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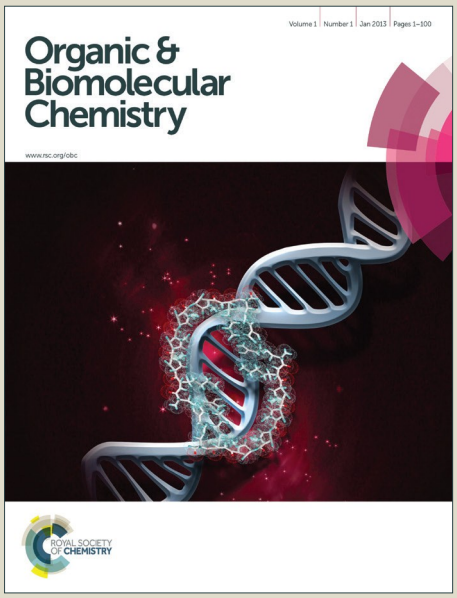

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ARTICLE

Transition-metal-free oxychlorination of alkenyl oximes: in situ generated radical with *tert*-butyl nitrite

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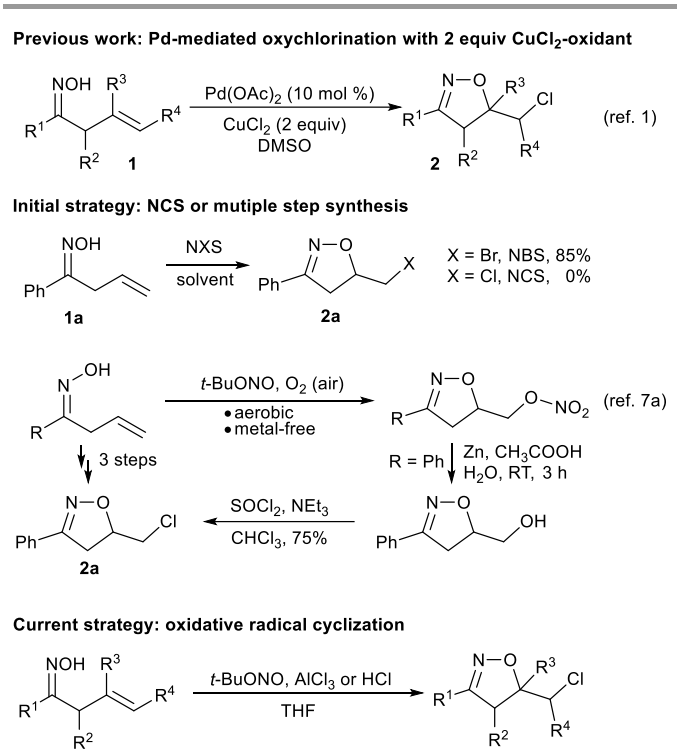
Oxychlorination of alkenyl oximes is harder compared to the analogous oxybromination or oxyiodination because of the difficulty associated to the formation of chlorine cations or radicals. A transition-metal-free oxychlorination of alkenyl oximes has been developed, using *t*-BuONO as a dual oxidant and $AlCl_3$ as chlorine source. This convenient and practical method has been used to construct chloroisoxazolines in moderate to good yields, whereas *N*-chlorosuccinimide (NCS) failed to promote this reaction.

Introduction

Chloromethyl dihydroisoxazoles are useful synthons for isoxazolidines, tetrahydropyrroles, and other synthetic intermediates. Although it seems simple to approach chloromethyl dihydroisoxazoles **2** directly from alkenyl oximes **1**, surprisingly, this straight forward synthetic method has been barely reported. Only one example could be achieved via SciFinder, which was the palladium-catalyzed oxychlorination of alkenyl oximes with 2 equiv of $CuCl_2$ as oxidant as well as Cl–source by Zhu *et al*. (Scheme 1, top).[1] Albeit the oxidative cyclization of alkenyl oximes to induce oxygens,[2] nitrogens,[3] iodines,[4] even carbons[5] and other atoms[6] to dihydroisoxazoles have been well established, the oxychlorination of **1** is relatively difficult because of the uneasy generation of Cl–radical or Cl–cation, compared to their iodine or bromine analogy. As a transition metal-free process, despite *N*–bromosuccinimide (NBS) gave high yield of oxybromination product of alkenyl oximes, *N*–chlorosuccinimide (NCS) was not reactive at all (Scheme 1, middle). A multiple step synthesis of chloromethyl dihydroisoxazole **2a** has been achieved on the basis of autoxidative nitrooxylation of alkenyl oximes.[7a] Hence a straight forward strategy is needed to synthesis of chloromethyl dihydroisoxazoles. On the basis of our previous work on nitrite-mediated promoted synthetic methods[7] as well as the self-hydride transferring rearrangement of *N*-methyl isoxazolidines and other reactions,[8] dihydroisoxazoles are good precursors for isoxazolidines. During the modification of the synthesis *cis*-isoxazolidines, we explored a transition-metal-free oxychlorination of alkenyl oximes *via* the strategy of radical cyclization-chlorination with *t*-BuONO (TBN) and $AlCl_3$. In this reaction, substoichiometric palladium and transition metal oxidant such as $CuCl_2$ have been avoided.



Scheme 1. Strategy for oxychlorination of alkene oximes.

