Ruthenium(II)-Catalyzed Enantioselective γ-Lactams Formation by Intramolecular C–H Amidation of 1,4,2-Dioxazol-5-ones

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Supporting Information Placeholder

ABSTRACT: *We report the Ru-catalyzed enantioselective annulation of 1,4,2-dioxazol-5-ones to furnish γ-lactams in up to 97% yield and 98% ee via intramolecular carbonylnitrene C–H insertion. By employing chiral diphenylethylene diamine (dpen) as ligands bearing electron-withdrawing arylsulfonyl substituents, the reactions occur with remarkable chemo- and enantioselectivities; the competing Curtius-type rearrangement was largely suppressed. Enantioselective nitrene insertion to allylic / propargylic C–H bonds was also achieved with remarkable tolerance to the C=C and C≡C bonds.*

Enantioselective direct C–H amidation of hydrocarbon feedstocks offers a direct access to chiral amines, which are prevalent motifs in pharmaceuticals and bioactive natural products.[1] Employing chiral dirhodium(II) catalysts, Müller,[2] Du Bois,[3] Davies[4] and Lebel[5] demonstrated successful enantioselective intra- and intermolecular sulfonylnitrene insertion to benzylic and allylic C–H bonds using hypervalent iodine(III) reagents as oxidant (Figure 1A). Likewise, chiral Ru complexes of metalloporphyrins[6] and pyridine bis(oxazoline) ligands[7] are also known to effect asymmetric benzylic C–H amidations. Katsuki and co-workers accomplished the highly enantioselective intra- and intermolecular C–H bond amidations with chiral Ru/Ir-salen complexes as catalysts using sulfonylazides as precursors for sulfonylnitrene formation (Figure 1B).[8] Recently, Arnold and co-workers employed directed evolution and developed successfully some iron-containing biocatalysts based on cytochrome P450 for enantioselective amidation of ethylbenzenes.[9]

While γ-lactams are important scaffolds in drug development, enantioselective nitrene insertion to C(sp^3)–H bonds to form chiral γ-lactams remain a formidable challenge. Due to the inherent instability, carbonylnitrenes would undergo spontaneously Curtius-type rearrangement to give isocyanates as the principal products.[10] An important breakthrough has recently been achieved by Chang and co-workers.[11] With dioxazolones as nitrene source, some Cp*Ir(III) complexes (Cp* = pentamethylcyclopentadienyl) ligated with strong σ-donating bidentate carboxamidoquinolines are found to catalyze chemoselective nitrene C(sp^3)–H insertion, resulting in γ-lactam formation. A combined computational and experimental investigation suggested the strong σ-donor ligands would facilitate the nitrene C–H insertion reactivity by raising the barrier of the competing Curtius-type rearrangement pathway. Prompted by Chang's work, we surmised that development of asymmetric γ-lactam synthesis by enantioselective nitrene C(sp^3)–H bond insertion should be feasible. Here we report the chemo- and enantioselective chiral γ-lactams synthesis by Ru-catalyzed nitrene C(sp^3)–H bond insertion with dioxazolones as the nitrogen source. With diphenyl-1,2-diamine (dpen) as ligand, the γ-lactams were obtained exclusively in up to 98% *ee*. The use of dpen ligand with *electron-withdrawing arylsulfonyl substituents* would deliver the best enantioselectivity with the competing Curtius-type rearrangement largely suppressed.

