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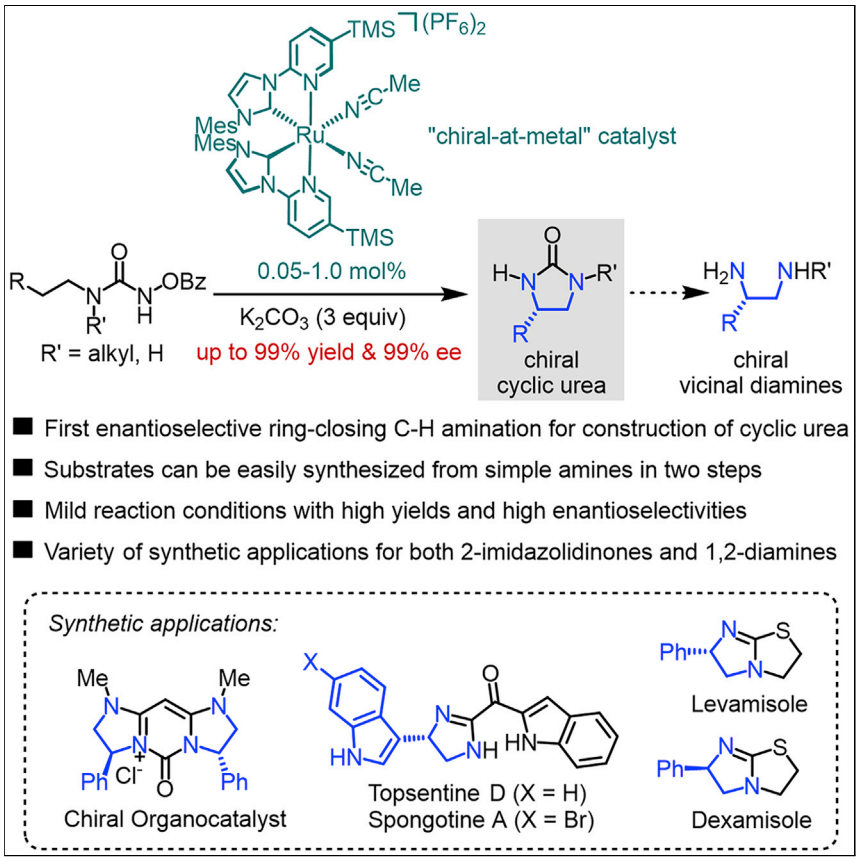
Enantioselective Ring-Closing C–H Amination of Urea Derivatives



Here, we report the first catalytic asymmetric ring-closing C(sp^3)–H amination of urea derivatives to construct chiral 2-imidazolidinones, which are prevalent in bioactive compounds and can be converted to chiral vicinal diamines. The simple and mild transformation is catalyzed by a recently developed chiral-at-ruthenium complex in high yields and with high enantioselectivities. Applications to the drugs levamisole and dexamisole, the bisindole alkaloids topsentine D and spongotine A, and a chiral organocatalyst demonstrate the synthetic value of this new method.

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HIGHLIGHTS

First enantioselective ring-closing C(sp^3)–H amination of urea derivatives

Simple access to chiral 2-imidazolidinones which can be converted to vicinal diamines

Applications to the synthesis of pharmaceuticals, natural products, and a chiral catalyst

Chiral-at-metal catalyst used in challenging asymmetric nitrenoid insertion chemistry

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Enantioselective Ring-Closing C–H Amination of Urea Derivatives

Zijun Zhou,[1] Yuqi Tan,[1] Tatsuya Yamahira,[2] Sergei Ivlev,[1] Xiulan Xie,[1] Radostan Riedel,[1] Marcel Hemming,[1] Masanari Kimura,[2] and Eric Meggers[1,3,*]

SUMMARY

An enantioselective intramolecular C(sp^3)–H amination of *N*-benzoyloxyurea by using a chiral-at-metal ruthenium catalyst is reported, providing chiral 2-imidazolidinones in yields of up to 99% and with up to 99% ee. Catalyst loadings down to 0.05 mol % are feasible. Control experiments support a stepwise nitrene insertion mechanism through hydrogen atom transfer of a ruthenium nitrenoid intermediate followed by a radical recombination. Chiral 2-imidazolidinones are prevalent in bioactive compounds and can be converted to chiral vicinal diamines in a single step. The synthetic value of the new method is demonstrated for the synthesis of intermediates of the drugs levamisole and dexamisole, the bisindole alkaloids topsentine D and spongotine A, and a chiral organocatalyst.

