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Asymmetric α-oxyamination of aldehydes by synergistic catalysis of imidazolethiones and metal salts †

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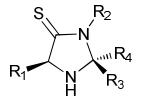
The novel and efficient imidazolethione catalysts combined with metal salts were successfully introduced to the asymmetric α-oxyamination of aldehydes. The desired products with high yields and good to excellent enantioselectivities were obtained via a one-pot oxidation-oxyamination reaction system.

Asymmetric organocatalysis played a pivotal role in synthesis of a variety of chiral molecules. Among them, oxygen-bearing stereocenters, especially the enantioselective α-oxygenated carbonyl formations are one of the fundamental structural motifs in natural and synthetic products, such as taxol, bestai, and zaragozic acid.[1] Many traditional methods including aminohydroxylations[2], olefin epoxydation[3] and dihydroxylation[4] exhibited good capability to provide these asymmetric oxygen-bearing stereocenters. Recently, the newly developed asymmetric α-oxidation of aldehydes as an important approach to form the enantioselective oxygen-bearing stereocenters has also been substantially studied with the presence of different catalytic systems.

MacMillan[5] and Zhong[6] reported the first direct α-oxidation of aldehydes using natural proline and nitrosobenzene in 2003. The catalytic enantioselective α-oxyamination of aldehydes using 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) as an electrophilic source of oxygen in the presence of imidazolidinone were reported by Sibi[7] and MacMillan[8] in their respective work in 2007 and 2010. In 2010, Kudo's group developed a bioinspired catalyst and used it to the asymmetric α-oxyamination of aldehydes via a tandem system with primary alcohol's oxidation.[9] Maruoka used binaphthyl-based chiral amine catalysts and an oxoammonium salt instead of metal reagents to obtain stable α-oxy aldehydes with excellent enantioselectivity.[10] Similar α-oxyamination reaction was also reported with using other catalyst systems, such as porous cross-linked polymers (PCPs) photocatalysts[11], TiO_2 photocatalyst[12], or electrochemical oxidation[13]. In 2012, MacMillan extended the scope of substrates and gained excellent enantioselectivity in low temperature using synergistic catalysis system of imidazolidinone and metal salts.[14] Meanwhile, these asymmetric α-oxyamination aldehydes can be also obtained by many related multistep reactions[15] and two of them were applied to the synthesis of Oxylipins[16] and Pentoses[17] successfully.

Although many of the reported organocatlysts show efficient in this asymmetric α-oxyamination of aldehydes, not all the substrates can be obtained with good enantioselectivity, and the yield still need to be improved via the one-pot reaction system. So new organocatlysts aimed to provide better yields and enantioselectivity with expanded substrate scopes are still worthwhile to investigate. In previous works,[18] we had reported the successful application of newly developed chiral imidazolethiones catalysts (Fig.1) in the enantioselective Friedel-Crafts reactions. The structure of thioamide was used to increase the rigidity of catalyst[17] and the more 'stiffer' imidazolethiones were anticipated to help improve the stereoselectivity in reactions. Base on the good catalytic activity and applications of imidazolethiones, the synergistic catalysis of imidazolethiones and metal salts were introduced to the reactions of α-oxyamination of aldehydes in this work to provide another useful choice for asymmetric C-O bond formation. The possible synergistic catalytic mechanism was also discussed.



R_1 = Bn; R_2 = CH_3; R_3, R_4 = CH_3, Cy.

Fig.1 Chiral imidazolethione catalysts

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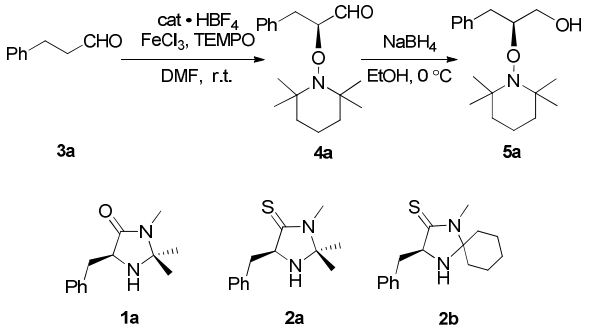
Table 1 α-Oxyamination of **3a** using different catalysts



