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Direct N–O bond formation *via* oxidation of amines with benzoyl peroxide†

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Herein, we report a general and efficient method for direct N–O bond formation without undesirable C–N bond (amide) formation starting from commercially available amines and benzoyl peroxide. The oxidation of 1,2-diamines to furnish bis-(benzoyloxy)-1,2-diamines is reported for the first time. We found that a significant amount of water (BPO : water = 3 : 1) in combination with Cs₂CO₃ is necessary to achieve high selectivity and yield. The reaction conditions are applicable to a wide range of 1,2-diamine and 1,2-disubstituted-1,2-diamine substrates. Additionally this method is highly applicable to primary and secondary amines. Further, the present method can access chiral bis-hydroxamic acids and bis-hydroxyl amines in just two steps from 1,2-diamines. The reaction conditions are simple, mild and inert atmosphere free. The synthetic potential of this methodology is further demonstrated in the short synthesis of a chiral BHA ligand.

Introduction

Despite the prevalence of nitrogen–oxygen bonds in biologically active molecules and natural products, methods that form these N–O bonds remain rare.¹ Recently, both industry and academia have paid significant attention to the N–O bond formation because of its synthetic utility.² Moreover, compounds containing the N–O bond can be useful synthetic intermediates such as N-oxides, hydroxyl amines, hydroxamic acids *etc.* Whereas tertiary N–O bond synthesis (N-oxide) from tertiary amines using oxidants are well studied,³ very few contributions have been made for primary and secondary N–O bond construction directly from amines which often suffer from competition from N–O *vs.* C–N bond formation. Significantly, direct construction of the N–O bond from amines provides an attractive approach to access hydroxamic acids and hydroxyl amines.⁴

Hydroxamic acid and its derivatives are an important class of biologically active molecules, principally known as strong polyfunctional metal ion chelators as they possess a wide range of biological activities such as antibacterial, antifungal, anti-inflammatory and anti-asthmatic behavior^{5a} and have been used in the design of therapeutic agents for cancer,^{5b,c} Alzheimer's disease,^{5d} haemochromatosis^{5e} and malaria.^{5f} Additionally, hydroxamic acids are vastly utilized as excellent ligands in synthetic organic chemistry.⁶ Interestingly, *N*-(benzoyloxy) amines (hydroxyl amine precursor) are known to serve as key

intermediates in the synthesis of amines (secondary and tertiary), amides, hydroxamic acids *etc.*⁷

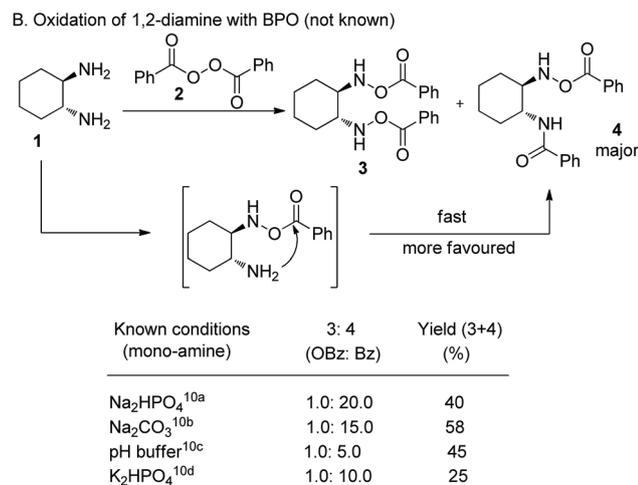
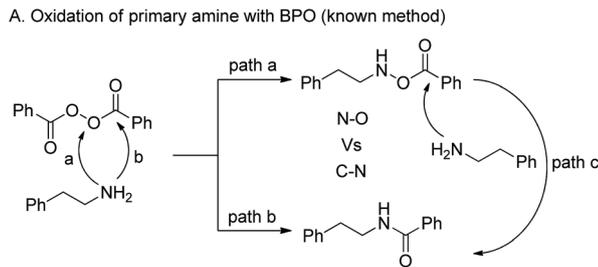
Meanwhile, it is well known that hydroxyl amine is the best source of reactive nitroso (N–O bond) intermediates⁸ and for a decade we have used these intermediates to synthesize various new types of N-selective (C–N–O) as well as O-selective (C–O–N) bond-containing synthetically useful chiral compounds as well as bioactive compounds.⁹ We are eager to investigate if N–O bond formation could be achieved by choosing suitable reaction conditions using amines and benzoyl peroxide.