INTRODUCTION

The direct catalytic asymmetric conversion of prochiral C(sp^3)–H into C–N bonds offers an efficient synthetic route to non-racemic chiral nitrogen-containing molecules.[1–3] In one mechanistic manifold, intermediate transition metal nitrenoids insert a nitrogen atom between C–H bonds in either a stepwise or concerted fashion (Figure 1A).[4–8] A variety of functional groups serving as nitrene precursors have been developed and the intramolecular version of the reaction renders directing groups obsolete while exerting high control over the regioselectivity. This has been applied to the catalytic asymmetric synthesis of cyclic sulfamidates,[9–11] sulfamides,[12–14] sulfonamides,[15–18] carbamates,[19,20] lactams,[21–24] Boc-protected pyrrolidines,[25,26] and related Boc-protected heterocycles (Figure 1B).[27] However, interestingly, urea derivatives as nitrene precursors leading to chiral cyclic urea, specifically 2-imidazolidinones, are absent from this list.[28] This is unfortunate considering the prevalence of chiral 2-imidazolidinones in bioactive compounds and their use as chiral auxiliaries.[29,30] Furthermore, chiral 2-imidazolidinones can be converted in a single step to chiral vicinal diamines, which are valuable building blocks for the synthesis of medicinal agents, natural products, chiral ligands, and chiral catalysts.[31–33]

Here, we report an intramolecular asymmetric C(sp^3)–H amination of *N*-benzoyloxyurea (Figure 1C). The enantioselective cyclization is highly efficient with catalyst loadings down to 0.05 mol %. To our knowledge, this is the first example of chiral cyclic urea synthesized through a catalytic enantioselective nitrene C–H insertion strategy.

RESULTS AND DISCUSSION

Initial experiments and optimization

We recently disclosed enantioselective nitrene insertion chemistry of organic azides and 1,4,2-dioxazol-5-ones by using "chiral-at-metal" ruthenium catalysts

The Bigger Picture

Direct C–H functionalization offers the prospect for streamlined synthesis with high atom economy. In this respect, the transition-metal-catalyzed enantioselective insertion of nitrenoids into prochiral sp^3 C–H bonds is a powerful tool for the efficient construction of non-racemic chiral nitrogen-containing molecules. Intramolecular versions have been used to synthesize chiral nitrogen heterocycles, but cyclic urea is still elusive through enantioselective nitrenoid insertion chemistry. Here, we fill this gap and report an enantioselective intramolecular C(sp^3)–H amination of *N*-benzoyloxyurea to provide chiral 2-imidazolidinones in high yields and with high enantioselectivities. The synthetic utility of this new method is illustrated with the catalytic asymmetric synthesis of medicinal agents, natural products, and a chiral organocatalyst. Our work emphasizes the usefulness of transition-metal-controlled asymmetric nitrene chemistry and the importance of tailored catalyst design.

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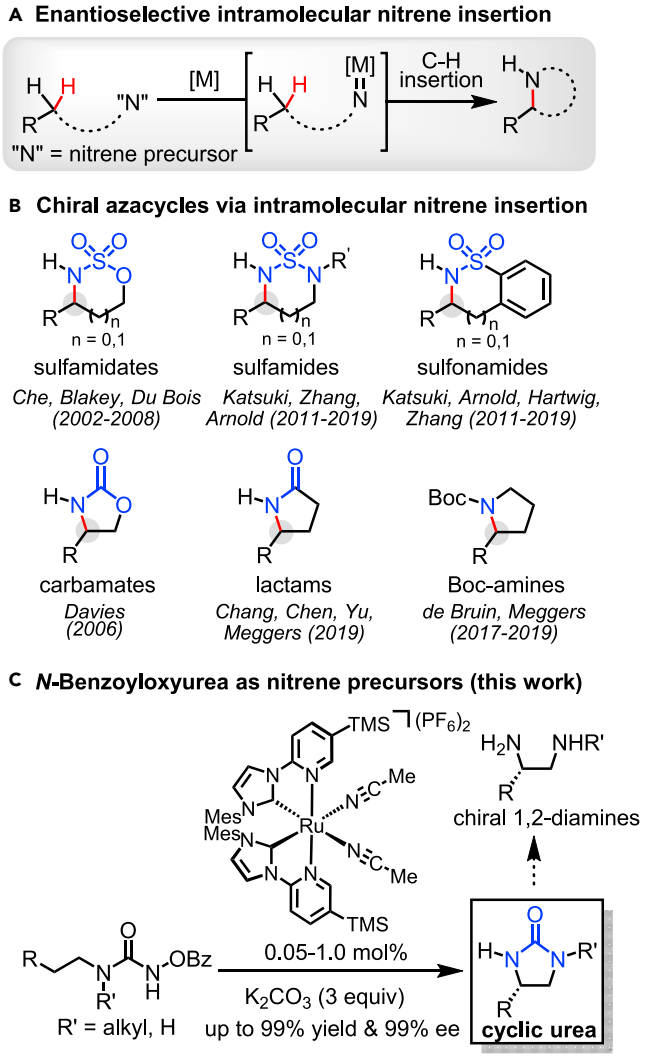

Figure 1. Enantioselective Intramolecular Amination of Prochiral C(sp^3)–H Bonds

(A) Transition metal nitrene intermediates.

