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Catalytic enantioselective synthesis of β-amino alcohols by nitrene insertion

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Chiral β-amino alcohols are important building blocks for the synthesis of drugs, natural products, chiral auxiliaries, chiral ligands and chiral organocatalysts. The catalytic asymmetric β-amination of alcohols offers a direct strategy to access this class of molecules. Herein, we report a general intramolecular C(sp^3)–H nitrene insertion method for the synthesis of chiral oxazolidin-2-ones as precursors of chiral β-amino alcohols. Specifically, the ring-closing C(sp^3)–H amination of *N*-benzoyloxycarbamates with 2 mol% of a chiral ruthenium catalyst provides cyclic carbamates in up to 99% yield and with up to 99% ee. The method is applicable to benzylic, allylic, and propargylic C–H bonds and can even be applied to completely non-activated C(sp^3)–H bonds, although with somewhat reduced yields and stereoselectivities. The obtained cyclic carbamates can subsequently be hydrolyzed to obtain chiral β-amino alcohols. The method is very practical as the catalyst can be easily synthesized on a gram scale and can be recycled after the reaction for further use. The synthetic value of the new method is demonstrated with the asymmetric synthesis of a chiral oxazolidin-2-one as intermediate for the synthesis of the natural product aurantioclavine and chiral β-amino alcohols that are intermediates for the synthesis of chiral amino acids, indane-derived chiral Box-ligands, and the natural products dihydrohamacanthin A and dragmacidin A.

asymmetric catalysis, nitrene, amination, chiral-at-metal, ruthenium

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1 Introduction

Chiral amines are key structural motifs of drugs, natural products, chiral auxiliaries, chiral bases, and chiral organocatalysts. Among them, chiral vicinal amino alcohols are indispensable synthetic building blocks [1]. For example, they are frequently used for the synthesis of bioactive compounds [2] and chiral auxiliaries [3], and are precursors of chiral oxazolines [4], which represent one of the most frequently used class of chiral ligands in asymmetric transition metal catalysis. Enantiomerically pure chiral β-amino alcohols are typically synthesized by accessing the chiral pool, using chiral auxiliaries, or by applying catalytic asymmetric methods (Figure 1(a)). However, all these standard methods face significant limitations and drawbacks. The reduction of α-amino acids is only attractive for naturally occurring amino acid side chains and the L-stereochemistry. Chiral auxiliaries, such as Ellman's sulfinamide [5], have to be employed in uneconomic equimolar amounts, and catalytic asymmetric aminooxygenations of alkenes often lack a high degree of regioselectivity [6], and entail other drawbacks such as the use of toxic osmium in the case of the Sharpless aminohydroxylation [7]. Biocatalytic approaches have also been reported but rely on substrates and reaction conditions that are compatible with enzymes [8].

An appealing strategy for the asymmetric synthesis of chiral β-amino alcohols starts from ubiquitous alcohols and

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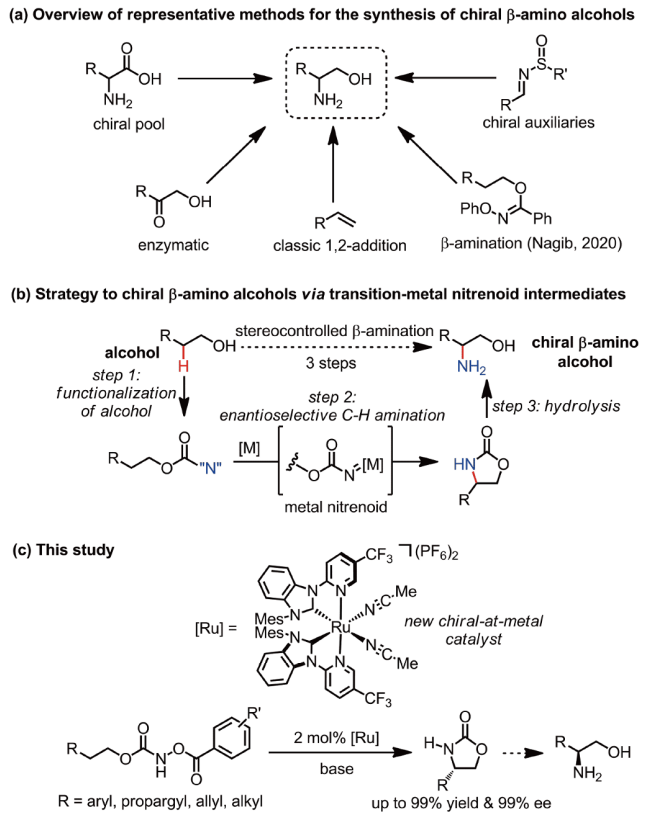