3a **4a** **5a**

1a **2a** **2b**

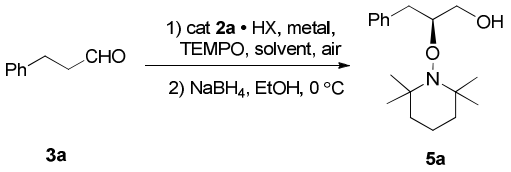
Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	1a	3	80	68
2	2a	3	75	73
3	2b	3	trace	n.d.[d]

[a] Reaction condition: **3a** (1 mmol), TEMPO (2 mmol), catalyst (20 mol%), HBF_4 (20 mol%), $FeCl_3$ (1 equiv.), DMF (2 mL); $NaBH_4$ (2 equiv.). [b] Isolated yield. [c] Enantiomeric excess determined by HPLC analysis. [d] not determined.

To evaluate the efficiency of catalysts, the reaction of 3-phenylpropanal **3a** and TEMPO was used as a model reaction based on the reaction conditions reported in literature.[7] The **3a** and TEMPO in DMF were treated with a stoichiometric amount of ferric chloride and a catalytic amount of different imidazolethione catalysts, respectively. Reduction of product α-aminoxy aldehyde **4a** to the primary alcohol **5a** was performed to aid analysis and the results were presented in Table 1. Compared with imidizolidinone **1a** (Table 1, entry 1), a better stereoselectivity were obtained in the presence of imidazolethione **2a** (Table 1, entry 2). The imidazolethione catalyst **2b** with a larger cyclohexyl group was also evaluated for its catalytic activity, however, nearly no product was observed (Table1, entry 3). The preliminary experiment results indicate that catalyst imidazolethione **2a** has a better catalytic efficiency against **1a** and **2b**. The (*S*)-configurations were the main products according to the HPLC data reported in the literature.[7]

With the optimized catalyst imidazolethione **2a** in hand, the reaction conditions including solvents, additives acids and synergistic metal salts were further examined with results summarized in table 2. Among DMF, CH_2Cl_2, acetone, *i*-PrOH, H_2O (Table 2, entries 1-5) and a series of mixed solvents (Table 2, entries 6-10), the proportion of H_2O affecting the yield of the reaction significantly and higher yield and good selectivity were obtained in H_2O at room temperature (Table 2, entry 5). Then additive acids that help to activate the substrates were evaluated and results showed that imidazolethione **2a** with trifluoroacetic acid gave the product in high yield and enantio-selectivity (Table 2, entries 5, 11, 12). To further improve the enantio-selectivity, the reaction was performed at 0 °C and -10 °C by adding a certain amount of acetone to H_2O to lower its freezing point, but the ee value was still unsatisfactory (Table 2, entries 13 and 14). The synergistic metal salts, including $FeCl_3$, $FeCl_2$, $CuCl_2$, $CuSO_4$ and CuCl were chosen to facilitate the catalytic system. And better enantioselectivity was obtained when 10 mol% $CuCl_2$ was used at -20 °C (Table 2, entry 23). At room temperature, both $CuCl_2$ and CuCl gave good yields and ee values (Table 2, entries 17 and 19) with reaction time at 3 h. Lower reaction temperatures were also investigated to obtain even better enantioselectivity albeit with