(B) Chiral heterocycles accessible by this strategy.

(C) Method developed in this report.

with exclusive metal-centered chirality (only achiral ligands).[24,26,27] We anticipated that this novel class of catalysts would allow us to address the challenge of accessing chiral 2-imidazolidinones by enantioselective C(sp^3)–H amination from judiciously chosen urea derivatives. We initiated our study with the *N*-benzoyloxyurea **1aa** (see Scheme S1 for substrate preparation) and envisioned that after release of the benzoate leaving group, an intermediate ruthenium nitrenoid would form and engage in an intramolecular C–H amination.[34] Indeed, in the presence of 1 mol % ruthenium catalyst (**Ru1**) and K_2CO_3 (3 equiv) in CH_2Cl_2 at room temperature for 16 h, the 2-imidazolidinone **2a** was formed in quantitative yield and with 86% enantiomeric excess (ee) (Table 1, entry 1). Optimization of the chiral-at-metal ruthenium catalyst (**Ru2**–**Ru5**,[26,27,35,36] entries 2–5) improved the enantioselectivity to 95% ee by using the trimethylsilyl-modified ruthenium catalyst **Ru5** (see Scheme S2 for catalyst preparation). Functionalization of the benzoate leaving group with an electron-donating methoxy (**1ab**) (entry 6) or electron-withdrawing CF_3-group (**1ac**)

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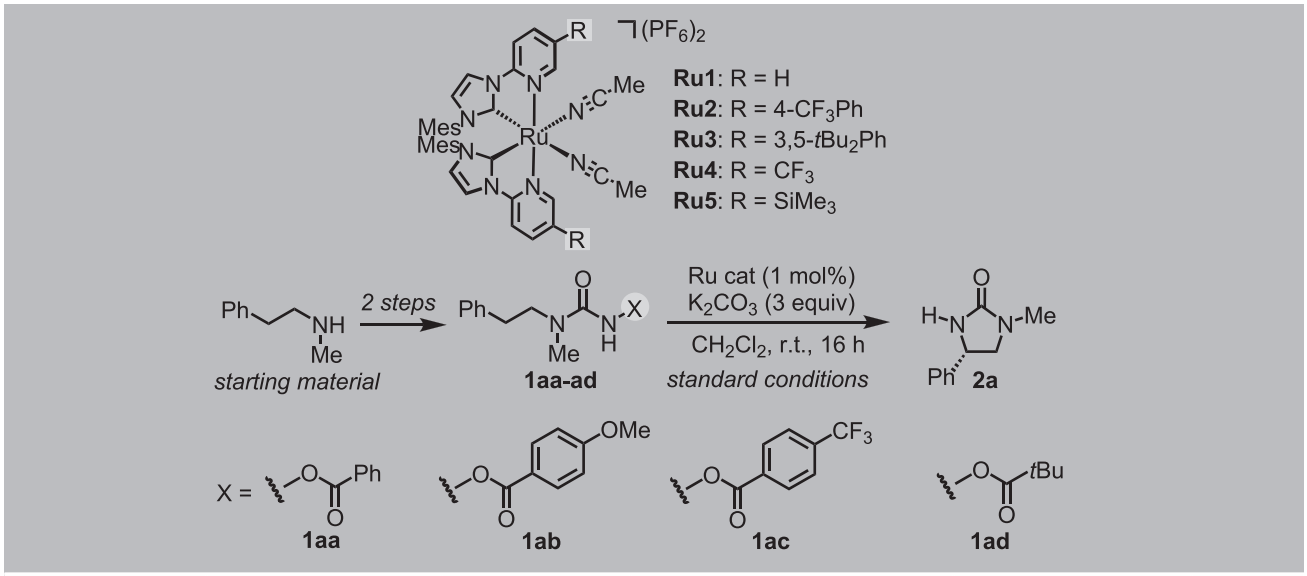
Table 1. Evaluation of the C(sp^3)–H Amination Reaction[a]