Figure 1 State of the art and this study on asymmetric synthesis of chiral β-amino alcohols (color online).

builds a C(sp^3)–N bond including a stereocenter in a single step through regio- and enantioselective ring-closing C–H amination chemistry. The Nagib group [9] recently introduced an impressive method to accomplish this task through a photoredox radical protocol. However, the method requires a complicated cocktail out of iridium photocatalyst and chiral copper catalyst, the use of expensive BARF counterions, in addition to 25 mol% camphoric acid. We envisioned to provide a stereocontrolled and regioselective β-C(sp^3)–H amination of alcohols by exploiting catalytic asymmetric nitrene insertion (Figure 1(b)). Great progress has been made for the catalytic asymmetric synthesis of chiral amines using transition metal nitrenoid chemistry under typically very mild reaction conditions [10]. However, a general access to chiral β-amino alcohols in high yields and with high enantioselectivity through enantioselective nitrene insertion remains an unsolved problem. Sulfamate esters have been demonstrated to undergo intramolecular ring closing C–H aminations in the presence of hypervalent iodine reagents to provide cyclic sulfamidates [11–13], but are difficult to hydrolyze and would preferably provide γ-amino alcohols. The formation of cyclic carbamates through ring-closing C(sp^3)–H amination would be advantageous [14]. Davies provided four examples using *N*-tosyloxycarbamates under chiral dirhodium catalysis [15]. Unfortunately, yields (62%–75%) and enantioselectivities (43%–82% ee) were only very modest and not of practical value.

Here we report an intramolecular catalytic asymmetric nitrene insertion as a general method to access chiral β-amino alcohols in high yields and with high enantioselectivities (Figure 1(c)). Specifically, the ring-closing C(sp^3)–H amination of *N*-benzoyloxycarbamates with a new chiral-at-ruthenium catalyst provides cyclic carbamates in up to 99% yield and with up to 99% ee. The obtained cyclic carbamates can be hydrolyzed subsequently to obtain chiral β-amino alcohols and we showcase applications to the synthesis of natural products, a chiral vicinal diamine, a chiral amino acid, and a chiral bisoxazoline ligand.

2 Experimental

Experimental procedures and analytical data, nuclear magnetic resonance (NMR) spectra, high performance liquid chromatography (HPLC) traces, and crystallographic data are listed in the Supporting Information online.

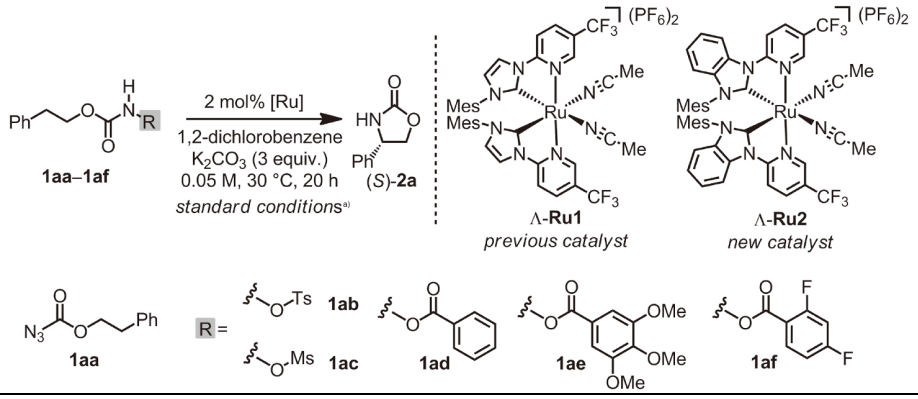
3 Results and discussion

3.1 Initial experiments and optimization

We commenced our study by screening precursors of alkoxylcarbonylnitrenes for their ability to undergo ring-closing C–H aminations catalyzed by a class of chiral-at-ruthenium catalysts recently developed in our group [16–18]. These ruthenium catalysts are composed of two chelating inert *N*-(2-pyridyl)-substituted *N*-heterocyclic carbene (NHC) ligands, which generate metal centered chirality, and two labile acetonitrile ligands. The dicationic complexes are complemented by two hexafluorophosphate anions. Such C_2-symmetric complexes are very suitable for intramolecular C–H aminations which was demonstrated by us for the asymmetric synthesis of pyrrolidines [19], imidazolidin-4-ones [20], and imidazolidin-2-ones [21].

