimal hydrolysis under these conditions. Notably, benzaldehyde was also detected as a byproduct in the reaction system, along with the isoxazolidinone product. When *N*-phenyl-1-phenylmethanimine oxide was used in place of the *N*-methyl analogue under identical conditions, no desired product was obtained (Scheme 4),

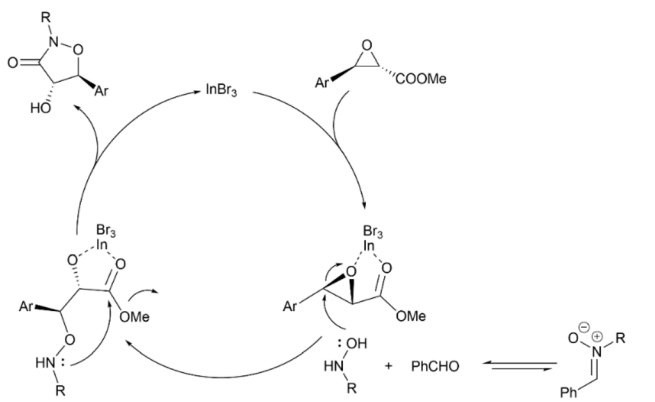
Table 2 Reaction of methyl 3-aryloxirane-2-carboxylate with *N*-alkyl-1-phenylmethylimine oxides[a]



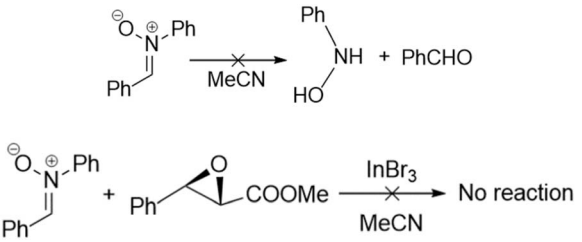
2 3 4

Entry	Ar	*ee*[b] [%]	R	Product	Yield[c] [%]	*ee*[d] [%]
1	Ph, **2a**	98	Me, 3a	**4a**	91	98
2	2-Cl-C_6H_4, **2b**	97	Me, 3a	**4b**	46	97
3	3-Cl-C_6H_4, **2c**	96	Me, 3a	**4c**	70	96
4	4-Cl-C_6H_4, **2d**	96	Me, 3a	**4d**	94	96
5	4-Br-C_6H_4, **2e**	98	Me, 3a	**4e**	73	98
6	3-Me-C_6H_4, **2f**	97	Me, 3a	**4f**	60	97
7	4-Me-C_6H_4, **2g**	96	Me, 3a	**4g**	49	96
8	4-NO_2-C_6H_4, **2h**	91	Me, 3a	**4h**	68	91
9	4-CN-C_6H_4, **2i**	98	Me, 3a	**4i**	61	96
10	3-CF_3-C_6H_4, **2j**	97	Me, 3a	**4j**	73	97
11	Ph, **2a**	98	Bn, 3b	**4k**	41	97

[a] Reaction conditions: under a nitrogen atmosphere, 2 (0.6 mmol, 1.0 equiv.), 3 (0.72 mmol, 1.2 equiv.), and $InBr_3$ (0.06 mmol, 0.1 equiv.) were added to acetonitrile (1 mL) and reacted at 50 °C for 8 h. [b] The *ee* values of α, β-epoxy esters, and were determined by chiral HPLC. [c] Isolated yield. [d] The *ee* values of product 4, and were determined by chiral HPLC.



Scheme 3 Possible reaction mechanism.



Scheme 4 Control reaction with benzyl-1-phenylmethylidene oxide.

and TLC analysis revealed no formation of benzaldehyde. Control experiments showed that stirring *N*-phenyl-1-phenylmethanimine oxide alone in CH_3CN for 3 hours also failed to generate benzaldehyde. These results indicate that the extended conjugation in the *N*-phenyl-substituted imine oxide enhances its stability, thereby preventing hydrolytic release of *N*-phenylhydroxylamine.

Therefore, the selection of a sustained-release agent must consider whether it possesses appropriate stability, as compounds that are either excessively stable or unstable are unsuitable for this substrate-controlled release strategy.

3. Experimental

3.1 Instruments & reagents

Melting points were determined using a Tech X-5 melting point apparatus. Nuclear magnetic resonance (^{1}H, ^{13}C, ^{13}F NMR) spectra were recorded on a Bruker Advance 400 MHz spectrometer with $CDCl_3$ as the internal standard (δ 7.26 ppm for ^{1}H NMR; δ 77.16 ppm for ^{13}C NMR). Chemical shifts are reported in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The following abbreviations denote multiplicity: s = singlet, d = doublet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were acquired on an AB SCIEX X500R QTOF mass spectrometer. Enantiomeric excess (ee) values were determined by HPLC analysis using a Shimadzu LC-20A system equipped with Daicel Chiralcel AD-H or OD-H columns, with *n*-hexane/isopropyl alcohol as the mobile phase. Column chromatography was performed using 200–300 mesh silica gel (Yantai Jiangyou Silica Gel Development Co., Ltd). Thin-layer chromatography (TLC) was conducted on pre-coated silica gel GF254 plates with UV visualization. All chemicals were purchased from commercial suppliers (Aladdin and Macklin Reagents) and used without further purification unless otherwise specified. Analytical grade solvents were employed as received.