Entry	Catalysts	X	Conditions[a,b]	Yield (%)[c]	ee (%)[d]
1	Λ-Ru1	1aa	Standard	100	86
2	Λ-Ru2	1aa	Standard	100	94
3	Λ-Ru3	1aa	Standard	100	95
4	Λ-Ru4	1aa	Standard	100	94
5	Λ-Ru5	1aa	Standard	100 (99)[e]	95
6	Λ-Ru5	1ab	Standard	100	94
7	Λ-Ru5	1ac	Standard	100	94
8	Λ-Ru5	1ad	Standard	27	91
9	Λ-Ru5	1aa	0.5 mol % catalyst)	100	94
10	Λ-Ru5	1aa	0.1 mol % catalyst[f]	100	94
11	Λ-Ru5	1aa	0.05 mol % catalyst[f]	66	93
12	Λ-Ru5	1aa	no base[g]	100	94

[a]Standard conditions: Substrate **1aa–1ad** (0.2 mmol), K_2CO_3 (0.6 mmol), Ru catalyst (0.002 mmol) in CH_2Cl_2 (2 mL) stirred at the indicated temperature for 16 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]Isolated yield in brackets.
[f]Reaction executed at 40°C for 24 h.
[g]Increased reaction time of 48 h.

(entry 7) slightly affected the enantioselectivity. A pivaloate leaving group (**1ad**) only provided the 2-imidazolidinone in 27% yield with 91% ee (entry 8). Interestingly, the catalyst loading can be reduced down to 0.05 mol % upon increasing the reaction time to 24 h and the temperature to 40°C. (entries 9–11.) The addition of a base is not required but increases the rate of reaction (entry 12) (see Table S1 for additional conditions).[37]

Mechanistic investigation

The proposed mechanism is shown in Figure 2. Upon release of benzoic acid from the *N*-benzoyloxyurea, the ruthenium catalyst forms a ruthenium nitrenoid

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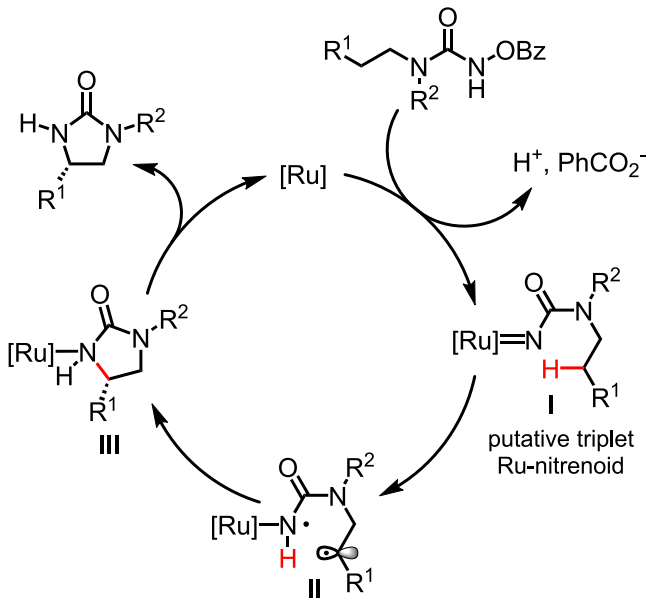

Figure 2. Proposed Mechanism through an Intermediate Triplet Ruthenium Nitrenoid

intermediate (I). The ruthenium nitrenoid from its triplet state subsequently performs a 1,5-hydrogen atom transfer (HAT) to provide the radical intermediate II. This is followed by C–N bond formation through radical-radical recombination to provide the ruthenium-coordinated product (III), which is released to regenerate the active catalyst for a new catalytic cycle.

The radical mechanism is supported by a significant kinetic isotope effect (KIE) of 4.35, which we determined with an intramolecular competition experiment by using the deuterated substrate **1aa'** to provide the cyclized products **2a'** and **2a''** with a ratio of 4.35:1 (Figures 3A and S1).[38–41] The high KIE value obtained is a strong indication for the formation of a triplet nitrene intermediate, which then engages in radical chemistry. This is in contrast to our previous work on nitrene insertion of 2-azidoacetamides in which a KIE value of 1.5 was determined by an analogous intramolecular competition experiment.[27] The assumption that the mechanism proceeds through intermediate radicals is further indicated by an experiment performed with the diastereomeric substrates (*Z*)-**1b** and (*E*)-**1b** (Figures 3B and S2–S4). Whereas (*E*)-**1b** formed (*E*)-**2b** under complete retention of the alkene configuration (80% yield, 76% ee), (*Z*)-**1b** (*E*:*Z* ratio > 20:1) was converted to **2b** with an eroded *Z*:*E* diastereomeric ratio of just 4.4:1 (73% yield, 91% ee). This can be rationalized with an isomerization from the thermodynamically less stable *Z*-isomer to the preferred *E*-isomer in the course of the C–H amination at the stage of the allyl radical intermediate. However, the radical is apparently short-lived so that no complete isomerization can occur. As expected, the *Z*:*E*-ratio is temperature dependent with a higher *Z*:*E*-ratio at lower temperature (5.1:1 at 4°C) and a lower *Z*:*E*-ratio at higher temperature (2.9:1 at 40°C). Finally, a radical mechanism is also supported by the ring-closing C–H amination of the chiral non-racemic substrate (*S*)-**1c** (89% ee) to provide (*R*)-**2c** under retention of configuration for both catalyst enantiomers (Figure 3C). However, although the Δ-catalyst provides (*R*)-**2c** with only slightly decreased enantioselectivity (85% ee), the mismatched Λ-catalyst leads to a strong erosion of the enantiomeric excess of (*R*)-**2c** (40% ee). This decrease in enantiomeric excess is not consistent