Very few reliable methods are known for N–O bond formation resulting in *N*-(benzoyloxy)amines in moderate yields directly from amines using benzoyl peroxide (BPO).¹⁰ However, most of the methods suffer from undesirable C–N bond (amide side product) formation, especially in the case of primary amines, which ultimately reduces the efficiency of the overall process (Scheme 1A).^{10a–c} Bis-hydroxamic acids (BHA) are extremely important molecules as chiral building blocks and chiral ligands in modern asymmetric catalysis.¹¹ Unfortunately, the direct synthesis of BHAs also suffers from serious problems from the above side reactions (Scheme 1B). A nucleophilic amine is able to react with BPO at both the peroxide oxygen and at the carbonyl centre, and both are almost equally reactive. The C–N bond (amide) is, however, more stable than the N–O bond (N–OBz). The carbonyl group in N–OBz is active enough to react with another amine leading to competition between intramolecular C–N bond *vs.* intermolecular N–O bond formation with another equivalent of BPO. The thermodynamically favourable intramolecular reaction leads to **4** as a major product. However, known mono-amine oxidation methods provide poor results (Scheme 1B). Thus, in order to improve the efficiency, controlling the reaction conditions to minimize side products remains a synthetic challenge.

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Scheme 1 Inherent problems associated with the oxidation of amines with benzoyl peroxide.

Previously, we introduced bis-hydroxamic acids as versatile chiral ligands for several asymmetric epoxidations of olefins to give synthetically challenging chiral epoxy alcohols and asymmetric ring opening of epoxides.¹² Although epoxy alcohols are synthesized with an excellent yield (up to 99%) and enantiopurity (ee up to >99%), the ligand synthesis suffers from multistep and time consuming processes (for a detailed scheme see ESI Section 7[†]).^{12a,b} Thus our current interest is to develop a general and efficient method for the synthesis of bis-hydroxamic acids and bis-hydroxyl amines. Following a retrosynthetic approach bis-hydroxamic acids and bis-hydroxyl amines could be achieved directly from the challenging bis-(benzoyloxy)-1,2-diamines (Fig. 1). Herein we report, for the first time, oxidation of 1,2-diamines with BPO to give bis(benzoyloxy)-1,2-diamines with a very good yield and selectivity. As far as we are aware, this oxidation process is unprecedented in product scope as there are no previous reports on the formation of bis(benzoyloxy)-1,2-diamines from 1,2-diamines.

Results and discussion

We began our investigation using commercially available benzoyl peroxide and *trans*-1,2-diaminocyclohexane as a model substrate and we decided to alter various parameters to optimize the reaction conditions. Preliminary studies showed that a base that removes the produced benzoic acid in the reaction mixture is necessary to improve the yield of the product. Initially, we chose K₂CO₃ (4.0 equiv.) as a base and tested it with

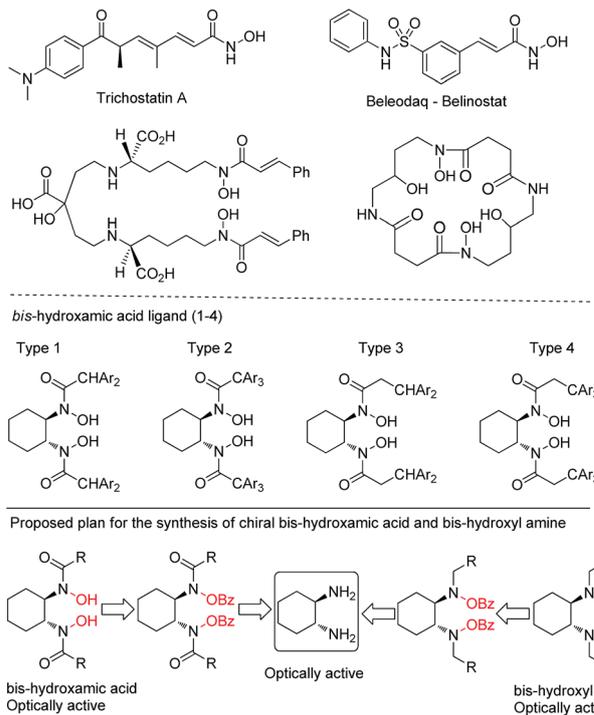


Fig. 1 Biologically and synthetically useful hydroxamic acid derivatives.