3.2 Experimental methods

3.2.1 Substrates 2, 3 were prepared according to the methods reported in the literature..[15–18]

3.2.1.1 Synthesis and structural characterization of (4S,5S)-4-hydroxy-2-alkyl-5-arylisoxazolidin-3-one. A mixture of substituted methyl (2*S*,3*R*)-3-phenyloxirane-2-carboxylate (0.6 mmol, 1.0 equiv.), *N*-alkyl-1-phenylmethanimine oxide (0.72 mmol, 1.2 equiv.), and $InBr_3$ (0.06 mmol, 0.1 equiv.) in acetonitrile (1 mL) was stirred at 50 °C for 8 hours. After completion, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (petroleum ether/ethyl acetate system) to afford (4*S*,5*S*)-4-hydroxy-2-alkyl-5-arylisoxazolidin-3-one.

*3.2.1.1.1 (4S,5S)-4-Hydroxy-2-methyl-5-phenylisoxazolidin-3-one (**4a**).* White solid, 91% yield, m.p. 93–95 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.49–7.29 (m, 5H), 5.19 (d, J = 9.8 Hz, 1H), 4.62 (d, J = 9.8 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.46, 135.37, 129.28, 128.92, 126.59, 85.80, 76.02, 31.93; HRMS (ESI) calcd for $C_{10}H_{11}NO_3$ $[M + H]^+$: 194.0812, found: 194.0811; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 6.2 min, t_R (major enantiomer) = 9.4 min, 98% ee.

*3.2.1.1.2 (4S,5S)-5-(2-Chlorophenyl)-4-hydroxy-2-methylisoxazolidin-3-one (**4b**).* White solid, 46% yield, m.p. 127–129 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.51–7.39 (m, 2H), 7.33 (dd, J = 5.9, 3.5 Hz, 2H), 5.63 (d, J = 7.7 Hz, 1H), 4.73 (d, J = 7.7 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.39, 133.88, 133.01, 130.48, 130.42, 128.16, 127.34, 83.38, 75.95, 31.93; HRMS (ESI) calcd for $C_{10}H_{10}ClNO_3$ $[M + H]^+$: 228.0422, found: 228.0420; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 6.7 min, t_R (major enantiomer) = 8.4 min, 97% ee.

*3.2.1.1.3 (4S,5S)-5-(3-Chlorophenyl)-4-hydroxy-2-methylisoxazolidin-3-one (**4c**).* White solid, 70% yield, m.p. 98–100 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.46 (s, 1H), 7.44–7.31 (m, 3H), 5.16 (d, J = 9.7 Hz, 1H), 4.55 (d, J = 9.8 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.18, 137.50, 134.93, 130.27, 129.40, 126.46, 124.61, 84.90, 75.99, 32.04; HRMS (ESI) calcd for $C_{10}H_{10}ClNO_3$ $[M + H]^+$: 228.0422, found: 228.0422; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 6.3 min, t_R (major enantiomer) = 8.3 min, 96% *ee*.

*3.2.1.1.4 (4S,5S)-5-(4-Chlorophenyl)-4-hydroxy-2-methylisoxazolidin-3-one (**4d**).* White solid, 94% yield, m.p. 118–120 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.39 (s, 4H), 5.16 (d, J = 9.9 Hz, 1H), 4.56 (d, J = 9.8 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.31, 135.17, 133.92, 129.16, 127.85, 85.06, 75.96, 32.02; HRMS (ESI) calcd for $C_{10}H_{10}ClNO_3$ $[M + H]^+$: 228.0422, found: 228.0422; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 6.7 min, t_R (major enantiomer) = 8.2 min, 96% *ee*.

*3.2.1.1.5 (4S,5S)-5-(4-Bromophenyl)-4-hydroxy-2-methylisoxazolidin-3-one (**4e**).* White solid, 73% yield, m.p. 105–107 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.58–7.52 (m, 2H), 7.37–7.30 (m, 2H), 5.14 (d, J = 9.9 Hz, 1H), 4.53 (d, J = 9.8 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.21, 134.45, 132.13, 128.10, 123.34, 85.09, 75.91, 32.04; HRMS (ESI) calcd for $C_{10}H_{10}BrNO_3$ $[M + H]^+$: 271.9917, found: 271.9918; the

enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 7.1 min, t_R (major enantiomer) = 8.7 min, 98% *ee*.

*3.2.1.1.6 (4S,5S)-4-Hydroxy-2-methyl-5-(m-tolyl)isoxazolidin-3-one (**4f**).* White solid, 60% yield, m.p. 93–95 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.34–7.17 (m, 4H), 5.15 (d, J = 9.8 Hz, 1H), 4.61 (d, J = 9.8 Hz, 1H), 3.30 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.43, 138.73, 135.22, 130.09, 128.86, 127.26, 123.70, 85.96, 75.98, 31.95, 21.54; HRMS (ESI) calcd for $C_{11}H_{13}NO_3$ [M + H]$^+$: 208.0968, found: 208.0963; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 5.9 min, t_R (major enantiomer) = 7.0 min, 97% *ee*.