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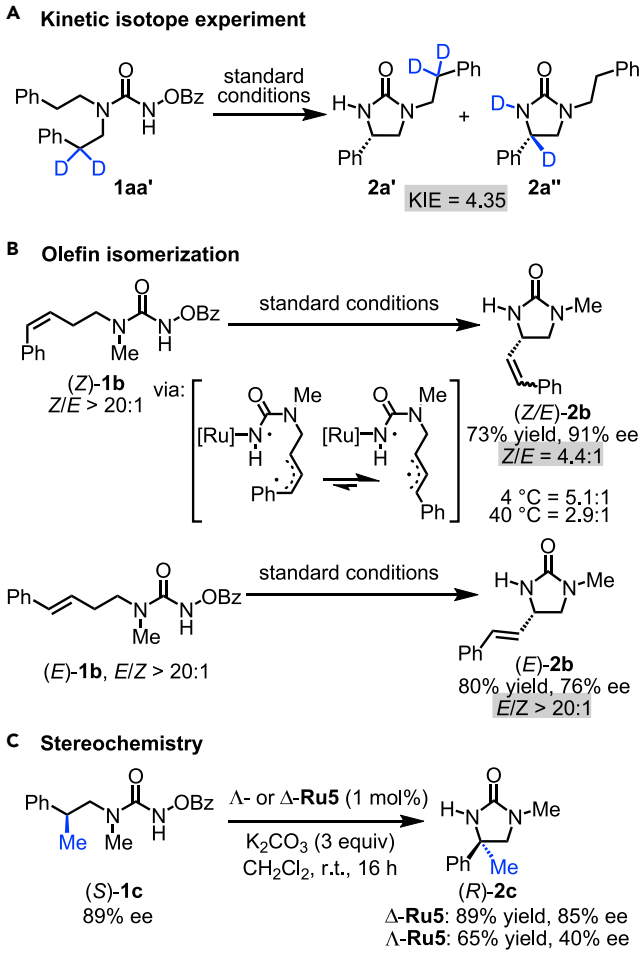

Figure 3. Control Experiments to Probe the Proposed Radical Mechanism

(A) Kinetic isotope experiments.

(B) Olefin isomerization experiments.

(C) Stereochemical considerations.

with a concerted C–H insertion mechanism but rather indicates a radical pathway in which the Δ-catalyst matches the *S*-configuration of the chiral substrate whereas the Λ-catalyst constitutes a mismatch, thus resulting in a slower radical recombination and subsequent partial racemization.

Scope and Limitation

To explore the scope of this new method, we applied the reaction conditions to a variety of *N*-benzoyloxyurea as shown in Figure 4. Benzylic C(sp^3)–H aminations to chiral 2-imidazolidinones occurred with high yields and high enantioselectivities. For example, a *para*-, *meta*-, and even a sterically very hindering *ortho*-methyl group in the phenyl moiety are well tolerated (products **2d–2f**, 92%–99% yield, 95%–97% ee), as well as an electron-withdrawing fluorine (**2g**) and chlorine substituent (**2h**, for crystallographic data see Table S2; Figure S34, CCDC number 1972573), and an electron-donating methoxy group (**2i**). A 1-naphthyl group provided the cyclic urea **2j** with 99% yield and 99% ee, whereas a 2-naphthyl group afforded the cyclic urea **2k** with 97% yield and 90% ee. The smaller 2-thiophene moiety provided the cyclic urea **2l** with 99% yield but a somewhat reduced 88% ee. We obtained 2-Imidazolidinone **2m** with stereocenters in the 4- and 5-position