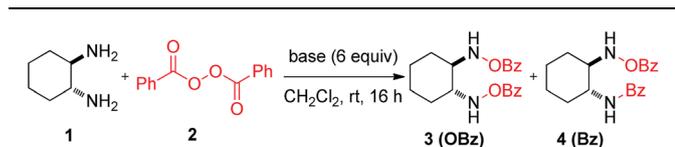
recrystallized BPO (3.0 equiv.) in various anhydrous solvents which resulted in a moderate yield (<50%) of the product but mostly amide 4 as a major product (OBz : Bz = 1.0 : 10.0). Further investigation showed that the presence of a small amount of water is very crucial to improve the yield and selectivity (see the ESI[†]). From these studies we found that a ratio of BPO : water = 3 : 1 is necessary to achieve good results. Interestingly, when we used commercially available 75% BPO (Aldrich, remaining 25% water) in combination with K₂CO₃, a sharp improvement in yield (88% for CHCl₃ and 82% for CH₂Cl₂) and selectivity (OBz : Bz = 1.0 : 1.2) was observed. Further, we tested various metal carbonates (4.0 equiv.) but only Cs₂CO₃ provided better results with promising selectivity (OBz : Bz = 5 : 1) and yield (90%). Then we tested various equivalents of Cs₂CO₃ to achieve high yield and selectivity. To our delight, when the amine solution (in 2 mL CH₂Cl₂) was added to a stirred mixture of BPO and Cs₂CO₃ (Table 1, entry 4), we observed a sharp change in selectivity (OBz : Bz = 10 : 1) and yield (95% yield). Significantly, other metal carbonates failed to improve the selectivity and yield (entries 1–3, entries 5–8). Further, we also tested various cesium salts (entries 9–11) and phosphate salts (entries 12–15) but they failed to improve the results (see details in the ESI[†]).

Bis-(benzoyloxy)-1,2-diamine synthesis

After having the optimized conditions in hand, we then explored the substrate scope and the generality of this reaction. We were pleased to find that the high efficiency demonstrated by the model oxidation reaction also applied to a broad range of



Table 1 Optimization of oxidation of (\pm)-*trans*-1,2-cyclohexanediamine with BPO^a



Entry	Base	3 : 4 (OBz : Bz) ^b	Yield (3 + 4) ^b
1	Li ₂ CO ₃	1.0 : 10.0	30
2	Na ₂ CO ₃	1.0 : 5.0	78
3	K ₂ CO ₃	1.0 : 1.2	88
4	Cs ₂ CO ₃	10.0 : 1.0	95
5	Rb ₂ CO ₃	1.0 : 2.0	70
6	CaCO ₃	1.0 : 15.0	20
7	MgCO ₃	1.0 : 6.0	30
8	BaCO ₃	1.0 : 10.0	25
9	CsOAc	1.0 : 3.0	25
10	CsI	—	<5
11	CsNTf ₂	1.0 : 25.0	60
12	Na ₂ HPO ₄	1.0 : 1.0	75
13	NaH ₂ PO ₄	2.0 : 1.0	65
14	Mg ₃ (PO ₄) ₂	3.0 : 1.0	80
15	K ₃ PO ₄	1.0 : 2.0	60