Table 2 Optimization of the reaction conditions



3a **5a**

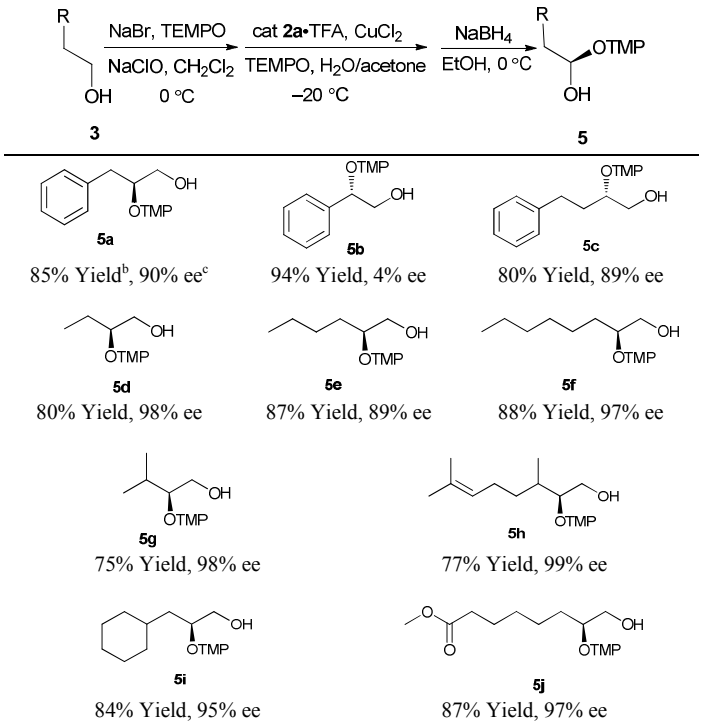
Entry	Solvent (v/v)	Acid	Metal	T (°C)	Yield[b] (%)	ee[c] (%)
1	DMF	TFA	$FeCl_3$	25	78	76
2	CH_2Cl_2	TFA	$FeCl_3$	25	trace	n.d.
3	acetone	TFA	$FeCl_3$	25	23	n.d.
4	*i*-PrOH	TFA	$FeCl_3$	25	15	n.d.
5	H_2O	TFA	$FeCl_3$	25	85	75
6	H_2O/CH_2Cl_2(4:1)	TFA	$FeCl_3$	25	85	74
7	H_2O/CH_2Cl_2(1:1)	TFA	$FeCl_3$	25	53	65
8	H_2O/CH_2Cl_2(1:4)	TFA	$FeCl_3$	25	8	n.d.
9	H_2O/acetone(4:1)	TFA	$FeCl_3$	25	83	70
10	H_2O/DMF (4:1)	TFA	$FeCl_3$	25	73	67
11	H_2O	HBF_4	$FeCl_3$	25	80	73
12	H_2O	*p*-TSA	$FeCl_3$	25	57	64
13[d]	H_2O	TFA	$FeCl_3$	0	80	79
14[e]	H_2O/acetone(4:1)	TFA	$FeCl_3$	-10	76	82
15	H_2O	TFA	$FeCl_2$	25	83	72
16	H_2O	TFA	$FeSO_4$	25	77	72
17	H_2O	TFA	$CuCl_2$	25	89	80
18	H_2O	TFA	$CuSO_4$	25	77	73
19	H_2O	TFA	CuCl	25	83	85
20[e]	H_2O/acetone(4:1)	TFA	CuCl	-10	74	78
21[f]	H_2O/acetone(2:1)	TFA	CuCl	-20	65	72
22[f]	H_2O/acetone(2:1)	TFA	$CuCl_2$	-20	83	89
23[g]	H_2O/acetone(2:1)	TFA	$CuCl_2$	-20	80	90

[a] Reaction condition: **3a** (1 mmol), TEMPO (2 mmol), **2a** (20 mol%), HX (20 mol%), metal (1 equiv.), solvent (2 mL), $NaBH_4$ (2 equiv.). [b] Isolated yield. [c] Enantiomeric excess determined by HPLC analysis. [d] 12 h. [e] 24 h. [f] 48 h. [g] $CuCl_2$ (10 mol%), TEMPO (1.5 equiv.), 48 h.

somewhat longer reaction time. Curiously, differences were observed between the synergistic metal salts of Cu(I) and Cu(II). The ee value decreased from 85% to 72% when the temperature was down to -20 °C in the presence of CuCl (Table 2, entry 21). However, the good ee value was obtained with $CuCl_2$ at -20 °C (Table 2, entry 22). High yield and enantioselectivity could also be observed when the amount of $CuCl_2$ and TEMPO were decreased to 10 mol% and 1.5 equiv. (Table 2, entry 23).

Allowed for the unstable properties of aldehydes and observed good yield and *ee* value in H_2O/CH_2Cl_2 (Table 2, entry 6). We developed a one-pot reaction system under the optimal reaction conditions (Table 2, entry 23) including oxidation of primary alcohols, followed by the asymmetic α-oxyamination of aldehydes, and then the $NaBH_4$ reduction of aldehydes to corresponding alcohols as shown in Table 3. The TEMPO and NaClO system was chosen as oxidizing agent in the first step due to its mild reaction condition and high conversion rates. The oxidation-oxyamination and reduction reactions of alcohols **3** provided products **5** in good yields and with high to excellent enantioselectivities except **3b**. It was observed that the reaction of 2-phenylethanol **3b** provided the product in very high yield but showed very low enantioselectivities with 4% ee, which might have resulted from the rapid racemization of phenylacetaldehyde. Both aromatic and aliphatic alcohols were applied in these sequential reaction systems. When 4-phenyl-1-butanol **3c** was used as substrate,

Table 3 One-pot oxidation–oxyamination of various alcohols.