Azidoformates are well-established precursors of alkoxylcarbonylnitrenes upon release of dinitrogen [22]. However, no reaction occured with phenethyl azidoformate **1aa** at room temperature in the presence of chiral-at-Ru catalyst Λ-**Ru1** (2.0 mol%) (entry 1, Table 1). Likewise, sulfonyloxycarbamates did not provide satisfactory results. For example, the *N*-toluenesulfonyloxycarbamate **1ab** afforded (*S*)-**2a** in 69% NMR yield with just 68% ee (entry 2). The related *N*-methylsulfonyloxycarbamate **1ac** afforded (*S*)-**2a** in a higher NMR yield of 94% but with a reduced enantioselectivity of just 62% ee (entry 3). We next turned our attention to *N*-benzoyloxycarbamates. Recent work from our laboratory on intramolecular C–H oxygenations [23] and aminooxgenations [24] revealed that our chiral-at-Ru catalysts effi-

Table 1 Initial experiments and optimization [a)]



Entry	Substrate	Catalyst	Conditions [b)]	NMR yield (%) [c)]	ee (%) [d)]
1	**1aa**	Λ-**Ru1**	CH_2Cl_2 at 25 °C without base	0	–
2	**1ab**	Λ-**Ru1**	CH_2Cl_2 at 25 °C	69	68
3	**1ac**	Λ-**Ru1**	CH_2Cl_2 at 25 °C	94	62
4 [e)]	**1ad**	Λ-**Ru1**	CH_2Cl_2 at 25 °C	97	78
5	**1ad**	Λ-**Ru1**	Standard	98	82
6	**1ad**	Λ-**Ru2**	Standard	95	86
7	**1ae**	Λ-**Ru2**	40 °C instead	97	90
8	**1af**	Λ-**Ru2**	Standard	Quant. (99) [f)]	90
9	**1af**	Λ-**Ru2**	No base	<5	N.D.
10	**1af**	Λ-**Ru2**	Under air	92	90

a) Standard conditions: **1a**(0.2 mmol), K_2CO_3(0.6 mmol), Ru catalyst (0.002 mmol) in 1,2-dichlorobenzene (4 mL) stirred at the 30 °C for 20 h under N_2 unless noted otherwise; b) deviations from standard conditions are shown; c) determined by ^{1}H NMR of the crude products using $Cl_2CHCHCl_2$ as internal standard; d) enantiomeric excess determined by HPLC analysis of the crude main product on a chiral stationary phase; e) compare with Ref. [21]; f) isolated yield in brackets. N.D.=not determined.

ciently generate ruthenium nitrenoid intermediates from *N*-benzoyloxycarbamates. In fact, in a recent preliminary single experiment we were able to convert the *N*-benzoyloxycarbamate **1ad** to (*S*)-**2a** in 88% yield but with unsatisfactory 78% ee (entry 4) [23]. Using carbamate **1ad** we next screened solvents and found that 1,2-dichlorobenzene is the solvent of choice and provided almost quantitative NMR yields (98%) with improved 82% ee (entry 5). However, this enantioselectivity was still not of synthetic value. Since we were not able to further improve the enantioselectivity by modifying the reaction conditions, we turned our attention to modifying the catalyst and discovered that by replacing the imidazol-2-ylidene carbene moieties of **Ru1** with the related benzimidazol-2-ylidenes (**Ru2**) provided an improved enantiomeric excess of 86% ee under otherwise identical reaction conditions (entry 6). Final improvements were accomplished by functionalizing the benzoate leaving group. Best results were obtained with 3,4,5-trimethoxybenzoate (**1ae**) (entry 7) and 2,4-difluorobenzoate (**1af**) (entry 8) in which both afforded the cyclic carbamate (*S*)-**2a** with 90% ee (see Supporting Information online for a complete overview of tested benzoates). The 2,4-difluorobenzoyloxycarbamate appears slightly more suitable due to a somewhat higher reactivity. Finally, without base the reaction proceeded very sluggish (entry 9) or performing the reaction under air resulted in a slightly reduced yield (entry 10).

