RSC Advances

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2025, **15**, 35292

Cu–diamine ligand-controlled asymmetric Henry reactions and their application in concise total syntheses of linezolid and rivaroxaban

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Received 8th August 2025
Accepted 8th September 2025

DOI: 10.1039/d5ra05795g

rsc.li/rsc-advances

A Cu-bis(sulfonamide)–diamine complex catalytic system was exploited in asymmetric Henry reactions to construct versatile chiral nitroalcohols with high enantioselectivity from carbamate-acetaldehydes and nitromethane. This elegant approach was further implemented to complete the asymmetric total syntheses of a series of oxazolidone skeleton drugs, such as linezolid (antibiotic) and rivaroxaban (anti-coagulant), in a concise and efficient way.

Introduction

The oxazolidinone skeleton with a unique antibacterial mechanism has attracted great attention due to its biological property against a variety of Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus* (MSSA), and vancomycin-resistant *Enterococcus faecium* (VRE) (Fig. 1).[1] Linezolid, as the first oxazolidinone antibacterial agent, was approved by the FDA in 2000 for the treatment of infections caused by multi-drug resistant (MDR) Gram-positive bacteria.[2] Ranbezolid's phase I clinical trial was performed in 2003 because the furan ring as the terminal unit could make stronger interaction with the target pathogen.[3] Rivaroxaban is a powerful inhibitor of factor Xa and was approved by the FDA and EMEA in 2011.[4] During the fight against the COVID-19 pandemic, the overuse of antibiotics has exacerbated bacterial resistance, posing a serious threat to global health and the economy.[5] Notably, active molecules containing an oxazolidinone unit are reliable candidates for treating drug-resistant bacterial infections.[6] Eperezolid, which is still in the preclinical research stage, was currently demonstrated to combat drug-resistant bacteria through siderophore-facilitated delivery of oxazolidinone and macrolide antibiotics into a number of Gram-negative species.[7]

The key step in the synthesis of this series of drugs is the formation of the versatile common chiral 5-substituted oxazolidinone unit. Although a variety of approaches have been developed to create these chiral skeletons, simple and efficient protocols to build the structural units are still quite underexplored. Most methods usually introduce the desired stereochemistry using commercially available chiral oxiranes,[8] such as epichlorohydrin or glycidol (Scheme 1 and eqn (1)). Direct coupling between aryl halogen and the oxazolidinone ring (generated from enantiopure aziridine-2-carboxamides) has been utilized to synthesize linezolid (Scheme 1 and eqn (2)).[9] Amino aldehydes, as very ingenious structural units, have been used to build various complex compounds.[10] Very recently, a catalytic enantioselective aldol reaction between amino aldehydes and acetone has been applied for the preparation of a 5-substituted oxazolidinone unit but with moderate enantioselectivity (Scheme 1 and eqn (3)).[11] Notably, an efficient asymmetric catalytic Henry reaction has been used to construct a chiral 3-amino-2-hydroxy-1-nitro skeleton but still giving unsatisfactory results (Scheme 1 and eqn (4)).[12–14] Among these methods for 3-amino-2-hydroxy-1-nitro skeleton synthesis, the catalytic asymmetric Henry approach is the most efficient and deserves further study.[15] Herein, we utilize a Cu–diamine complex catalytic system to construct chiral 3-amino-2-hydroxy-1-nitro derivatives in excellent yields and enantioselectivities *via* asymmetric Henry reactions (Scheme 1 and eqn (5)); then, 5-substituted oxazolidinones, as important building blocks, were

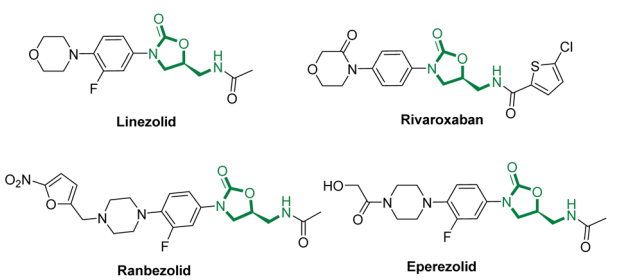

Fig. 1 Examples of some drug molecules bearing the oxazolidinone unit.