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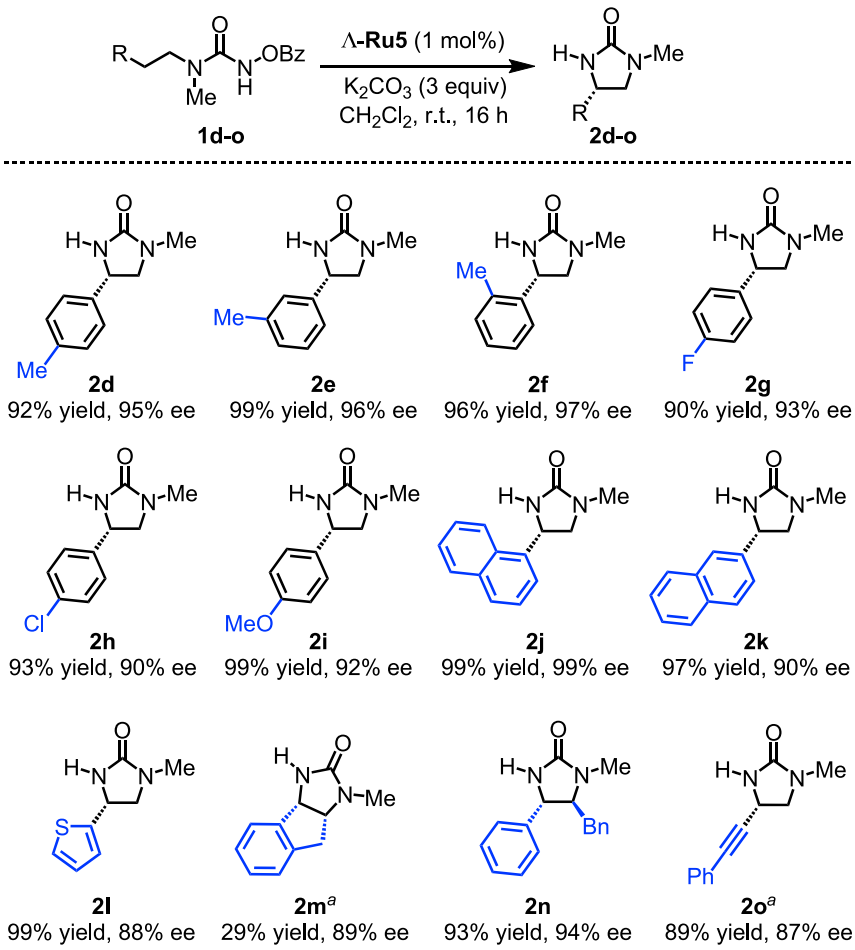

Figure 4. Substrate Scope

[a]Λ-**Ru4** was used as the catalyst instead.

in sluggish 29% yield but 89% ee by desymmetrization of an indane substrate by using the ruthenium catalyst Λ-**Ru4** instead of Λ-**Ru5**. However, the desymmetrization of a *N*-benzoyloxyurea derived from 1,3-diphenyl-2-propanamine provided the 4,5-difunctionalized 2-imidazolidinones **2n** with two adjacent stereocenters as a single diastereomer in 93% yield with 94% ee (see Table S3; Figures S35–S38 for the assignment of the relative configuration by NMR). Besides C(sp^3)–H aminations at benzylic and allylic positions (see Figure 3B), ring-closing C(sp^3)–H amination is also possible at a propargylic position in 89% yield and with 87% ee (**2o**). However, methylene groups without any adjacent activation group do not provide significant amounts of cyclization product (see Supplemental Information for more details). The substrate was completely consumed but did not provide any significant amount of useful product (e.g., 6-membered ring-close urea and nitrene reduction side-product).

The ring-closing C(sp^3)–H amination to 2-imidazolidinones tolerates different *N*-alkyl substituents as shown in Figure 5. Ethyl, *n*-butyl, isobutyl, and phenethyl substituents are well tolerated providing the corresponding *N*-alkylated 2-imidazolidinones **2p–2s** in 68%–99% yield and with 92%–95% ee. However, a benzyl substituents results in reduced yields of 37% yield for **2t** (93% ee). Importantly, the ring-closing C(sp^3)–H amination is applicable to non-alkylated substrates