Results and discussion

Initially, we chose alkene oxime **1a** as the substrate of the model reaction to investigate reaction conditions. First, **1a** was treated with NCS, unfortunately, no conversion of **1a** was observed (Table 1, entry 1). A new strategy was then applied by using the in situ generated chlorine radical from Cl^- and TBN. When hydric chloride (37% aq.) was utilized, **2a** was obtained in 52% yield. A series of other cheap [Cl]-source such as LiCl, *n*-Bu_4NCl, NH_4Cl and $AlCl_3$ were further screened, however, trace or even no desired product was observed except $AlCl_3$ (entries 3–6), where $AlCl_3$ gave the desired product **2a** in 79% yield in the presence of 2 equiv of water. Water was add to this reaction in consideration of the poor solubility of $AlCl_3$ in CH_3CN. To

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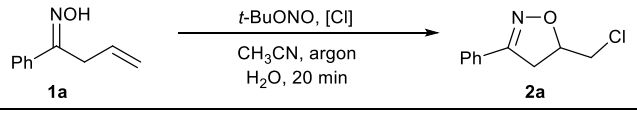
our surprise, the amount of water is important to this oxychlorination reaction (entries 6–9). The addition of 2 equiv of water gave rise to the increase of yield to 80% from 48% (entries 6 and 7). Switching the argon atmosphere to an open air atmosphere, the yield was nearly unchanged, suggesting that this reaction is not air- or moisture-sensitive (entries 6 and 10). Since it is too humid in summer in southern China, the reactions were still run under the argon atmosphere. The yield increased to 88% when the amount of $AlCl_3$ lowered to 0.5 equivalent as THF was used as the solvent (entry 15). The reaction conditions in entry 15 was finally chosen as the standard conditions for further investigation the reaction scope and limitation. It's worth noting that **2a** was obtained in 83% yield with acetic acid as solvent (entry 16), indicating that the carbocation should not be involved because the carbocation should be trapped by AcOH immediately.

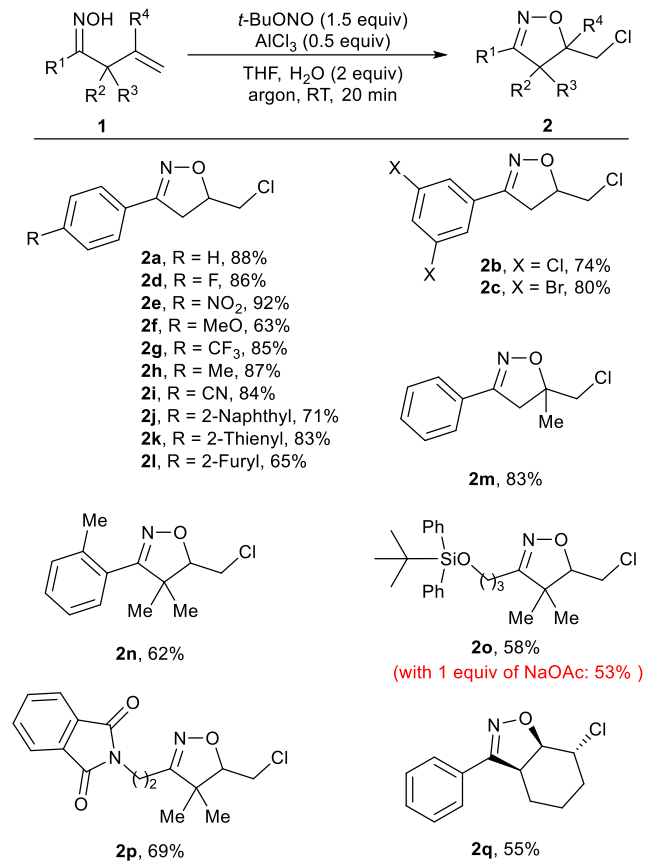
Table 1. Optimization of the conditions



entry[a]	[Cl] (equiv)[b]	*t*-BuONO (equiv)	H_2O (equiv)[b]	**2a** (%)[c]
1	NCS	1.5	–	0
2	HCl (2, 37%)	1.5	–	52
3	LiCl (1.5)	1.5	2	trace
4	NH_4Cl (1.5)	1.5	2	trace
5	nBu_4NCl (1.5)	1.5	2	trace
6	$AlCl_3$ (1.2)	1.5	2	80
7	$AlCl_3$ (1.2)	1.5	–	48
8	$AlCl_3$ (1.2)	1.5	5	59
9	$AlCl_3$ (1.2)	1.5	10	54
10[d]	$AlCl_3$ (1.2)	1.5	2	79
11	$AlCl_3$ (0.5)	1.5	2	84
12[e]	$AlCl_3$ (0.5)	0.5	2	46
13[e]	$AlCl_3$ (0.5)	1.0	2	75
14[e]	$AlCl_3$ (0.5)	0.25	2	20
15[e]	$AlCl_3$ (**0.5**)	**1.5**	2	**88**
16[f]	$AlCl_3$ (0.5)	1.5	2	83

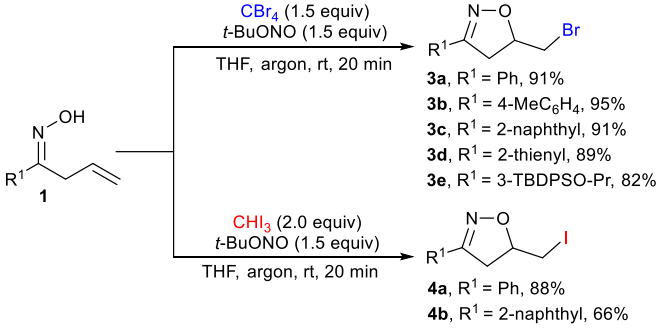
[a] Reaction conditions: **1a** (0.25 mmol), *t*-BuONO (1.5 equiv), CH_3CN (2 mL), argon, room temperature. [b] [Cl] (0.5–1.5 equiv), H_2O (0–10 equiv). [c] Isolated yields. [d] Under air. [e] Using THF as solvent instead of CH_3CN. [f] Using AcOH as solvent instead of CH_3CN.