3.2 Benzylic asymmetric C–H aminations

With the optimized reaction conditions in hand we investigated the substrate scope. *N*-Benzoyloxycarbamates bearing different aryl substituents at the β-position were tested first. As shown in Figure 2, oxazolidin-2-ones with electron donating methoxy substituents in *para*- (**2b**), *meta*- (**2c**) or *ortho*- (**2d**) positions of the phenyl moiety were obtained in almost quantitative yields and with excellent enantioselectivities (90%–93% ee). A substrate bearing a sterically very hindering *ortho*-methyl substituent was also well tolerated and provided 99% yield and 92% ee (**2e**). A 4-phenyl substituent on the phenyl moiety provided almost quantitative yield together with an excellent enantioselectivity of 98% ee (**2f**). Different electron-withdrawing groups are also accommodated in *para*-position as demonstrated for an electron-withdrawing fluorine (**2g**, 99% yield, 91% ee), chlorine (**2h**, 92% yield, 88% ee), or bromine (**2i**, 99% yield, 90% ee). A 1-naphthyl group provided the cyclic carbamate

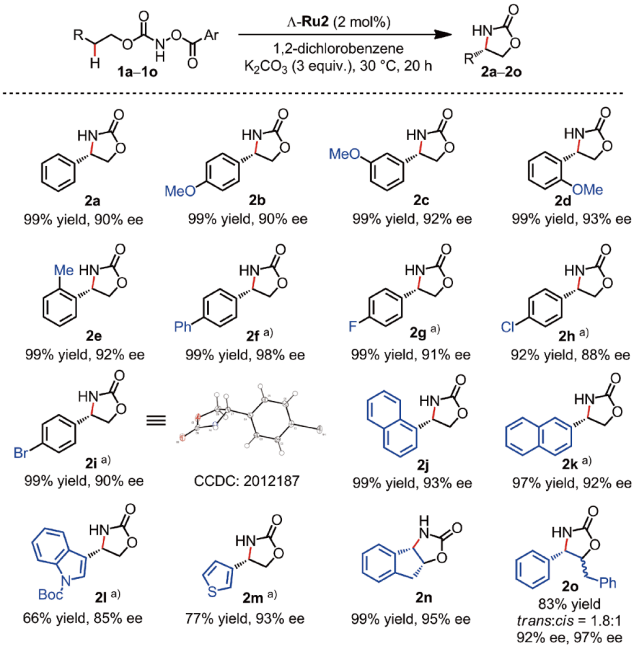


Figure 2 Substrate scope with respect to benzylic C–H aminations. Ar=2,4-difluorophenyl unless noted otherwise. Superscript a) refers modified substrate and reaction conditions: Ar=3,4,5-trimethoxyphenyl and reacted at 40 °C for 20 h (color online).

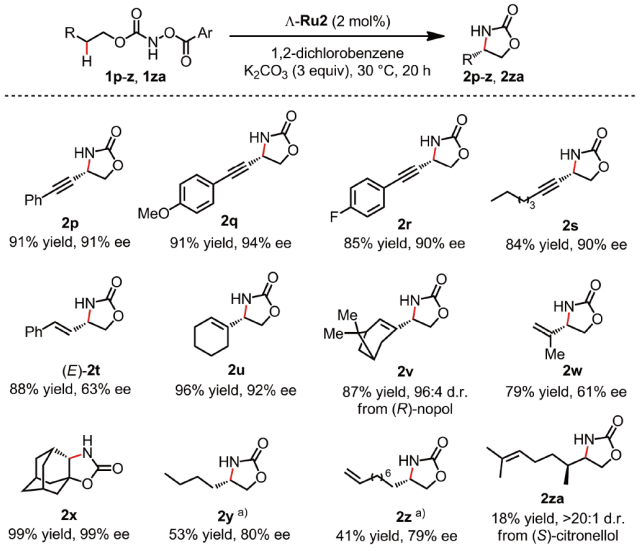


Figure 3 Substrate scope with respect to non-benzylic C–H aminations. Ar=2,4-difluorophenyl unless noted otherwise. Superscript a) refers Ar=Ph (color online).