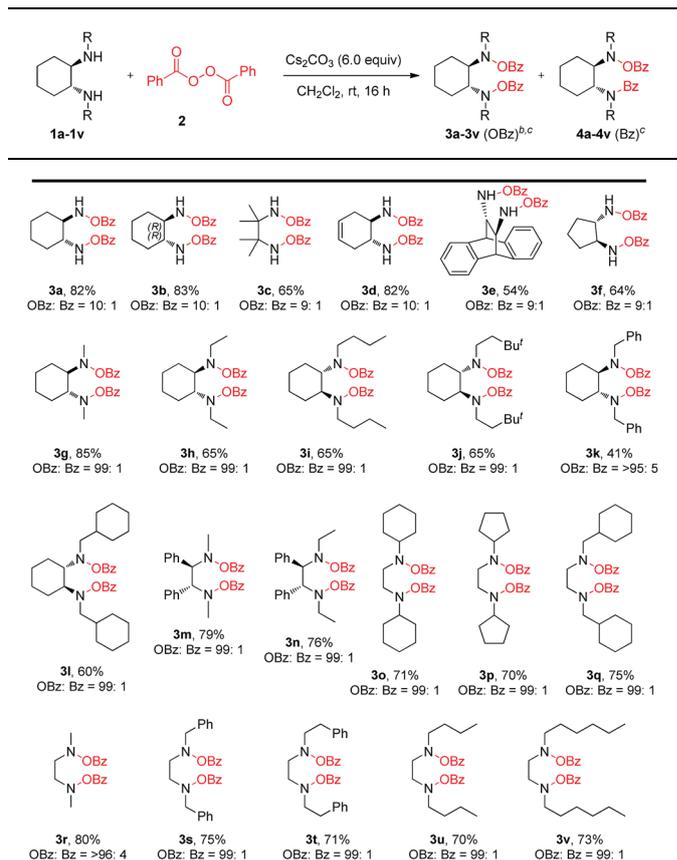
^a Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), **2** (2.0 mmol, 4.0 equiv.), base (3.0 mmol, 6.0 equiv.), CH₂Cl₂ (7 mL), r.t., 16 h. ^b Determined by ¹H NMR spectroscopy of the crude reaction mixture using 1,1',2,2'-tetrachloroethane as an internal standard.

cyclic as well as acyclic 1,2-diamines. Cyclic and acyclic free diamines such as **1a–1f** are good substrates for this reaction, delivering the desired products (**3a–3f**) in good yields (54 to 83%) and high selectivity (up to OBz : Bz = 10 : 1) (Table 2). Interestingly, cyclic as well as acyclic 1,2-disubstituted-1,2-diamine substrates are found to be excellent substrates with excellent selectivity. Substrates **3h**, and **3k** derived from (1*R*,2*R*)-(–)-1,2-diaminocyclohexane and substrates **3i**, **3j** and **3l** derived from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane were found to be excellent in terms of selectivity (OBz : Bz = 99 : 1) as a single isomer with good yields (41–65%). Furthermore, substrates **3m** and **3n** prepared from (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine also provided excellent selectivity (OBz : Bz = 99 : 1) with good yields (76–79%). Interestingly, products **3h–3n** could be a good precursor for a novel bis-hydroxyl amine ligand which is not known in the literature. Similarly, *N,N'*-disubstituted acyclic 1,2-diamines **3o–3v** proved to be good substrates under the reaction conditions with good yields (70–80%) and excellent selectivity (OBz : Bz = 99 : 1) as a single product. The reaction proceeds with high stereoselectivity with no racemization. Additionally, the reaction can be carried out on more than a gram scale (see the ESI†).

One pot bis-(benzoyloxy)hydroxamic acid synthesis

After synthesizing a large number of bis-(benzoyloxy)-1,2-diamines, we then focused on the efficient synthesis of bis-(benzoyloxy)hydroxamic acids in one pot. In practice, synthesis of bis-(benzoyloxy)hydroxamic acids from bis-(benzoyloxy)-1,2-

Table 2 Substrate scope of oxidation of 1,2-diamines with benzoyl peroxide^a



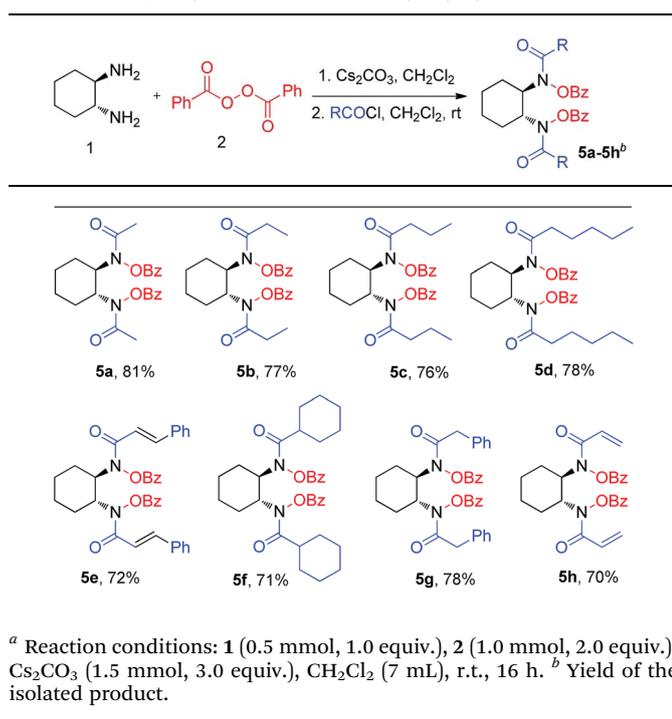
^a Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), **2** (2.0 mmol, 4.0 equiv.), Cs₂CO₃ (3.0 mmol, 6.0 equiv.), CH₂Cl₂ (7 mL), r.t., 16 h. ^b Yield of the isolated product. ^c Determined by ¹H NMR spectroscopy of the crude reaction mixture using 1,1',2,2'-tetrachloroethane as an internal standard.