Various substrates were subjected to the standard conditions, affording desired oxychlorination products **2a**–**2q** in generally moderate to good yields (Scheme 2). For example, products **2a**–**2i** bearing various substituted phenyl groups, regardless difference in electronic properties and substitution patterns, were obtained in good to high yields in 20 minutes at room temperature. Besides phenyl groups, naphthyl and heteroaryl substituted products **2j**, **2k** and **2l** were also achieved in good yields. Multiple substituted 4,5-dihydroisoxazoles **2m** and **2n** could also be obtained in 83% and 62% yields, respectively. This reaction also worked well for the alkenyl oxime **1q** with an internal C=C bond and afforded the *trans*-product **2q** in 55% yield. Only trace amount of *cis*-isomer of **2q** could be observed in the ^1H NMR spectrum of the crude product. The configuration of **2q** was assigned by comparison of the ^1H NMR spectrum with that of literature.[1,9] Aliphatic substrates with protecting groups such as TBDPS and 4-phthalimidyl were also tolerable in the standard condition (**2o** and **2p**). Despite TBDPS group is sensitive to acidic conditions, it still survived in this reaction. To make sure if the reaction could be carried out under near neutral conditions in the presence of 1 equiv of NaOAc and the yield of **2o** kept almost unchanged. Thus the drawback of the acidic reaction media could be solved by the addition of base such as NaOAc.



Scheme 2. Reaction scope. Conditions: **1** (0.25 mmol), $AlCl_3$ (0.125 mmol), H_2O (0.5 mmol), THF (2 mL), *t*-BuONO (0.375 mmol), RT, 20 min, argon. Isolated yield.

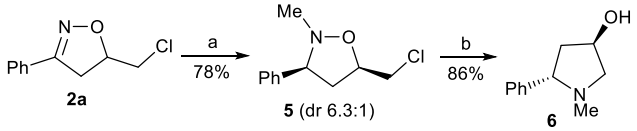
The oxybromination and oxyiodination have been investigated with randomly selected substrates (Scheme 3). Using CBr_4 as the bromine source, the oxybromination products **3a** to **3e** were obtained in generally high yields. CBr_4 is reactive to generate Br-radical, whereas **2a** could not be obtained from CCl_4. The oxyiodination products **4a** and **4b** were also afforded in 88% and 66% yields, respectively.



Scheme 3. Oxybromination and oxyiodination.

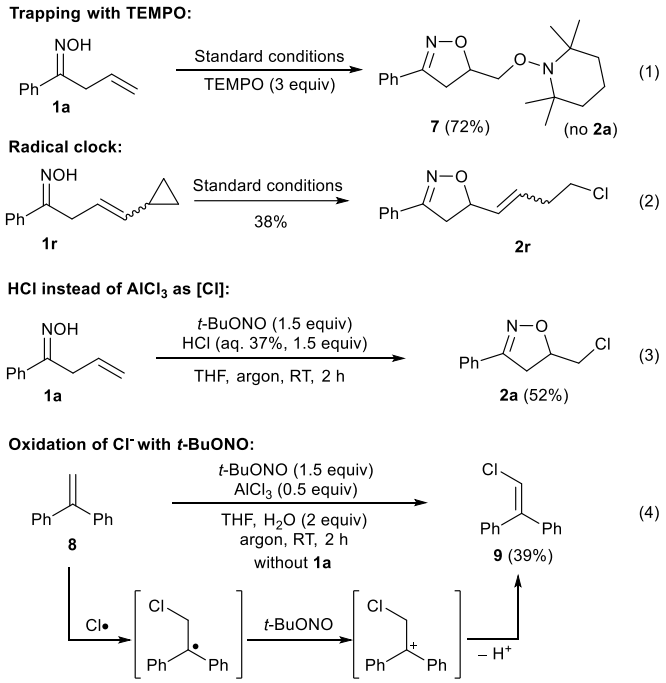
This synthetically practical oxychlorination reaction has been evaluated by the synthesis of pyrrolidine (Scheme 4). Isoxazoline **2a** was transformed to isoxazolidine **5** through methylation and

reduction with the selectivity of 6.3/1 (*cis*/*trans*). The major *cis*-compound **5** was smoothly converted to pyrrolidin-3-ol **6** in 86% yield.



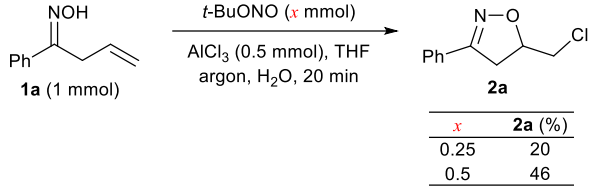
Scheme 4. Synthesis of pyrrolidin-3-ol. (a) Me_3OBF_4, CH_3NO_2, RT, 5 h; then $NaBH_4$, EtOH, –30 °C, 3 h. (b) Zn, CH_3CO_2H, H_2O, 50 °C, 4 h.