2j with 99% yield and 93% ee, while a 2-naphthyl group afforded the cyclic carbamate **2k** with 97% yield and 92% ee. A tryptophol-derived substrate provided oxazolidin-2-one in 66% yield and 85% ee (**2l**). The smaller 3-thiophene moiety provided the cyclic carabamate **2m** with 77% yield and 93% ee. Oxazolidin-2-one **2n** with stereocenters in the 4- and 5-positions was obtained in 99% yield and 95% ee by desymmetrization of an indane substrate. A *N*-benzoyloxycarbamate derived from 1,3-diphenyl-2-propanol provided the 4,5-difunctionalized oxazolidin-2-one **2o** with two adjacent stereocenters as a 1.8:1 *trans*/*cis* mixture with respective 92% and 97% ee in overall 83% yield.

3.3 Non-benzylic asymmetric C–H aminations

Non-benzylic C–H amination reactions are of particular interest since they are more difficult to achieve in high yields and with high enantioselectivities. In fact, previous reported ruthenium catalyzed enantioselective intramolecular C–H aminations at non-benzylic positions from our group often failed to get satisfactory results [19,21]. As shown in Figure 3, we investigated propargylic C–H aminations first and encouragingly found the product **2p** was formed in 91% yield and 91% ee under standard reaction conditions. An electron-donating methoxy substituent on the phenyl moiety provided cyclic carbamate **2q** with 91% yield and 94% ee while an electron-withdrawing fluorine substituent provided cyclic carbamate **2r** with slightly reduced 85% yield and 90% ee. Replacement of the phenyl moiety with an alkyl group is also accommodated as shown by the alkyne product **2s** (84% yield and 90% ee). The aminated C(sp^3)–H bond can also be flanked by an alkenyl group. While (*E*)-**1t** converted to (*E*)-**2t** under complete retention of the alkene configuration (88% yield, 63% ee), (*Z*)-**1t** (*Z*/*E* ratio>20:1) was converted to (*Z*/*E*)-**2t** with an eroded *Z*/*E* diastereomeric ratio (d.r.) of 10.3:1 (56% yield, 45% ee). This can be explained with an isomerization from the thermodynamically less stable *Z*-isomer to the preferred *E*-isomer in the course of the C–H amination through an intermediate allyl radical. However, the radical is apparently not long-lived enough to furnish complete isomerization (see Supporting Information online for more mechanistic details). We were delighted to find that a cyclohexene substitutent provided cyclic carbamate **2u** in 96% yield and 92% ee. It is noteworthy that the late-stage functionalization of (*R*)-nopol provided cyclic carbamate **2v** in 87% yield with 96:4 d.r. In this example, the stereoselectivity of the C–N bond formation was controlled only by chiral ruthenium catalyst since the racemic ruthenium catalyst lead to the formation of **2v** with only 1:1 d.r. In addition, C–H amination next to a small isopropenyl substituent provided the product **2w** in 79% yield with 61% ee. Besides C(sp^3)–H aminations at propargylic and allylic positions, ring-closing C–H amination was also possible at aliphatic methylene groups without any adjacent activating group. The adamantyl substituted cyclic carbamate **2x** was formed in 99% yield with 99% ee. The *n*-butyl substituted oxazolidin-2-one **2y** was formed in 53% yield with 80% ee. The late-stage functionalization of 10-undecen-1-ol provided **2z** in 41% yield and 79% ee. Finally, a substrate bearing an adjacent chiral center was also employed, which is the late-stage functionalization of (*S*)-citronellol, providing **2za** in

18% yield and >20:1 d.r. as determined by ^{1}H NMR [25,26].

3.4 Gram-scale reactions, catalyst recovery and synthetic applications

For practical purposes it is important to note that our ruthenium catalyst can be easily prepared on a gram scale. Accordingly, reaction of $RuCl_3$ hydrate with the benzimidazolium ligand **3** in ethylene glycol at 200 °C and afterwards treated with $AgPF_6$ afforded 1.05 g (81% yield) of racemic ruthenium catalyst *rac*-**Ru2** (Figure 4(a)). The racemic mixture was next reacted with the chiral auxiliary (*S*)-2-(4-isopropyl-4,5-dihydrothiazol-2-yl)phenol (**4**) in the presence of Et_3N to provide the complex Λ-(*S*)-**Aux-Ru2** as a single stereoisomer in 43% yield. Treatment with trifluoroacetic acid and exchange of the counteranion to a hexafluorophosphate finally afforded the complex Λ-**Ru2** in 95% yield. The chiral auxiliary (*S*)-**4** was recovered in 87% yield.