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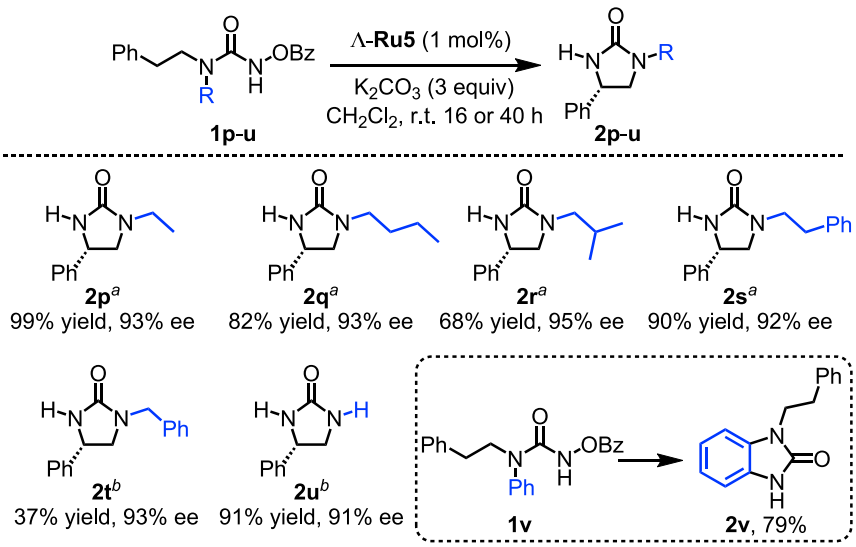

Figure 5. Substrate Scope

Products **2p–2r** formed with regioisomeric ratios of more than 20:1. [a]40 h reaction time. [b]16 h reaction time.

as demonstrated with the product **2u** containing two N–H groups which was afforded in 91% yield and 91% ee. It is worth noting that a substrate bearing a *N*-phenyl substituent (**1v**) only provided the corresponding C(sp^2)–H amination product (**2v**), which is not desired in this context but by itself a useful transformation.

Synthetic Applications

Chiral 2-imidazolidinones are highly valuable building blocks for the synthesis of bioactive compounds, such as medicinal agents and natural products. For example, (*S*)-4-phenyl-2-imidazolidinone [(*S*)-**2u**] can be obtained from the *N*-benzoyloxyurea **1u** and just 0.2 mol % Λ-**Ru5** in a yield of 74% with almost perfect enantioselectivity of 99.6% ee after a single recrystallization step (Figure 6A). According to reported procedures, this enantiomerically pure 2-imidazolidinone (*S*)-**2u** can be converted to the drug levamisole[42] by first thiation of the urea with Lawesson's reagent[43] followed by cycloalkylation with 1,2-dibromoethane.[44,45] Analogously, the drug dexamisole, which is the enantiomer of levamisole,[46] can be synthesized from (*R*)-**2u**, which we obtained from **1u** by using Δ-**Ru5** instead of Λ-**Ru5**.[47–49]

A second example provides a concise route to the bisindole alkaloids topsentine D and spongotine A (Figure 6B). Accordingly, ring-closing C(sp^3)–H amination of the indole-containing substrates **1w** and **1x** provided, under standard conditions, the 4-indolyl-2-imidazolidinones **2w** and **2x**, respectively, in high yields and with high ee. These 2-imidazolidinones can be hydrolyzed with concentrated HCl in AcOH at 85°C under microwave conditions[50] for 10 min to the respective vicinal diamines **3a** and **3b** with almost unchanged enantiomeric excess and constitute intermediates of the natural products topsentine D[51] and spongotine A,[52] respectively. A third example provides access to the mono-*N*-methylated 1,2-diamine **3c**, which was reported as an intermediate for the synthesis of a chiral organocatalyst (Figure 6C).[53]

Our method, introduced here, to access chiral vicinal diamines complements a catalytic, enantioselective *syn*-diamination of alkenes to 1,3-ditosylimidazolidin-2-ones recently reported by Denmark[54] and related work by Muñiz,[55,56] but which

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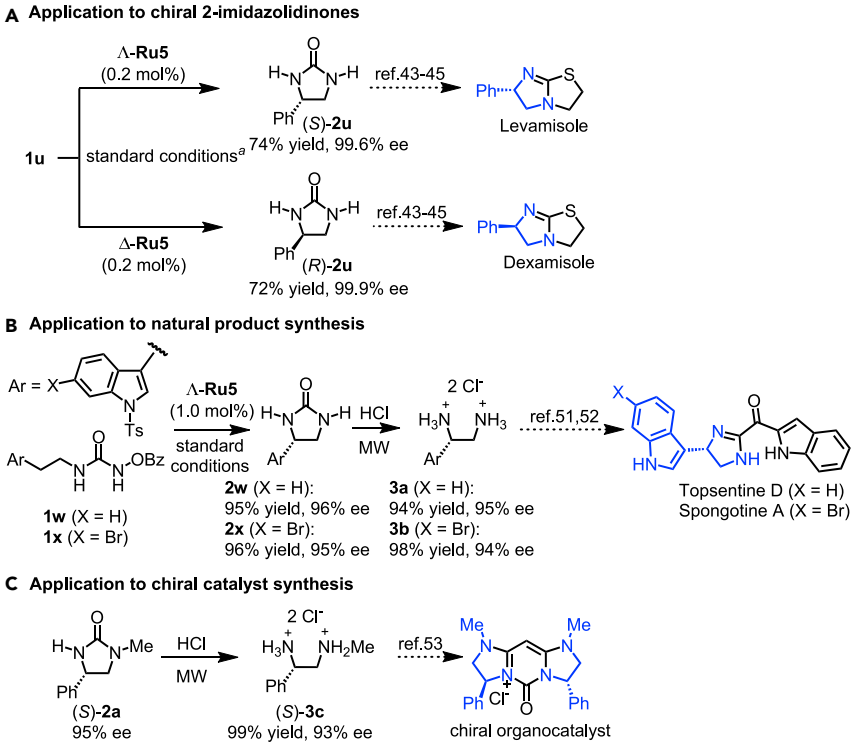