To explore the reaction mechanism, control experiments were designed and carried out (Scheme 5). The oxychlorination reaction were completely shut down when 3 equiv of TEMPO was added to the standard conditions, affording the TEMPO-adduct **7** in 72% yield (eqn 1), whereas **2a** or **7** could not be obtained without *t*-BuONO. Hence *t*-BuONO plays the role of radical initiator. Compound **1r** was subjected to the standard conditions to give the ring opening product **2r** in 38% yield (eqn 2). When $AlCl_3$ and H_2O were replaced by 1.5 equiv of HCl 37%, aq.), **2a** was isolated in 52% yield (eqn 3), suggesting that low concentration of HCl generated by the hydrolysis of the $AlCl_3$ could be the active Cl-source for this reaction. The chlorine radical trapping experiment was carried out.[10] The reaction was carried out in the presence of trapping reagent **8**,[11] trapping product **9** was isolated in 39% yield (eqn 4). On the basis of above experimental evidence, it was assumed that this reaction should pass through a radical pathway, where *t*-BuONO works as dual role of a radical initiator and an oxidant.



Scheme 5. Control experiments.

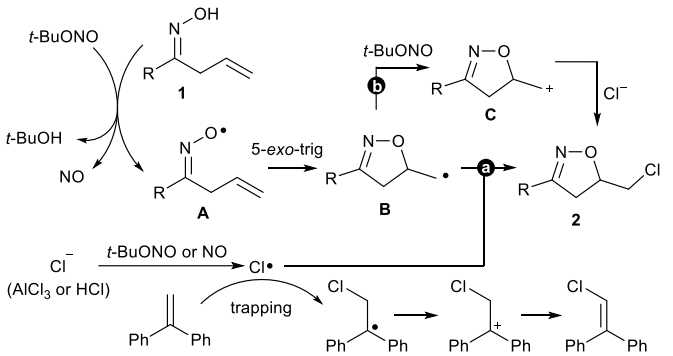
To verify NO or *t*-BuONO is the oxidant to convert Cl-anion to Cl-radical, the relationship between the yield of **2a** and the amount of *t*-BuONO was examined. The yield of **2a** was found to be dependent on the amount of *t*-BuONO (Scheme 6). The hypothesis that *t*-BuONO rather than NO works as the oxidant for the generation of Cl-radical is not supported by these results because that at least 2 equiv of *t*-BuONO should be necessary, one equiv for oxidative generation of nitroxyl radical and another equiv for oxidation of chlorine anion to radical. Alternatively, HNO_2 and/or NO_2 generated form the hydrolysis of TBN under acidic conditions could also act as the oxidant, however, the generation of key intermediate **A** needs 1 equiv of *t*-BuO-radical, whereas it could not be generated by such way. Therefore, NO or its dimer should act as the oxidant.



x	**2a** (%)
0.25	20
0.5	46

Scheme 6. Relationship between yield and the amount of *t*-BuONO.

A plausible mechanism for this reaction is demonstrated in Scheme 7. First, *t*-BuONO oxidizes oxime **1** to intermediate **A**, with the generation of NO and *tert*-butanol. Oxime radical **A** experiences a 5-*exo*-trig cyclization and generated the intermediate **B** which bearing an unstable carbon radical. Simultaneously, nitric oxide oxidizes Cl-anion to chlorine radical. Considering only 1.5 equiv of *t*-BuONO has been used for the oxychlorination and 1 equiv of *t*-BuONO was consumed to oxidize compound **1** into oxime radical, we believe that nitric oxide may directly play the role of oxidant. Finally, intermediate **B** combined with chlorine radical to afford product **2**. Alternatively, intermediate **B** might be oxidized to carbocation **C** which spontaneously traps chlorine anion to form product **2**. Considering the difficulty of oxidizing a primary carbon radical to carbocation under such conditions as well as the evidence of Cl-radical (Scheme 5, eqn 4), the radical pathway is preferred. The carbocation pathway should be ruled out because the reaction run in AcOH gave 83% of **2a** without AcOH trapping product (Table 1, entry 16).



Scheme 7. Proposed reaction mechanism.

Conclusions

In conclusion, a highly efficient radical oxychlorination of alkenyl oximes with *t*-BuONO and $AlCl_3$ has been developed. Various chloroisoxazolines bearing aryl, heteroary, and alkyl groups could be obtained in moderate to high yields, avoiding using toxic radical initiator or transition-metal reagents such as palladium and copper reagents. This convenient and practical method has been used to construct chloroisoxazolines, which could be further elaborated to useful hydroxyl pyrrolidine. The control experiments suggested the radical nature of this reaction, and a plausible reaction mechanism was proposed accordingly. The oxybromination and oxyiodination could also be achieved.

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Experimental section

General procedure A for oxychlorination

$AlCl_3$ (0.5 equiv) was weighed directly into a Schlenk tube and dried under high vacuum for 5 min, then the solution of oxime **1** (0.25 mmol) in THF (2 ml), *t*-BuONO (1.5 equiv) and water (2 equiv) were added sequentially under argon atmosphere. The reaction mixture was stirred at room temperature for 20 min, then the mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EA/PE) to give the product.