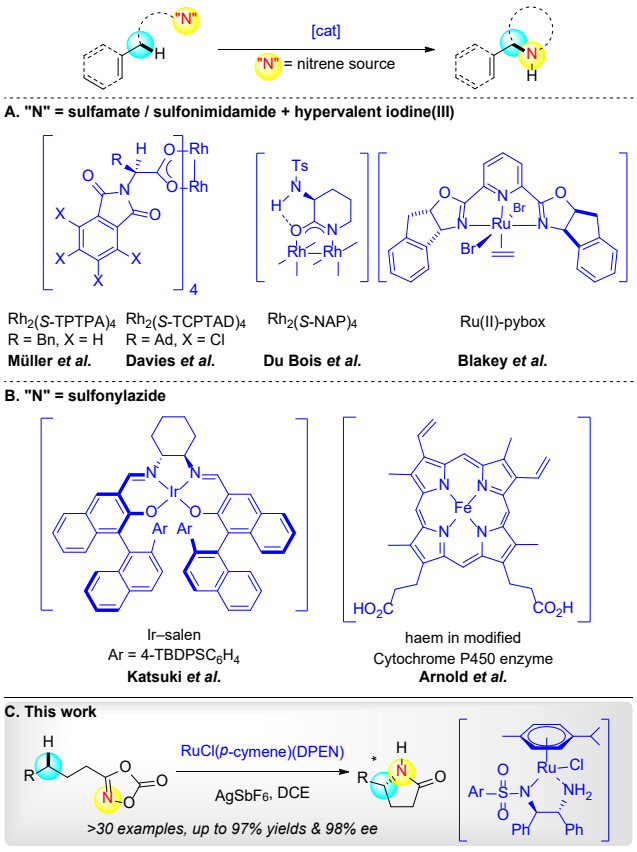
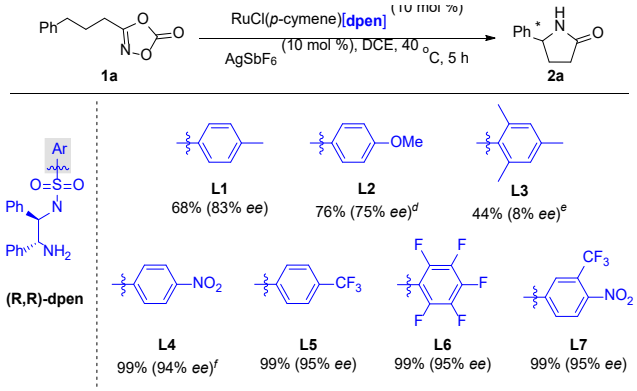


Figure 1. Examples of catalytic enantioselective inter- and intramolecular amidation by nitrene C–H insertion. Bn = benzyl, Ad = adamantyl, Ts = tosyl.

We began by examining the activity of [$RuCl_2$(*p*-cymene)]$_2$ for catalytic nitrene C–H insertion since the π-basic d^6 Ru(II) center is known to stabilize the isoelectronic carbene ligand for selective transformations.[12] Using phenyl-1,4,2-dioxazol-5-lones **1a** as

model substrate, [(*p*-cymene)$RuCl_2$]$_2$ was an ineffective catalyst. After extensive screening, the cymene-ruthenium complexes with chelating diphenyl-1,2-ethylenediamine (dpen) was discovered to be a promising candidate for optimization. Treating **1a** with RuCl(p-cymene)[(*R,R*)-Ts-dpen] **Ru-L1** (10 mol %) in toluene gave **2a** in 54% yield and 66% *ee*. Gratifyingly, performing the same transformation in DCE afforded **2a** in 68% yield and 83% *ee*. As depicted in Table 1, reactions employing ligands bearing electron-donating substituents such as 4-methyl (**L1**), 4-methoxy (**L2**) and 2,4,6- trimethyl (**L3**) on the aryl moieties gave lower (44–76%) lactam yields and enantioselectivities (8–83% *ee*). Apparently, those dpen ligands bearing electron-withdrawing groups [e.g. 4-nitro (**L4**), 4-trifluoromethyl (**L5**), 1,2,3,4,5-pentafluoro (**L6**) and 3-trifluoromethyl-4-nitro (**L7**)] would afford **2a** in 99% yield and >94% *ee*. [see Supporting Information for full screening results].

Table 1. Ligand Optimization[a-c]



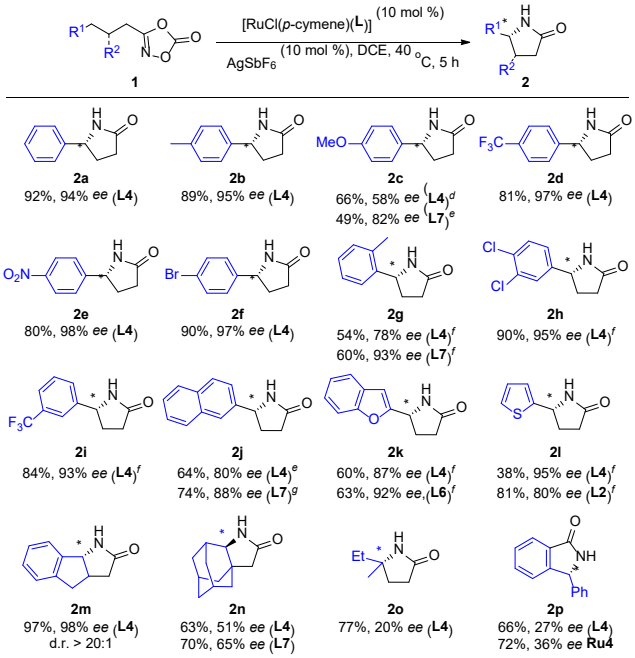
[a]Reaction conditions: **1a** (0.1 mmol), **[Ru]** (10 mol %), $AgSbF_6$ (10 mol %) in DCE (1 mL) under N_2 at 40 °C for 5 h. [b]Yield of product was determined by ^{1}H-NMR analysis of the crude reaction mixture. [c]Enantiomeric excess was determined by chiral HPLC. [d]Reaction with [Cp*Ir(**L2**)Cl], 67% yield, 65% *ee*. [e]Reaction with (*S,S*)-dpen. [f]Reaction with [Cp*Ir(**L4**)Cl] 62% yield, 56% *ee*.