The catalytic intramolecular C–H amination of substrate **1af** was tested on a gram scale and proceeded smoothly under standard reaction conditions to provide (*S*)-**2a** in 99% yield with 90% ee (Figure 4(b)). Upon a following simple recrystallization step, (*S*)-**2a** could even be obtained with >99% ee. Furthermore, upon addition of the auxiliary (*S*)-**4** after the reaction, the chiral-at-Ru catalyst was recycled in 78% yield and with >99:1 d.r. as the auxiliary complex Λ-(*S*)-**Aux-Ru2**.

We also investigated follow-up conversions of the carbamate products. Accordingly, the oxazolidin-2-one (*S*)-**2a** (recrystallized with >99% ee) was converted to the Boc-protected β-amino alcohol (*S*)-**5** without any loss of enantiomeric excess (Figure 4(c), method A). The aminoalcohol (*S*)-**5** was reported as a valuable synthetic intermediate

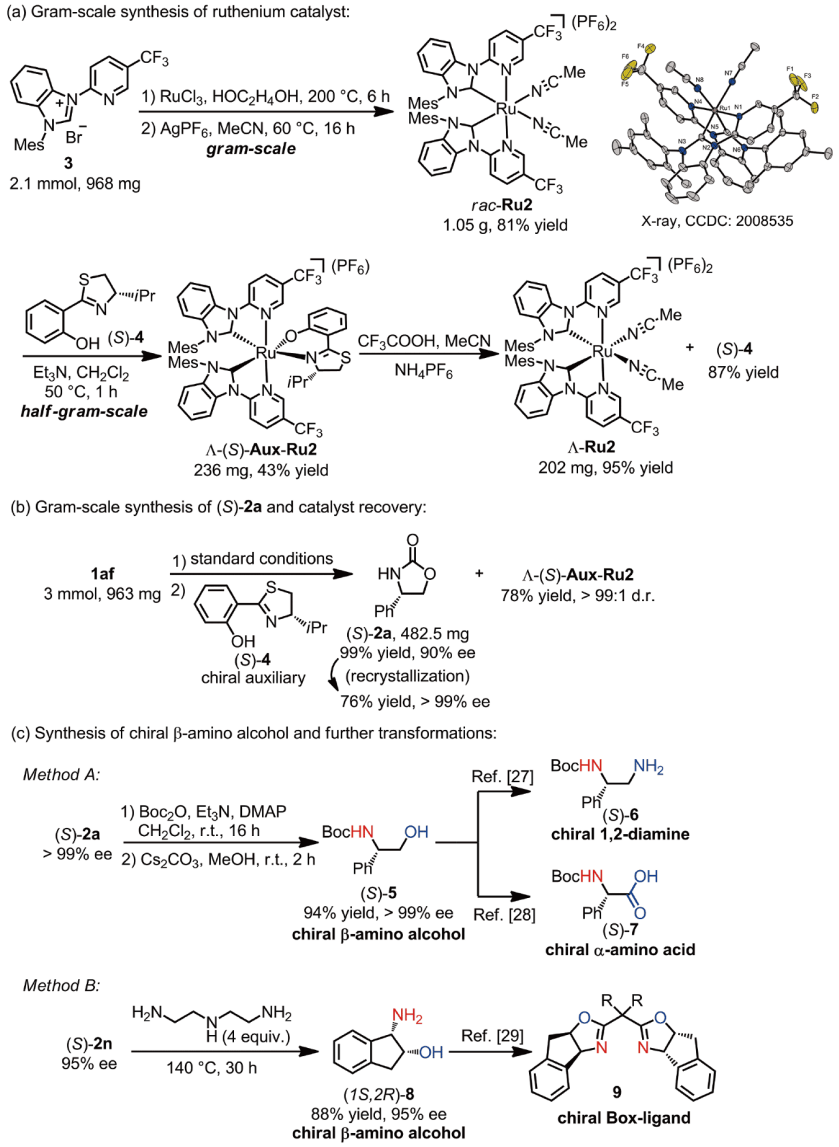


Figure 4 Gram-scale reactions, catalyst recovery and further transformations (color online).