Figure 6. Applications to the Synthesis of Medicinal Agents, Natural Products, and a Chiral Organocatalyst

[a]Standard conditions followed by recrystallization in EtOAc:*n*-hexane. MW, microwave.

(A) Application to the synthesis of medicinal agents.

(B) Application to natural product synthesis.

(C) Application to the synthesis of a chiral catalyst.

all require the use of sulfonyl protection groups. Furthermore, Arnold recently reported an enzymatic C(sp^3)–H amination platform for the enantioselective synthesis of cyclic sulfamides as building blocks for diverse chiral 1,2- and 1,3-diamines.[14] Although the described method is very powerful, diamines with two primary amines are apparently not accessible, and therefore, Arnold's enzymatic method through sulfamides is not suitable for the applications shown in Figure 6.

To conclude, here, we reported the first example of a ring-closing C(sp^3)–H amination of urea substrates to chiral 2-imidazolidinones in a catalytic enantioselective fashion. Starting from abundant primary or secondary amines, *N*-benzoyloxyurea can be synthesized in just two steps and enantioselectively cyclized to cyclic urea under mild reaction conditions and by using low loadings of a chiral-at-metal ruthenium catalyst. We anticipate that this method will be of significant synthetic interest because the furnished chiral 2-imidazolidinones and their corresponding chiral 1,2-diamines, obtained through efficient hydrolysis with HCl, are highly valuable chiral building blocks.

EXPERIMENTAL PROCEDURES

Resource Availability

Lead Contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Eric Meggers (meggers@chemie.uni-marburg.de).

Materials Availability

Unique and stable reagents generated in this study will be made available on request, but we might require a payment and/or a completed materials transfer agreement if there is potential for commercial application.

Data and Code Availability

The crystal structure data of compound (*S*)-**2h** has been deposited in the Cambridge structural database under reference number 1972573.

Representative Method for Asymmetric C–H Amination Process

A dry Schlenk tube (10 mL) was charged with substrate **1aa** (59.6 mg, 0.2 mmol), chiral ruthenium catalyst **Ru5** (0.002 mmol, 1.0 mol %), and K_2CO_3 (82.8 mg, 0.6 mmol) under an atmosphere of N_2. Freshly distilled dichloromethane (2.0 mL) was added via syringe. The reaction mixture was stirred at ambient temperature for 16 h under an atmosphere of N_2. Thereafter, the mixture was transferred to a column and purified by flash chromatography on silica gel (EtOAc:*n*-hexane = 2:1 to EtOAc:MeOH 95:5) to afford the analytical pure product (*S*)-**2a** (34.9 mg, 99% yield) as a white solid. An enantiomeric excess of 95% ee was determined by high performance liquid chromatography (HPLC) analysis on a chiral stationary phase (column: Daicel Chiralpak IA 250 × 4.6 mm, absorption: λ = 220 nm, mobile phase: *n*-hexane:isopropanol = 90:10, flow rate: 1.0 mL/min, column temperature: 30°C, retention times: t_r (major) = 13.2 min, t_r (minor) = 11.4 min).

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.05.017.

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AUTHOR CONTRIBUTIONS

E.M. and M.K. coordinated the project; E.M. and Z.Z. wrote the manuscript with the help of all co-authors; E.M. and Z.Z. conceived the project and designed the majority of the experiments; Z.Z. carried out the majority of the experiments; Y.T., T.Y., and M.H. contributed to the catalyst synthesis and synthesized some substrates; X.X. assigned the relative configuration of product **2n** by NMR experiments; S.I. and R.R. collected the crystallographic data and solved and refined the X-ray crystal structure of **2h**.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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