2a was obtained from **1a** according to the general procedure A as a white solid, (43.3 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 2 H), 7.45-7.38 (m, 3 H), 5.02-4.94 (m, 1 H), 3.71 (dd, *J* = 11.2, 4.4 Hz, 1 H), 3.58 (dd, *J* = 11.2, 7.2 Hz, 1 H), 3.49 (dd, *J* = 16.8, 10.4 Hz, 1 H), 3.33 (dd, *J* = 16.8, 6.4 Hz, 1 H).[1]

2b was obtained from **1b** according to the general procedure A as a brown solid mp 106-108 °C (70.4 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 1.6 Hz, 2 H), 7.41 (t, *J* = 1.6 Hz, 1 H), 5.09-5.01 (m, 1 H), 3.72 (dd, *J* = 11.6, 4.4 Hz, 1 H), 3.60 (dd, *J* = 11.6, 7.2 Hz, 1 H), 3.45 (dd, *J* = 16.8, 10.4 Hz, 1 H), 3.30 (dd, *J* = 17.2, 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 135.9, 132.3, 130.4, 125.4, 80.7, 45.0, 38.3. HRMS (ESI) calcd for $C_{10}H_9NOCl_3$ $[M+H]^+$ 263.9750, found 263.9752.

2c was obtained from **1c** according to the general procedure A as a white solid mp 122-123 °C (48.8 mg, 74%); ^{1}H NMR (400 MHz, CDCl3) δ 7.75-7.74 (m, 2 H), 7.72-7.71 (m, 1 H), 5.08-5.00 (m, 1 H), 3.72 (dd, *J* = 11.6, 4.0 Hz, 1 H), 3.60 (dd, *J* = 11.6, 7.2 Hz, 1 H), 3.44 (dd, *J* = 16.8, 10.4 Hz, 1 H), 3.29 (dd, *J* = 17.2, 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 135.9, 132.8, 128.7, 123.7, 80.7, 45.0, 38.3. HRMS (ESI) calcd for $C_{10}H_9NOClBr_2$ $[M+H]^+$ 351.8739, found 351.8736.

2d was obtained from **1d** according to the general procedure A as a colourless crystal (45.7 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.64 (m, 2 H), 7.14-7.07 (m, 2 H), 5.04-4.96 (m, 1 H), 3.72 (dd, *J* = 11.2, 4.4 Hz, 1 H), 3.58 (dd, *J* = 11.6, 7.6 Hz, 1 H), 3.49 (dd, *J* = 17.2, 10.8 Hz, 1 H), 3.33 (dd, *J* = 17.2, 6.4 Hz, 1 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.4.[1]

2e was obtained from **1e** according to the general procedure A as a white solid mp 153-154 °C (55.5 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30-8.26 (m, 2 H), 7.87-7.83 (m, 2 H), 5.14-5.07 (m, 1 H),), 3.75 (dd, *J* = 11.2, 4.0 Hz, 1 H), 3.65 (dd, *J* = 11.2, 7.2 Hz, 1 H), 3.54 (dd, *J* = 16.8, 10.8 Hz, 1 H), 3.39 (dd, *J* = 17.2, 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 149.0, 135.4, 127.9, 124.4, 81.0, 45.0, 38.2. HRMS (ESI) calcd for $C_{10}H_{10}N_2O_3Cl$ $[M+H]^+$ 241.0380, found 241.0378.

2f was obtained from **1f** according to the general procedure A as a colourless crystal (35.3 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.59 (m, 2 H), 6.95-6.90 (m, 2 H), 4.99-4.91 (m, 1 H), 3.71 (dd, *J* = 11.2, 4.4 Hz, 1 H), 3.56 (dd, *J* = 11.2, 7.6 Hz, 1 H), 3.48 (dd, *J* = 16.8, 10.4 Hz, 1 H), 3.32 (dd, *J* = 16.8, 6.4 Hz, 1 H).[1]

2g was obtained from **1g** according to the general procedure A as a white solid mp 65-66 °C (56.2 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 8.4 Hz, 2 H), 5.10-5.02 (m, 1 H), 3.74 (dd, *J* = 11.2, 4.0 Hz, 1 H), 3.62 (dd, *J* = 11.2, 7.2 Hz, 1 H), 3.52 (dd, *J* = 17.2, 10.8 Hz, 1 H), 3.37 (dd, *J* = 16.8, 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 132.8, 132.6, 132.2, 127.4, 126.1 (q, *J* = 3.8 Hz), 125.4, 122.6, 80.7, 45.1, 38.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9. HRMS (ESI) calcd for $C_{11}H_{10}NOClF_3$ $[M+H]^+$ 246.0403, found 246.0404.

2h was obtained from **1h** according to the general procedure A as a white solid (45.7 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 5.00-4.93 (m, 1 H), 3.71 (dd, *J* = 11.2, 4.4 Hz, 1 H), 3.56 (dd, *J* = 11.2, 7.6 Hz, 1 H), 3.49 (dd, *J* = 16.8, 10.4 Hz, 1 H), 3.33 (dd, *J* = 16.8, 6.4 Hz, 1 H), 2.38 (S, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 141.0, 129.8, 127.1, 126.5, 79.9, 45.1, 39.0, 21.8. HRMS (ESI) calcd for $C_{11}H_{13}NOCl$ $[M+H]^+$ 210.0686, found 210.0683.