In this work, changing the loading of **L4** from 10 mol % to 2.5 mol % Ru catalysts did not affect the product enantioselectivity (94–95% *ee*). Yet, the yield of **2a** dropped from 99% (10 mol %) to 62% (2.5 mol %) due to slower reaction. The structure of the γ-lactam **2a** was assigned to (*R*)-configuration by comparing the reported chromatographic and optical rotation data with our in-house data. For comparison, we tested the analogous amidation with **1a** using a related Cp*Ir(III) catalyst. It was found to give **2a** in only 62–67% yield and 56-65% *ee*.

For the substrate scope study (Table 2), the dioxazolones were prepared in excellent yields from readily available carboxylic acids through a straightforward two-step sequence involving hydroxamic acid formation and carbonylative cyclization. With **L4** as ligand, dioxazolones **1a**–**1f** containing benzylic C–H bonds were transformed to produce the corresponding γ-lactams (**2a**–**2f**) in excellent yields (~90%) and >90% *ee* regardless of the nature of the para-substituents. For substrate **1c** bearing a *p*-OMe substituent, **2c** was obtained in 66% yield and 58% *ee* with **L4** as ligand. Yet, higher enantioselectivity (82% *ee*) can be realized with **L7** as ligand. Effective cyclizations were achieved for substrates containing ortho- / meta- substitutions, 3,4-disubstituted aryl, and bicyclic naphthyl groups, and ca. 90% *ee* were attained in most cases (**2g**–**2j**). Importantly, heteroaryl moieties such as benzofuranyl (**2k**) and thiophenyl groups (**2l**) are well tolerated, and the desired lactams were formed in >92% *ee*.

Asymmetric desymmetrization of the indane-derived dioxazolone by benzylic C–H amidation furnished *cis*-tricyclic γ-lactam **2m** in 98% *ee*. The molecular structure of **2m** has been established by X-ray crystallography. With (*R,R*)-dpen as the chiral ligand, the structure of **2m** is confirmed to be (2*R,3S*)-configuration. Cyclization onto the non-benzylic secondary C–H bonds as exemplified in **2n** was successful, and the corresponding γ-lactams were formed in 63% yields albeit in 51% *ee*. With **L7** as ligand, **2n** was obtained in slightly better yield (70%) and enantioselectivity (65% *ee*). Yet, the lactamization of **1o** involving amidation of tertiary C-H bond afforded less satisfactory enantioselectivity (20% ee) despite attaining synthetically useful lactam yields. For the dioxazolones **1p** derived from benzoic acids, the Ru-catalyzed reaction with **L4** as ligand afforded the isooxindolin-1-one **2p** in 66% yield and 27% *ee*.

Table 2. Scope of Dioxazolones [a-c]