diamines is not easy and it requires additional steps using an appropriate base and acyl derivative. According to our plan, after completion of the first step before work-up we added acyl chloride (in CH₂Cl₂) and stirred for another 6 h at room temperature followed by work-up giving the crude product. The pure bis-(benzoyloxy)hydroxamic acids **5a–5h** were achieved with very high yields (70–81%) in one pot without using further base and extra steps (Table 3).

N-Benzoyloxyamine synthesis

After exploring the model reaction, oxidation of 1,2-diamines to bis-(benzoyloxy)hydroxyl amines and bis-(benzoyloxy)hydroxamic acids with a wide substrate scope, we then wanted to test this oxidation method for mono-amine substrates. Interestingly, when we treated simple commercially available **6a** (1.0 equiv.) under similar reaction conditions such as treating with BPO (2.0 equiv.) and Cs₂CO₃ (3.0 equiv.), we observed an excellent yield (95%) of the product **7a** with excellent selectivity (N–O : C–N = 98 : 2). This inspiring result led us to test the reactivity of other amines (Table 4). Cyclic amines **6a–6d** provide

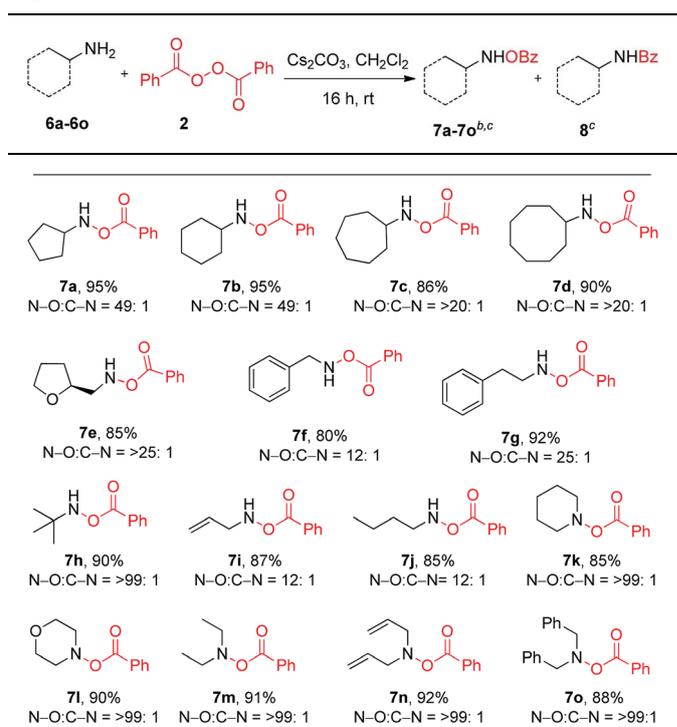


Table 3 One pot synthesis of bis-(benzoyloxy)hydroxamic acid^a

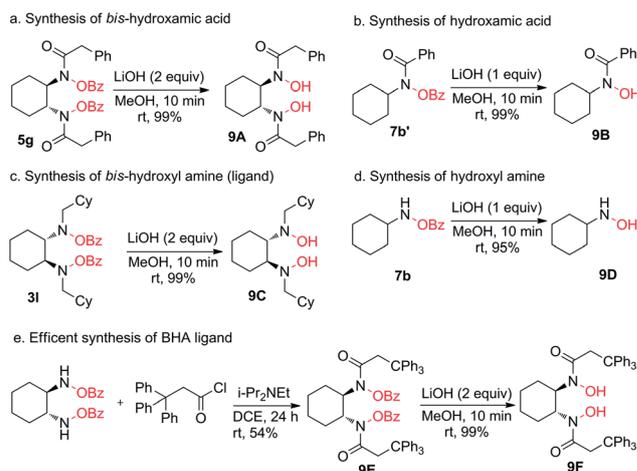
very good yields (85–95%) of the products (**7a–7d**) with good to excellent selectivity (up to N–O : C–N = 98 : 02). In order to test the stereochemical integrity, we carried out HPLC analysis of chiral and racemic **7e**. As expected no racemization of product **7e** was observed (for details see the ESI[†]). Further acyclic primary amines such as aromatic, aliphatic and allyl substituted amines furnished products **7f–7j** in good yields (80–92%) and good selectivity (up to N–O : C–N = >25 : 1). The substrate **7g** provided almost a single product (N–O : C–N = 25 : 1) with 92% yield, a result better than that reported in the literature (60% yield, N–O : C–N = 5.4 : 1).^{10c} Further, *tert*-butylamine **6h** as well as secondary amines **6k–6o** provide excellent selectivity (N–O : C–N = >99 : 1) as a single product with very high yields (85–92%).¹³ In addition, we have tested some mono-amines with a known method in ref. 10d (the only method for which no amide side product was observed) and compared with the results of our reaction conditions which clearly shows that our method is better than any known method in terms of selectivity and yield (for detailed results see the ESI[†]).

Applications