[a] Reaction condition: 3 (1 mmol), TEMPO (1.5 mmol), CH_2Cl_2 (1 mL), 2a (20 mol%), TFA (20 mol%), $CuCl_2$ (10 mol%), H_2O/acetone (v/v = 2:1), $NaBH_4$ (2 equiv.). [b] Isolated yield. [c] Enantiomeric excess determined by HPLC analysis.

the product **5c** can be obtained in good yield and enantioselectivity. This was the case with several long-chain and short-chain aliphatic alcohols **3d, 3e** and **3f**. It was worth noting that the yields of product **5g** and **5h** were decreased when the *γ*-position substituted alcohols were used. It might be due to the presence of the steric groups hinder the attack of TEMPO. Olefin, cyclohexyl, ester containing alcohols **3h, 3i** and **3j** were also confirmed to be the competent substrates, which yielded the corresponding products in good yields and excellent enantioselectivity. Overall, the above results demonstrate that this one-pot sequential reaction system with optimized reaction conditions catalyzed by imidazolethione **2a** can be applied to a broad substrate scope.

There existed two mainly differential opinions about the mechanism of asymmetric *α*-oxyamination of aldehydes. In 2007, Sibi[7] proposed a singly occupied molecular orbital (SOMO) activation mechanism. In 2010, MacMillan and his co-workers[8] revealed the reaction proceeded via a more traditional enamine addition pathway. Based on the enamine addition mechanism[8,19] and experimental results in this work, we proposed a synergistic catalysis mechanism (Scheme 1). The catalysts imidazlethiones coupled with Cu(II) activated aldehydes and TEMPO in their own catalytic cycles, respectively. The two activated intermediates narrowed the energy gap and facilitated reaction. Firstly, aldehyde was activated by chiral imidazolidinone catalysts and formed the enamine intermediate Ⅰ. Simultaneously, TEMPO as another substrate was activated by Cu(II) and formed the Cu(II)-TEMPO complex Ⅱ. Then, the complex as electrophile attacked enamine intermediate to produce the iminium ion Ⅲ. The hydrolysis of intermediate Ⅲ released imidazolethiones and Cu(I). The Cu(I) was reoxidized by ambient oxygen to regenerate the Cu(II) salt and worked in the cycle again.

Conclusions

In summary, the imidazolethione catalyst **2a** is successfully applied to the asymmetric *α*-oxyamination of aldehydes *via* the efficient one-pot sequential reaction system. The corresponding products are obtained in good yields and high to excellent enantioselectivities. Applications of this synergistic catalysis system to *α*-functionalization of carbonyl compounds are underway in our laboratory.

Acknowledgements

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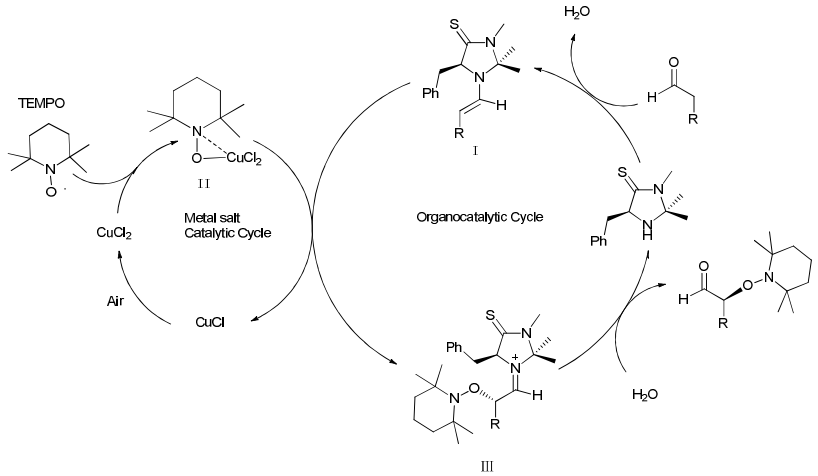

Scheme 1 The possible synergistic catalytic mechanism

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