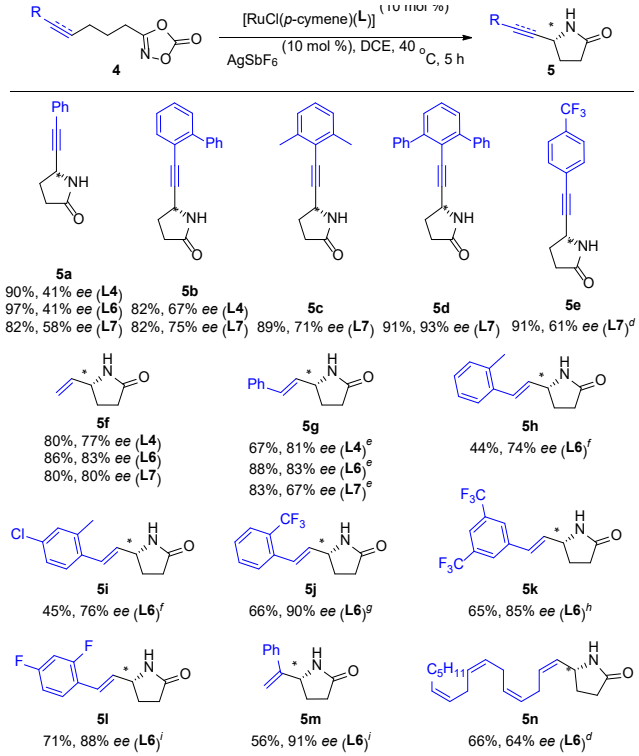
[a]Reaction conditions: **1** (0.1 mmol), [RuCl(*p*-cymene)(**L**)] (10 mol %), $AgSbF_6$ (10 mol %) in DCE (1 mL) under N_2 at 40 °C for 5 h. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral HPLC. [d]Reaction for 4 days. [e]Reaction for 10 h. [f]Reaction for 12 h. [g]Reaction for 36 h.

A gram-scale synthesis of enantioenriched γ-lactams by the Ru-catalysis has been pursued. When 5 mmol of **1m** was subjected to the Ru-catalyzed conditions, the desired tricyclic γ-lactam **2m** was obtained in 79% yield and 96% *ee* (see Supporting Information).

Despite high reactivity of the putative ruthenium-nitrene species, the C=C / C≡C bonds in the same substrates are well tolerated (Table 3). For instance, the lactamization of dioxazolones containing propargylic C–H bonds afforded the desired lactams in ca. 90% yields. Initially with **L4** as ligand, the lactamization of **4a** occurred with 41% *ee*. When **L7** was the ligand, the analogous reaction proceeded with 58% *ee*. Apparently, substrates with bulkier groups such as **4d** bearing two ortho-phenyl groups was lactamized in 93% *ee versus* 71% *ee* for **4c** bearing two ortho-methyl groups.

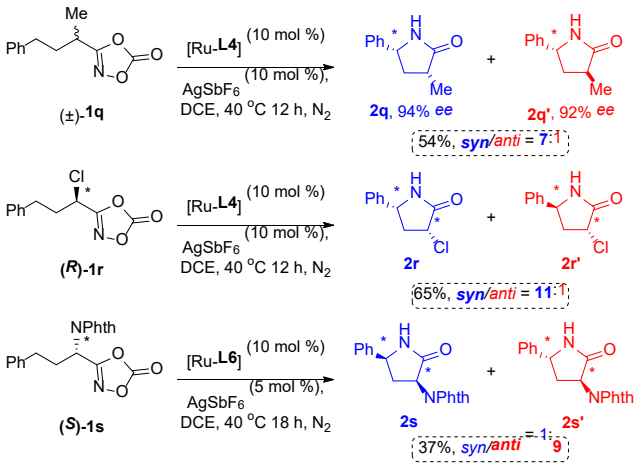
For the allylic C–H amination of **4f** (Table 3), the use of **L6** as ligand seems to afford the best enantioselectivity (83% *ee*) compared to those with **L4** (77% *ee*) and **L7** (80% *ee*). With **L6** as ligand, the enantioselectivities of 74–91% *ee* were accomplished for the reactions of **4g**–**4m**. Higher enantioselectivities were achieved for those substrates bearing relatively electron-poor allylic C–H bonds. The high C–H versus C=C selectivity is further exemplified by the successful lactamization of the arachidonic acid-derived dioxazolone **4n**; the corresponding γ-lactam **5n** was obtained exclusively in 66% yield and 64% *ee*. Notably, no aziridines products were detected.

Table 3. Substrate Scope for Dioxazolones with C=C / C≡C Bonds[a-c]



[a]Reaction conditions: **4** (0.1 mmol), [RuCl(*p*-cymene)(**L**)] (10 mol %), $AgSbF_6$ (10 mol %) in DCE (1 mL) under N_2 at 40 °C for 5 h. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral HPLC. [d]Reaction for 10 h. [e]Reaction for 48 h. [f]Reaction under 50 °C for 36 h. [g]Reaction under 50 °C for 10 h. [h]Reaction under 30 °C for 12 h. [i]Reaction for 24 h.