2i was obtained from **1i** according to the general procedure A as a white solid mp 146-147 °C (46.2 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 5.11-5.03 (m, 1 H), 3.73 (dd, *J* = 11.6, 4.4 Hz, 1 H), 3.63 (dd, *J* = 11.6, 6.8 Hz, 1 H), 3.50 (dd, *J* = 16.8, 10.8 Hz, 1 H), 3.35 (dd, *J* = 17.2, 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 133.6, 132.9, 127.5, 118.6, 114.0, 80.9, 45.1, 38.1. HRMS (ESI) calcd for $C_{11}H_{10}NOCl$ $[M+H]^+$ 221.0482, found 221.0486.

2j was obtained from **1j** according to the general procedure A as a white solid mp 84-86 °C (43.5 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.91 (m, 2 H), 7.87-7.84 (m, 3 H), 7.56-7.50 (m, 2 H), 5.09-5.01 (m, 1 H), 3.76 (dd, *J* = 11.2, 4.4 Hz, 1 H), 3.66-3.58 (m, 2 H), 3.47 (dd, *J* = 16.8, 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 134.4, 133.3, 128.9, 128.7, 128.2, 127.6, 127.5, 127.1, 126.9, 123.8, 80.3, 45.2, 38.9. HRMS (ESI) calcd for $C_{14}H_{13}NOCl$ $[M+H]^+$ 246.0686, found 246.0686.

2k was obtained from **1k** according to the general procedure A as a colourless oil (41.8 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.41 (m, 1 H), 7.25-7.23 (m, 1 H), 7.09-7.06 (m, 1 H), 5.03-4.95 (m, 1 H), 3.72 (dd, *J* = 11.2, 4.0 Hz, 1 H), 3.58 (dd, *J* = 11.2, 7.6 Hz, 1 H), 3.52 (dd, *J* = 12.8, 6.4 Hz, 1 H), 3.37 (dd, *J* = 16.8, 6.0 Hz, 1 H).[1]

2l was obtained from **1l** according to the general procedure A as a white solid mp 68-69 °C (30.2 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 1.6 Hz, 1 H), 6.75 (d, *J* = 3.6 Hz, 1 H), 6.50 (q, *J* = 1.6 Hz, 1 H), 4.99-4.91 (m, 1 H), 3.70 (dd, *J* = 11.6, 4.4 Hz, 1 H), 3.55 (dd, *J* = 11.2, 7.2 Hz, 1 H), 3.46 (dd, *J* = 16.8, 10.4 Hz, 1 H), 3.31 (dd, *J* = 16.8, 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 144.9, 144.7, 112.6, 112.1, 79.8, 44.8, 38.8. HRMS (ESI) calcd for $C_8H_9NO_2Cl$ $[M+H]^+$ 186.0322, found 186.0322.

2m was obtained from **1m** according to the general procedure A as a white solid (43.3 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 2 H), 7.42-7.40 (m, 3 H), 3.65-3.51 (m, 3 H), 3.13-3.08 (m, 1 H), 1.62 (s, 3 H).[1]

2n was obtained from **1n** according to the general procedure A as a white solid mp 61-62 °C (370. mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 2 H), 7.25-7.15 (m, 2 H), 4.45 (t, *J* = 6.4 Hz, 1 H), 3.83 (dd, *J* = 11.6, 6.4 Hz, 1 H), 3.73 (dd, *J* = 11.6, 7.2 Hz, 1 H), 2.36 (s, 3 H), 1.34 (s, 3 H), 1.21 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 138.1, 131.2, 129.7, 129.3, 128.2, 125.8, 88.5, 54.2, 41.3, 25.7, 20.6, 18.8. HRMS (ESI) calcd for $C_{13}H_{17}NOCl$ $[M+H]^+$ 238.0999, found 238.0995.

2o was obtained from **1o** according to the general procedure A as a white solid mp 75-77 °C (64.2 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4 H), 7.45-7.36 (m, 6 H), 4.20 (dd, *J* = 7.6, 6.0 Hz, 1 H), 3.75 (t, *J* = 6.0 Hz, 2 H), 3.70 (dd, *J* = 11.6, 6.0 Hz, 1 H), 3.60 (dd, *J* = 11.6, 7.6 Hz, 1 H), 2.32-2.28 (m, 2 H), 1.94-1.87 (m, 2 H), 1.26 (s, 3 H), 1.12 (s, 3 H), 1.06 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 135.9, 134.1, 130.0, 128.0, 87.8, 63.3, 52.2, 41.3, 29.2, 27.2, 25.2, 21.3, 19.6, 18.4. HRMS (ESI) calcd for $C_{25}H_{34}NO_2NaSiCl$ $[M+Na]^+$ 466.1945, found 466.1945.

2p was obtained from **1p** according to the general procedure A as a white solid mp 157-159 °C (55.1 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.82 (m, 2 H), 7.73-7.70 (m, 2 H), 4.23 (t, *J* = 7.0 Hz, 1 H), 4.00 (t, *J* = 7.4 Hz, 2 H), 3.70 (dd, *J* = 11.6, 6.4 Hz, 1 H), 3.60 (dd, *J* = 11.6, 7.4 Hz, 1 H), 2.58 (t, *J* = 7.4 Hz, 2 H), 1.31 (s, 3 H), 1.16 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 163.7, 134.4, 132.3, 123.7, 87.8, 52.1, 41.1, 35.1, 25.1, 23.8, 18.4. HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3NaCl$ $[M+Na]^+$ 343.0825, found 345.0828.