*3.2.1.1.7 (4S,5S)-4-Hydroxy-2-methyl-5-(p-tolyl)isoxazolidin-3-one (**4g**).* White solid, 49% yield, m.p. 113–115 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.34 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 5.14 (d, J = 9.8 Hz, 1H), 4.61 (d, J = 9.9 Hz, 1H), 3.29 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.40, 139.34, 132.17, 129.62, 126.71, 85.93, 75.89, 31.95, 21.39; HRMS (ESI) calcd for $C_{11}H_{13}NO_3$ [M + H]$^+$: 208.0968, found: 208.0964; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 6.2 min, t_R (major enantiomer) = 7.2 min, 96% *ee*.

*3.2.1.1.8 (4S,5S)-4-Hydroxy-2-methyl-5-(4-nitrophenyl) isoxazolidin-3-one (**4h**).* White solid, 68% yield, m.p. 130–132 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 8.31–8.25 (m, 2H), 7.68–7.62 (m, 2H), 5.30 (d, J = 9.9 Hz, 1H), 4.54 (d, J = 9.8 Hz, 1H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.01, 148.35, 142.72, 126.89, 124.15, 84.28, 75.96, 32.17; HRMS (ESI) calcd for $C_{10}H_{10}N_2O_5$ [M + H]$^+$: 239.0662, found: 239.0661; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 13.0 min, t_R (major enantiomer) = 15.5 min, 91% *ee*.

*3.2.1.1.9 4-((4S,5S)-4-Hydroxy-2-methyl-3-oxoisoxazolidin-5-yl)benzonitrile (**4i**).* White solid, 61% yield, m.p. 107–109 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.71 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 5.25 (d, J = 9.9 Hz, 1H), 4.53 (d, J = 9.9 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.08, 140.84, 132.72, 126.74, 118.45, 112.99, 84.45, 75.95, 32.11; HRMS (ESI) calcd for $C_{11}H_{10}N_2O_3$ [M + H]$^+$: 219.0764, found: 219.0763; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 13.1 min, t_R (major enantiomer) = 14.8 min, 96% *ee*.

*3.2.1.1.10 (4S,5S)-4-Hydroxy-2-methyl-5-(3-(trifluoromethyl) phenyl)isoxazolidin-3-one (**4j**).* White solid, 73% yield, m.p. 92–94 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.73 (s, 1H), 7.66 (d, J = 7.9 Hz, 2H), 7.55 (t, J = 7.8 Hz, 1H), 5.24 (d, J = 9.8 Hz, 1H), 4.59 (d, J = 9.7 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.22, 136.63, 131.42 (q, J = 32.5 Hz), 129.80, 129.51, 126.05 (q, J = 3.6 Hz), 123.97 (d, J = 272.5 Hz), 123.12 (q, J = 4.1 Hz), 84.94, 75.99, 32.08; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.71; HRMS (ESI) calcd for $C_{11}H_{10}F_3NO_3$ [M + H]$^+$: 262.0686, found: 262.0678; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 5.4 min, t_R (major enantiomer) = 6.7 min, 97% *ee*.

*3.2.1.1.11 (4S,5S)-2-Benzyl-4-hydroxy-5-phenylisoxazolidin-3-one (**4k**).* White solid, 41% yield, m.p. 103–105 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.41–7.32 (m, 10H), 5.11 (d, J = 9.8 Hz, 1H), 4.90 (d, J = 15.6 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 4.63 (d, J = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.45, 135.31, 134.47, 129.29, 128.89, 128.36, 128.33, 126.60, 86.11, 76.08, 49.19; HRMS (ESI) calcd for $C_{16}H_{15}NO_3$ [M + H]$^+$: 270.1125, found: 270.1114; the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (*n*-hexane/i-PrOH = 85/15, λ = 254 nm, 1.0 mL min^{-1}); t_R (minor enantiomer) = 6.6 min, t_R (major enantiomer) = 9.2 min, 97% *ee*.

4. Conclusions

This study establishes a Lewis acid-catalyzed ring-opening-cyclization between methyl α, β-epoxy esters and *N*-alkyl-1-phenylmethanimine oxides *via* a substrate sustained-release strategy. This method enables the synthesis of diverse isoxazolidin-3-ones in moderate to excellent yields (46–94%). The reaction conditions are mild and the operation is simple. Moreover, the use of chiral α, β-epoxy esterss as substrates results in excellent retention of enantioselectivity (91–98% ee) in the products. This strategy effectively resolves the conflict between catalyst activation of the substrate and catalyst poisoning. Research on the application of this imine oxide as a controlled-release source of hydroxylamine in reactions with other substrates is still under investigation.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: preparation of raw materials, NMR spectra and HPLC chromatograms of the compounds. See DOI: https://doi.org/10.1039/d6ra02399a.

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