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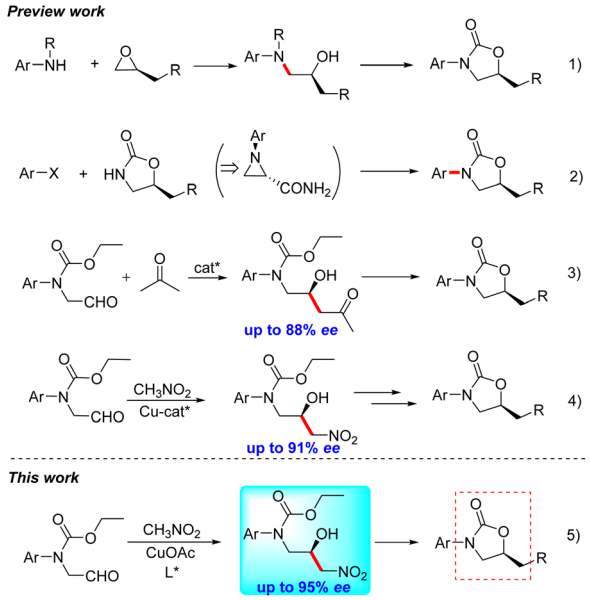
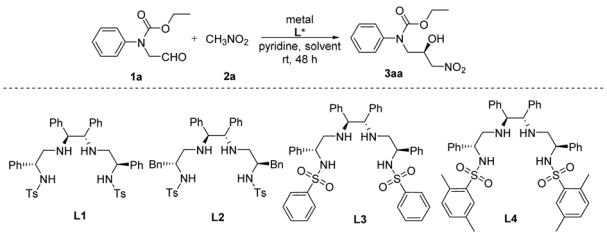


Scheme 1 Chiral source (eqn (1) and (2)) and asymmetric catalytic (eqn (3)–(5)) synthesis strategies for chiral 5-substituted oxazolidinone units.

synthesized, which further opened the door to the total synthesis of an elaborate series of oxazolidinones, such as linezolid, rivaroxaban, and the formal synthesis of radezolid, eperezolid and ranbezolid.

Table 1 Optimization of Henry reactions[a]



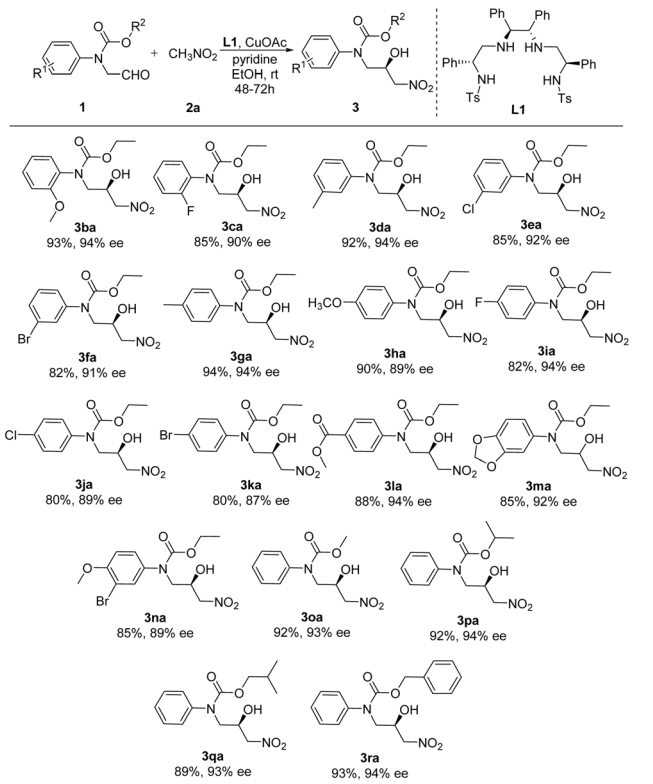
Entry	Metal catalyst	Ligand	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	$Cu(OAc)_2 \cdot H_2O$	**L1**	EtOH	48	91	93
2	CuI	**L1**	EtOH	48	94	95
3	$Cu(CN)_4PF_6$	**L1**	EtOH	48	90	89
4	**CuOAc**	**L1**	**EtOH**	**48**	**95**	**95**
5	CuOAc	**L2**	EtOH	48	87	77
6	CuOAc	**L3**	EtOH	48	94	93
7	CuOAc	**L4**	EtOH	48	92	93
8	CuOAc	**L1**	THF	48	88	86
9	CuOAc	**L1**	Toluene	48	85	80
10[d]	CuOAc	**L1**	EtOH	72	88	95
11[e]	CuOAc	**L1**	EtOH	72	90	91
12[f]	CuOAc	**L1**	EtOH	72	89	90
13	CuOAc	**L1**	EtOH	24	76	94
14	CuOAc	**L1**	EtOH	12	49	95

[a] Reaction conditions unless specified otherwise: 0.2 mmol of **1a**, 10 equiv. of **2a**, 10 mol% of ligand, 10 mol% of metal catalyst, 1.0 equiv. of pyridine, 0.6 mL of solvent, room temperature. [b] Isolated yield. [c] The *ee* values determined by HPLC. [d] At 5 °C. [e] 5 mol% of CuOAc, 5 mol% of **L1**. [f] 2.5 mol% of CuOAc, 2.5 mol% of **L1**.