2q was obtained from **1q** according to the general procedure A as a white solid mp 92-94 °C (32.3 mg, 55%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70-7.67 (m, 2 H), 7.44-7.40 (m, 3 H), 4.58 (dd, *J* = 7.2, 3.0 Hz, 1 H, H7a), 4.55 (q, *J* = 3.6 Hz, 1 H, H7), 3.59 (ddd, *J* = 10.2, 7.2, 7.2, Hz, 1 H, H3a), 2.08-1.98 (m, 3 H), 1.82-1.76 (m, 1 H), 1.54-1.50 (m, 1 H), 1.39-1.33 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 130.7, 129.2, 128.8, 127.4, 84.1, 55.1, 43.0, 29.5, 25.9, 17.3. HRMS (ESI) calcd for $C_{13}H_{15}NOCl$ $[M+H]^+$ 236.0842, found 236.0841.

2r was obtained from **1r** according to the general procedure A as a colourless oil (23.7 mg, 38%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (s, 2 H), 4.21 (dd, *J* = 7.2, 6.0 Hz, 1 H), 3.70 (dd, *J* = 11.2, 6.0 Hz, 1 H), 3.62-3.57 (m, 3 H), 3.35 (s, 3 H), 2.31-2.26 (m, 2 H), 1.99-1.92 (m, 2 H), 1.28 (s, 3 H), 1.14 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 96.8, 87.8, 67.2, 55.6, 52.2, 41.2, 26.3, 25.2, 21.7, 18.4. HRMS (ESI) calcd for $C_{11}H_{20}NO_3NaCl$ $[M+Na]^+$ 272.1029, found 272.1023.

General procedure B for oxybromination

CBr_4 (1.5 equiv) was weighed directly into a Schlenk tube and dried under vacuum for 5 min, then the solution of oxime **1** (0.25 mmol) in THF (2 mL), *t*-BuONO (1.5 equiv) were added sequentially under argon atmosphere. After stirring at RT for 20 min, the mixture was concentrated under reduced pressure and purified by silica gel column chromatography (EA/PE) to give the product.

3a was obtained from **1a** according to the general procedure B as a light yellow solid (54.8 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 2 H), 7.42-7.39 (m, 3 H), 5.03-4.95 (m, 1 H), 3.57 (dd, *J* = 10.4, 4.4 Hz, 1 H), 3.51 (dd, *J* = 17.2, 10.8 Hz, 1 H), 3.41 (dd, *J* = 10.8, 8.4 Hz, 1 H), 3.32 (dd, *J* = 17.2, 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 130.6, 129.3, 129.0, 127.0, 79.9, 39.8, 33.5.[1]

3h was obtained from **1h** according to the general procedure B as a white solid (60.3 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 5.01-4.93 (m, 1 H), 3.57 (dd, *J* = 10.4, 4.4 Hz, 1 H), 3.49 (dd, *J* = 17.2, 10.4 Hz, 1 H), 3.40 (dd, *J* = 10.4, 8.4 Hz, 1 H), 3.30 (dd, *J* = 17.2, 6.4 Hz, 1 H), 2.38 (S, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 141.0, 129.8, 127.0, 126.4, 79.8, 40.0, 33.5, 21.7.[1]

3j was obtained from **1j** according to the general procedure B as a white solid mp 94 °C (65.8 mg, 91% yield). ^{1}H NMR (400 MHz, CDCl3) δ 7.96 (dd, J = 8.8, 1.6 Hz, 1 H), 7.91-7.90 (m, 1 H), 7.87-7.83 (m, 3 H), 7.56-7.50 (m, 2 H), 5.09-5.01 (m, 1 H), 3.66-3.58 (m, 2 H), 3.48-3.41 (m, 2 H). ^{13}C NMR (100 MHz, CDCl3) δ 156.5, 134.4, 133.2, 128.9, 128.7, 128.2, 127.6, 127.5, 127.1, 126.9, 123.8, 80.2, 39.8, 33.6. HRMS (ESI) calcd for C14H13NOBr [M+H]+ 290.0175, found 290.0180.

3k was obtained from **1k** according to the general procedure B as a light yellow oil (54.6 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (m, 1 H), 7.23-7.21 (m, 1 H), 7.09-7.05 (m, 1 H), 5.04-4.95 (m, 1 H), 3.59-3.48 (m, 2 H), 3.40 (dd, *J* = 10.4, 8.4 Hz, 1 H), 3.37-3.29 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 131.7, 129.2, 129.0, 127.7, 80.2, 40.7, 33.4.[1]

3o was obtained from **1o** according to the general procedure B as a colorless oil (99.7 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4 H), 7.45-7.36 (m, 6 H), 4.27 (dd, *J* = 7.6, 6.0 Hz, 1 H), 3.75 (t, *J* = 6.0 Hz, 2 H), 3.53 (dd, *J* = 10.4, 6.0 Hz, 1 H), 3.42 (dd, *J* = 10.8, 7.6 Hz, 1 H), 2.30 (dd, *J* = 9.2, 7.2 Hz, 2 H), 1.94-1.87 (m, 2 H), 1.27 (s, 3 H), 1.11 (s, 3 H), 1.06 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 135.9, 134.1, 130.0, 128.0, 87.7, 63.3, 52.3, 29.2, 28.3, 27.2, 25.3, 21.4, 19.6, 18.4. HRMS (ESI) calcd for $C_{25}H_{35}NO_2SiBr$ $[M+H]^+$ 488.1615, found 488.1620.