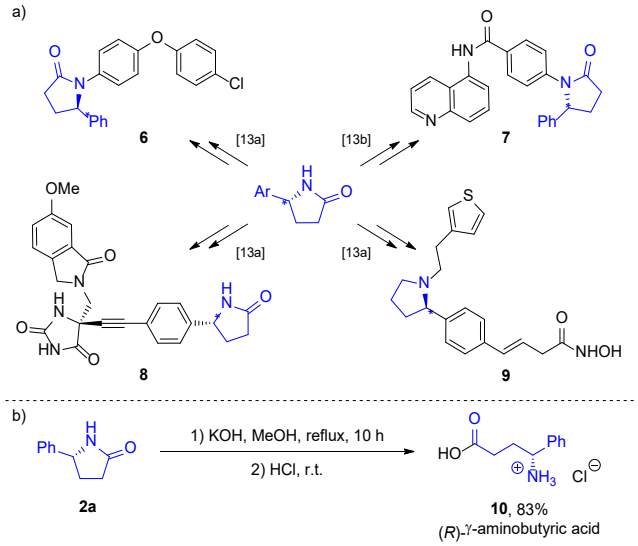
Scheme 1. Diastereoselectivity Study



The diastereoselectivity of the Ru-catalyzed lactamization has been examined (Scheme 1). When racemic 3-(4-phenylbutan-2-yl)-1,4,2-dioxazol-5-one **1q** was employed as substrate, the corresponding chiral γ-lactam was furnished in 54% yield with a *syn*/*anti* ratio of 7:1. The enantiopurities of *syn*-**2q** (94% *ee*) and *anti*-**2q'** *(*92% *ee)* were determined by chiral HPLC. Similar diastereoselectivity was observed for the analogous reaction with enantiopure (*R*)-3-(1-chloro-3-phenylpropyl)-1,4,2-dioxazol-5-one (*R*)-**1r** (>98% *ee*), and **2r**+**2r'** were produced in 65% yield with *syn*/*anti* ratio of 11:1. When a dioxazolone (*S*)-**1s** derived from unnatural L-homophenylalanine was subjected to the Ru-catalyzed conditions, the corresponding **2s** and **2s'** were isolated in 37% combined yield with the *anti*-isomer being the major product *(syn/anti ratio* = 1:9). (see Supporting Information for the proposed transition state model).

According to the literature, chiral lactam **2a** can be transformed to cannabinoid receptor 1 (CB1) inhibitor **6**[13a] and modified IWR-1 tankyrase inhibitor **7**[13b] using the conventional Cu-catalyzed C–N cross coupling reactions. Furthermore, chiral lactam **2f** can be converted to **8,** which is a drug candidate for treating inflammatory disorders. For pyrrolidine **9**,[13a] it is a hydroxamated-based inhibitor of deacetylases B (Scheme 2a). In this work, chiral γ-lactam **2a** was transformed to (*R*)-γ-aminobenzenebutanoic acid **10** in 83% yield by simple hydrolysis (Scheme 2b).[14] γ-Aminobutyric acid (GABA), analog of **10**, is a major class of inhibitory neurotransmitters for reducing neuronal excitability; it is directly responsible for the regulation of muscle tone in human.[15]

Scheme 2. Representative Product Transformations



By performing two independent competitive reactions: with **1a** and **1b** in one set and 3-(3-phenylpropyl-3,3-d_2)-1,4,2-dioxazol-5-one **1a'** and **1b** in another set, the primary kinetic isotope effect (k_H/k_D) value = 1.49±0.02 was evaluated based on the product yield ratios (see Supporting Information). This value is comparable to those observed for Rh(II)-catalyzed amidation of sulfamates (k_H/k_D = 1.9),[16] Cp*Ir(III)-catalyzed lactamization of dioxazolones (k_H/k_D = 1.51)[11] and P411$_{CHA}$ enzymatic C–H amination (k_H/k_D = 1.6).[9c] The rather small KIE values are reminiscent of a concerted nitrene C–H insertion pathway. Apparently, a hydrogen-atom abstraction mechanism is characterized by a larger KIE value as exemplified in some reported systems: Ru-porphyrin (k_H/k_D = 11).[6a]

The lactamization likely proceeds via reactive ruthenium-nitrene intermediates. We anticipated that the frontside and backside coordination of the dioxozalones would afford two diastereomeric ruthenium-nitrene complexes, which in turn react via two diastereomeric transition states **TS1** (*frontside approach*) and **TS1'** (*backside approach*). Apparently, intramolecular hydrogen bonding seems to stabilize the transition state conformations. To account for the observed enantioselectivity (Figure 2), with (*R,R*)-dpen scaffold insertion to the pro-(*R*) γ-C–H bond is preferred by having the aryl group *anti* to the hydrocarbon skeleton and distal from the chiral auxiliary (**TS1-A,** Figure 2a). Insertion of the pro-(*S*) γ-C–H bond on **TS1-B** is energetically less favored due to steric interaction between the aryl and the chiral auxiliary. Considering **TS1'** (Figure 2b), insertion to either pro-(*R*) or pro-(*S*) γ-C–H bonds are not favored as inferred by the conformational analysis. This transition

state model is consistent with the diastereoselectivity studies (see Supporting Information).