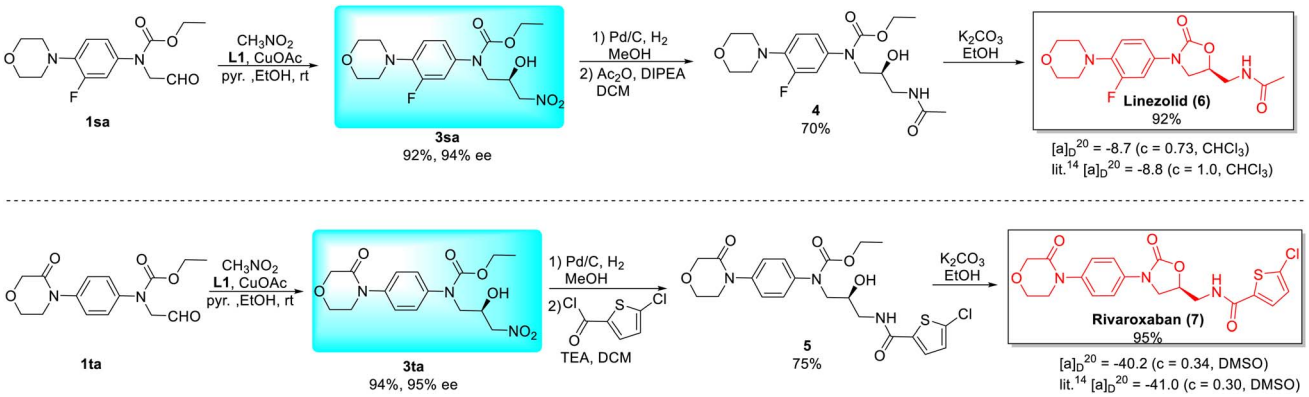
We initially selected the reaction between aminoacetaldehyde **1a** and nitromethane **2a** as the model reaction to find the optimum catalytic system for the Henry reactions (Table 1). To our delight, the chiral bis(sulfonamide)–diamine ligand **L1** and the copper salt could efficiently catalyze the reaction (entries 1–4). CuOAc, as a metal catalyst, showed the highest activity, giving the key chiral nitroalcohol **3aa** in 95% yield and 95% *ee*. Meanwhile, other chiral diamine ligands (**L2–L4**) could not significantly improve the reaction efficiency (entries 5–7). Solvent played an important role in the nitroaldol reaction (entries 8 and 9). Reducing the temperature could still maintain excellent enantioselectivity but slightly decreased the yield and prolonged the reaction time (entry 10). When the amounts of the ligand and metal catalyst were reduced, low yields and low enantioselectivities were achieved (entries 11 and 12). Reaction time had a significant impact on the reaction yield. When the reaction time was reduced to 24 h or even 12 h, a large amount of raw material **1a** remained unreacted, resulting in a decrease in the yield (entries 13 and 14).

Under the optimal conditions, we investigated the application scope of different substituted amino aldehydes **1** and nitromethane **2a** and summarized the results in Scheme 2.