General procedure C for oxyiodination

CHI_3 (2.0 equiv) was weighed directly into a Schlenk tube and dried under vacuum for 5 min, then the solution of oxime **1** (0.25 mmol) in THF (2 mL), *t*-BuONO (1.5 equiv) were added sequentially under argon atmosphere. After stirring at RT for 20 min, the mixture was concentrated under reduced pressure and purified by silica gel column chromatography (EA/PE) to give the product.

4a was obtained from **1a** according to the general procedure C as a white solid (63.2 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 2 H), 7.42-7.36 (m, 3 H), 4.91-4.83 (m, 1 H), 3.47 (dd, *J* = 16.8, 11.2 Hz, 1 H), 3.38 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.22 (dd, *J* = 10.0, 8.8 Hz, 1 H), 3.18 (dd, *J* = 16.8, 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 130.6, 129.3, 129.0, 127.0, 80.6, 41.2, 8.0.[12]

4j was obtained from **1j** according to the general procedure C as a light yellow solid mp 101-103 °C (55.6 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.83 (m, 5 H), 7.56-7.50 (m, 2 H), 5.09- 5.01 (m, 1 H), 3.66-3.58 (m, 2 H), 3.48-3.41 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 134.4, 133.2, 128.9, 128.7, 128.2, 127.6, 127.4, 127.1, 126.9, 123.7, 80.9, 41.2, 8.0. HRMS (ESI) calcd for $C_{14}H_{13}NOI$ $[M+H]^+$ 338.0036, found 338.0038.

Synthesis of 6. To a solution of **2a** (0.4 mmol) in nitromethane (3 mL) was added trimethyloxonium tetrafluoroborate (2 equiv). The mixture was stirred at room temperature for 5 h and concentrated in *vacuo*. The crude tetrafluoroborate product was dissolved in ethanol (4 mL) and stirred at -30 ˚C, while sodium borohydride (10 equiv) was added portionwise. The mixture was stirred at this temperature for 3 h before saturated ammonium chloride solution was added to quench the reaction. Then, the mixture was extracted with ethyl acetate and the combined organic layers were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in *vacuo*. The crude material was purified by flash column chromatography (PE/EA = 30:1) and gave compound 5, 66.1 mg, 78% yield with 6.3:1 *cis*-selectivity. White solid mp 59-60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5 H), 4.42-4.34 (m, 1 H), 3.82 (dd, *J* = 10.8, 6.8 Hz, 1 H), 3.57 (dd, *J* = 10.8, 6.8 Hz, 2 H), 2.91-2.83 (m, 1 H), 2.58 (s, 3 H), 2.19-2.12 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 129.1, 128.4, 127.9, 76.7, 73.8, 47.1, 44.5, 43.4. HRMS (ESI) calcd for $C_{11}H_{15}NOCl$ $[M+H]^+$ 212.0842, found 212.0840.

The *cis*-product **5** (0.2 mmol) and activated zinc powder (10 equiv) were weighed directly into a flask before acetic acid (2 mL) and water (2 mL) were added. The reaction was stirred at 50 ˚C for 4 h, then neutralized by NaOH solution, filtrated, and the mixture was extracted with DCM and the combined organic layers were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in *vacuo*. The crude material was purified by flash column chromatography (DCM/MeOH = 50:1), and gave 38.2 mg of **6** with a yield of 86%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.30 (m, 4 H), 7.29-7.23 (m, 1 H), 4.56-4.51 (m, 1 H), 3.65 (dd, *J* = 10.0, 6.4 Hz,

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1 H), 3.44 (dd, *J* = 9.6, 7.2 Hz, 1 H), 2.42 (br s, 1 H), 2.32 (dd, *J* = 10.0, 5.2 Hz, 1 H), 2.19 (s, 3 H), 2.13-2.04 (m, 2 H). ^{13}C NMR (0 MHz, $CDCl_3$) δ 142.1, 128.8, 127.9, 127.7, 69.9, 69.8, 66.0, 46.2, 40.5. HRMS (ESI) calcd for $C_{11}H_{16}NO$ $[M+H]^+$ 178.1232, found 178.1234.

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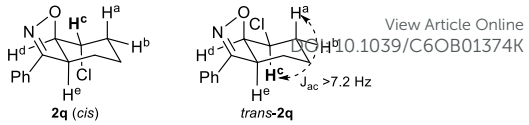
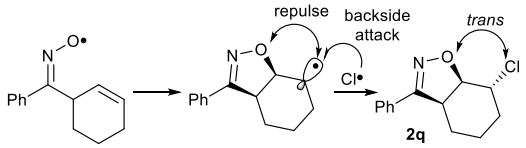
9. 600M ^{1}H-NMR spectrum of **2q** shows that H^c is pseudo-quartet with a small *J*-value (3.56 Hz). If H^c is at the axial position (*trans* to oxygen), the diaxial $J_{a\text{-}c}$ should be larger than 7.2 Hz (below). The *trans*-configuration could be explained by the model below.





10. Hydric chloride is a medium strong acid, which will result in the decomposition of oxime substrate. A low concentration of HCl is generated by the hydrolysis of $AlCl_3$ in the present of water, which is much milder.

$AlCl_3 + H_2O \rightleftharpoons Al(OH)Cl_2 + HCl$

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