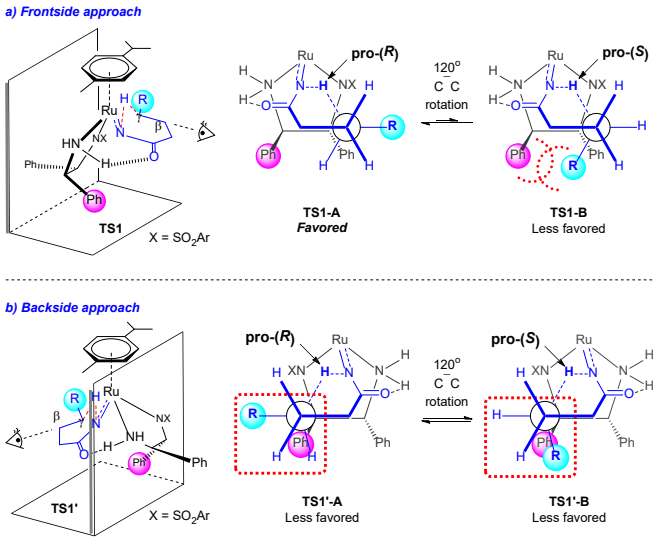


Figure 2. Conformational analysis of the proposed transition state models by Newman projections (120° rotation along C_β–C_γ), X = SO_2Ar. (a) Dioxazolone coordinating from the frontside of the Ru. (b) Dioxazolone coordinating from the backside of the Ru.

The observed preference for nitrene C–H insertion over the Curtius-type rearrangement is striking. While the origin of this high chemoselectivity remains unclear, we hypothesized that the strong π-back bonding of the Ru(II) may play a role to stabilize the nitrene ligand and would somehow disfavor the competing Curtius-type rearrangement pathway. Yet, stronger σ-donor ligands may promote stronger π-bonding effect and should thereby further weaken the electrophilicity of the nitrene ligand. The weakened nitrene electrophilicity may probably slow down the C–H insertion pathway and render the Curtius-type rearrangement becoming more competitive.

In conclusion, a chemoselective [(*p*-cymene)Ru]-catalyzed γ-C(sp^3)–H bond amidation of dioxazolones has been developed, and the γ-lactams were obtained in excellent yields without the Curtius-type rearrangement products being formed. Successful enantiocontrol of the lactamization has also been achieved. With chiral diphenylethylene diamine as scaffold, enantioselectivities (up to 97% yield and 98% *ee*) have been attained involving benzyl C–H amidation. Noted that the dioxazolones can be easily prepared from readily available carboxylic acid feedstocks, this asymmetric Ru-catalyzed C–H bond amidation strategy represents a powerful tool for easy transformation of hydrocarbon feedstocks to chiral γ-lactams core, which can be derived to high valued pharmaceuticals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Exploratory investigation, experimental conditions and procedures, characterization data (PDF)

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Notes

The authors declare no competing financial interests.

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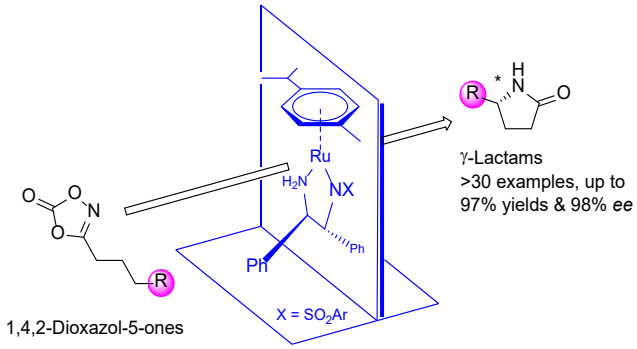
Ru
H2N
NX
Ph
Ph
X = SO2Ar
R
H
N
O
γ-Lactams
>30 examples, up to
97% yields & 98% ee
1,4,2-Dioxazol-5-ones