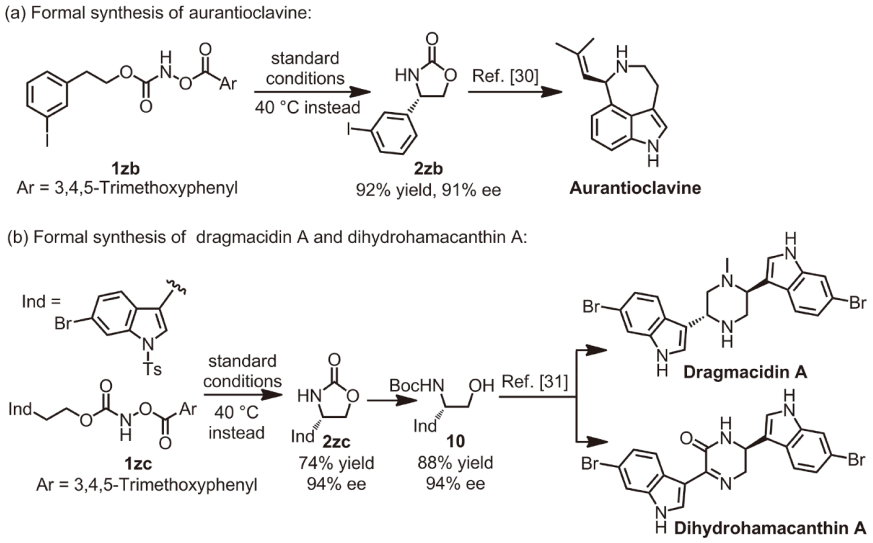


Figure 5 Synthetic application to natural products.

for the synthesis of chiral 1,2-diamine (*S*)-**6** [27] and also the chiral α-amino acid (*S*)-**7** [28]. In another follow-up chemistry using bis(2-aminoethyl)amine as the ring-opening reagent, the oxazolidin-2-one **2n**, bearing two vicinal stereochenters, was converted to the corresponding chiral amino alcohol (*1S,2R*)-**8** which is a building block for the frequently used chiral Box-ligand **9** (Figure 4(c), method B) [29].

3.5 Synthetic applications to natural products

The utility of our new method for the straightforward synthesis of natural products is shown in Figure 5. Substrate **1zb** undergoes an intramolecular enantioselective cyclization to provide in 92% yield and with 91% ee (*S*)-**2zb** which was reported as an intermediate for the synthesis of the natural product (−)-aurantioclavine (Figure 5(a)) [30]. A second example provides a concise route to the bisindole alkaloids hamacanthin A and dragmacidin A. Accordingly, ring-closing C–H amination of the indole containing substrate **1zc** provided under standard conditions the cyclic carbamate intermediate (*S*)-**2zc** in 74% yield and 94% ee. Further ring-opening provided the chiral β-amino alcohol **10** in 88% yield with 94% ee which was reported as an intermediate for the synthesis of natural products dihydrohamacanthin A and dragmacidin A (Figure 5(b)) [31].

4 Conclusions

In summary, we here reported an economic and practical method to chiral oxazolidin-2-ones and corresponding β-amino alcohols, both of which are highly valuable chiral building blocks. The method is based on a ring-closing C(sp^3)–H amination of *N*-benzoyloxycarbamates using a new benzimidazol-2-ylidene carbene chiral-at-ruthenium catalyst. 2,4-Difluorobenzoate and 3,4,5-trimethoxy benzoate leaving groups afford for most substrates the best results. The intramolecular C–H amination provides cyclic carbamates in up to 99% yield and with up to 99% ee for benzylic, allylic, and propargylic C–H bonds. Completely non-activated C(sp^3)–H bonds can also be aminated but provide somewhat reduced yields and enantioselectivities. We demonstrated the synthetic value of this new method with the catalytic enantioselective synthesis of chiral oxazolidin-2-ones as intermediates of the natural products aurantioclavine, dihydrohamacanthin A and dragmacidin A, chiral amino acids, and indane-derived chiral Box ligand.

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Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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