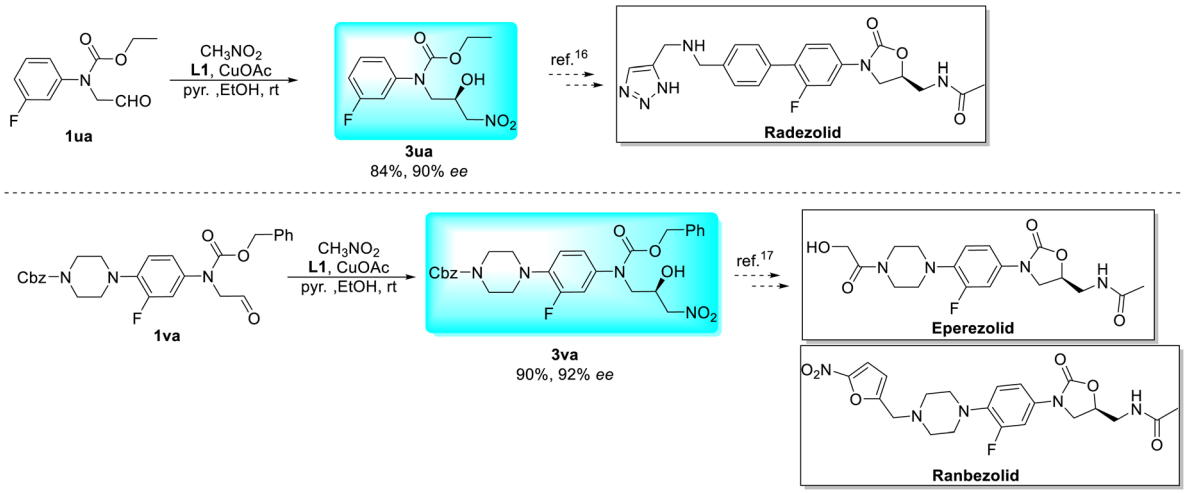
What made us happy was that various substituted aldehydes worked smoothly with nitromethane **2a** to give the desired products in high yields and excellent enantioselectivities. In contrast to a benzene ring with electron-withdrawing groups,



Scheme 2 Substrate scope of aryl aldehydes. [a]Reaction conditions unless specified otherwise: 0.2 mmol of **1**, 10.0 equiv. of **2**, 10 mol% of **L1**, 10 mol% of CuOAc, 1.0 equiv. of pyridine, 0.6 mL of EtOH, room temperature, 48–72 h.



Scheme 3 Applications in asymmetric total syntheses of linezolid and rivaroxaban.



Scheme 4 Applications in the formal syntheses of radezolid, eperezolid and ranbezolid.

a benzene ring with electron-donating groups was slightly favorable for the Henry reactions (**3ba–3la**). In addition, disubstituted phenyl aldehydes proceeded smoothly to generate chiral nitroalcohols **3ma** and **3na** with 90–92% enantiomeric excess. Moreover, excellent results were obtained when different ester groups were investigated (**3oa–3ra**). It was worth noting that the benzyl alcohol ester substrate provided **3ra** in 93% yield and 94% *ee*.

Next, we conducted the concise asymmetric total syntheses of linezolid (**6**) and rivaroxaban (**7**) based on the Henry reactions (Scheme 3).

Using the Cu–diamine complex catalytic system, the key synthetic intermediate **3sa** was obtained in 92% yield and with 94% *ee*, which was once reported in only 76% yield and with 71% *ee*.[13] The intermediate **3sa** on further reaction with Pd/C and H_2 underwent amidation reaction, providing compound **4** in 70% yield. The treatment of **4** with K_2CO_3 provided linezolid **6** in 92% yield, with its optical rotation value very close to the standard value.[14] The key chiral intermediate **3ta** of rivaroxaban **7** could also be obtained in 94% yield with 95% *ee* through a similar way based on the Henry reaction from **1ta**, which was synthesized in only 72% yield and 87% *ee*.[12] The optical rotation result of rivaroxaban **7** was close to those reported in the literature.[14]

We further utilized similar Henry reactions to synthesize other oxazolidone medicines. Fortunately, we discovered that it has a wide range of applications (Scheme 4). The chiral nitroalcohol compound **3ua** was obtained with 90% *ee*, which could further make radezolid.[16] Meanwhile, compound **3va** was obtained with 92% *ee*, which could then transform to eperezolid and ranbezolid, according to a method reported in the literature.[17] We are glad to see that it is possible to synthesize more oxazolidone drugs using this catalytic system.

Conclusions

In summary, we have developed a simple and efficient strategy to synthesize the 3-amino-2-hydroxy-1-nitro skeleton with high enantioselectivity through Cu–chiral diamine complex catalyzed asymmetric Henry reactions. Notably, linezolid and rivaroxaban were constructed from this key skeleton. In addition, the core structures of radezolid, eperezolid and ranbezolid

were synthesized with excellent *ee*. This concise synthetic strategy could provide new ideas for the asymmetric total syntheses of similar drugs and compounds.

Author contributions

Yiwei Zhang: formal analysis, investigation, methodology, validation. Wei Xiao: conceptualization, methodology, investigation, formal analysis, validation, data curation, funding acquisition, project administration, supervision, writing – original draft, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study, including NMR and HPLC spectra are available in the published article and its SI. See DOI: **https://doi.org/10.1039/d5ra05795g**.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (82202576) and the Chongqing Natural Science Foundation (CSTB2024NSCQ-MSX0013).

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