So far, we have shown a broad substrate scope for our oxidation method from a variety of 1,2-diamines and monoamines and all these products are good precursors for various synthetically useful intermediates and building blocks. From that aspect we wanted to show some applications of the products because on hydrolysis of N–OBz to N–OH valuable compounds such as hydroxylamines and hydroxamic acids are afforded. We found that LiOH (2.0 equiv.) in MeOH solvent is the best reagent for

Table 4 Oxidation of mono-amines with benzoyl peroxide and Cs₂CO₃^a

the hydrolysis of the bis-*O*-benzoyl group. Thus, **5g** on hydrolysis with LiOH/MeOH gave bis-hydroxamic acid **9A** in 99% yield (Scheme 2a) whereas **7b'** gave hydroxamic acid **9B** in 99% yield (Scheme 2b). Similarly, **31** on hydrolysis gave bis-(hydroxy)-1,2-diamine **9C** which is also a new chiral ligand (Scheme 2c) whereas **7b** gave hydroxylamine **9D** in 95% yield (Scheme 2d). The application of this method was further extended to the

Scheme 2 Application of *N*-(benzoyloxy)amine derivatives.

short synthesis of the highly useful chiral BHA ligand **9F** in high yield with retention of configuration. The spectroscopic data were in good accordance with the data reported previously by our group.^{11b}

Conclusions

In summary, we have developed for the first time a general and efficient method for N–O bond synthesis from 1,2-diamines by eliminating undesirable amide (C–N bond) formation in most cases. The oxidation of 1,2-diamines using commercially available 75% BPO and Cs₂CO₃ furnished the challenging bis-(benzoyloxy)-1,2-diamines with a good yield (up to 85%). The presence of a small amount of water and Cs₂CO₃ plays a crucial role in achieving high selectivity. The method was successfully explored in the efficient synthesis of bis-(benzoyloxy)hydroxamic acids and bis-hydroxamic acids. Further, this method was extended to the efficient synthesis of bis-(benzoyloxy)-1,2-disubstituted-1,2-diamines and a new type of bis-hydroxyl amine ligand. Excitingly, all of these products can be transformed to a variety of building blocks and chiral ligands, some of them are shown. The reaction proceeds stereoselectively without any racemization. The synthetic utility of this methodology was further demonstrated in the efficient synthesis of a chiral BHA ligand. Currently, a detailed mechanistic study and synthetic application to biologically active molecules is under progress in our laboratory. We believe that the present method will be able to provide the direct synthesis of chiral bis-hydroxyl amines and bis-hydroxamic acids for future use.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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- 13 According to reviewer's suggestion we tested 2,2,6,6-tetramethylpiperidine under our reaction conditions and the results are summarized below.

