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Stereodefined Access to Lactams via Olefin Difunctionlization: Iridium Nitrenoids as a Motif of LUMO-Controlled Dipoles

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Supporting Information

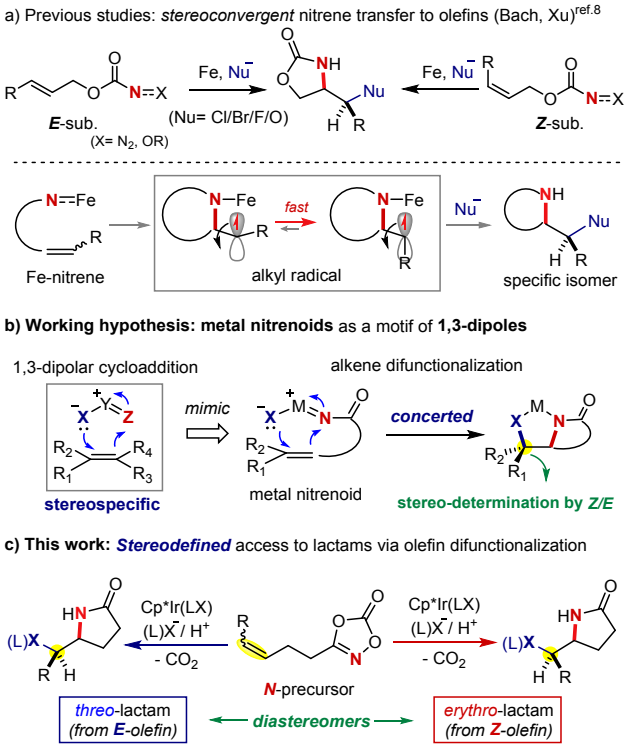
ABSTRACT: Reported herein is a general platform of a stereodefined access to γ-lactams via Cp*Ir-catalyzed olefin difunctionalization, where *in situ* generated Ir-nitrenoid is utilized as a key motif of 1,3-dipoles to enable amido transfer in a *syn*-selective manner. Computational studies suggested that the stereodefined process can be attributed to the proposed working mode of concerted [3+2] cyclization. Frontier molecular orbital (FMO) analysis implied that a low-lying LUMO of the Ir-imido fragment engages in the olefin interaction. Mechanistic understanding on the nitrene transfer process led us to develop mild catalytic protocols of stereoselective difuctionalization of alkenyl dioxazolones to furnish α-(haloalkyl)- or (oxyalkyl)lactam products which are of high synthetic and medicinal utility. Product stereochemistry (*threo* and *erythro*) was found to be designated by the olefin geometry (*E*/Z) of substrates.

■ INTRODUCTION

Olefin difunctionalization is an attractive approach for introducing two functional groups in alkene substrates.[1] Especially when the installed moieties have high synthetic utility for further transformations, it can offer a unique opportunity to build molecular complexity and functional diversity which are highly sought after in organic synthesis and pharmaceutical chemistry.[2,3] Among those methods, reactions initiated by an amino transfer into double bonds are particularly appealing to obtain synthetically versatile amine products.[4] In this context, a two-step sequence of olefin aziridination and subsequent ring-opening with proper nucleophiles has been well-established in synthesis.[5] In parallel, a direct difunctionalization of alkenes has also been actively pursued. Representatively, the osmium-catalyzed alkene aminohydroxylation is already at its high synthetic standard pioneered by Sharpless.[6,7] The intrinsic oxophilicity of osmium, however, suffers from developing other types of difunctionalization approaches with this catalyst system.

On the other hand, open-shell catalysis has significantly extended the entries of functional groups that can be installed at the double bonds (Scheme 1a). For instance, Bach and Xu groups, independently, reported Fe-catalyzed cyclization reactions with organic azides or hydroxylamines as the nitrene sources to obtain halogenated (Cl, Br, or F) and oxygenated carbamate products.[8] The salient feature of this approach is the formation of one type of stereoisomeric products regardless of double bond geometry (*E*/*Z*) in olefin-tethered substrates. This stereo-convergence was attributed to the intermediacy of readily rotatable alkyl radical species generated *in situ* by the *exo* cyclization of a putative Fe-nitrenoid. This synthetically attractive olefin difunctionalization has been advanced even in an asymmetric manner.[9]

Scheme 1. Difunctionalization of alkenes via nitrene transfer



Continuing our research efforts toward the development of efficient and selective amidiation reactions via the nitrenoid intermediacy,[10] we wondered whether this mechanistic approach can serve as a motif in the olefin difunctionalization via a formal 1,3-dipolar cycloaddition manner (Scheme 1b).[11] We envisaged to take advantage of a presupposed concerted pathway in this case, thereby

achieving high stereoselectivity in a stereodefined manner where each diastereomeric product (*threo* and *erythro*) can be generated depending on the olefin geometry (*E*/Z).

Herein, we present a general platform of a stereodefined access to *γ*-lactams via Cp*Ir-catalyzed olefin difunctionalization (Scheme 1c). Model studies with Cp*Ir(III)(κ^2-chelate) species laid a mechanistic basis for this strategy especially on the use of metal nitrenoids as a motif of 1,3-dipoles in a stereoselective cycloaddition with double bonds. Computational studies suggested that the stereodefined process can be attributed to a concerted [3+2] cyclization where a low-lying LUMO of the Ir-imido fragment engages in the olefin interaction. Based on the mechanistic understanding of the nitrene transfer, catalytic protocols of stereoselective difuctionalization of olefin-tethered dioxazolones were developed to give *α*-(haloalkyl)- or (oxyalkyl)lactam products.

■ RESULTS AND DISCUSSION

We recently demonstrated that pentamethylcyclopentadienyl (Cp*)-based Ir(III) complexes are highly effective in generating a putative acylnitrenoid to enable a catalytic haloamidation of *alkynes*.[12] Key to this achievement was to utilize a strategy of ligand participation with effective suppression of the Curtius-type decomposition path although detailed mechanistic description is still lack. Motivated by this result, we wondered if Cp*Ir(III) complexes can also facilitate an acylnitrene transfer to *alkenes* in a stereoselective manner.[13]

To validate our working hypothesis, we commenced our present study by testing Cp*Ir(III)(κ^2-*N,N'*-chelate) species with a model substrate, γ-alkenyl dioxazolones. In fact, this type of complexes was shown to readily generate high valent Ir-imido species which are subsequently engaged in C(sp^3)–H amidation in our recent report.[10f] Firstly, an iridium complex **I** was prepared from $[Cp^*IrCl_2]_2$ and 8-(methyloxycarbonyl)aminoquinoline ligand.[10f] When a neutral complex **I** was treated with (*E*-alkenyl)dioxazolone **1** in the presence of $NaBAr^F_4$, a 5-membered cationic iridacycle **II** was formed in quantitative yield (Figure 1a). Significantly, a reaction of **I** with isomeric (*Z*-alkenyl)dioxazolone **2** also furnished an amino-lactam Ir species (**III**) in excellent yield. A notable difference in chemical shifts of benzylic protons between **II** and **III** was seen in ^{1}H NMR spectroscopy: δ 3.0 ppm (doublet, J = 11.1 Hz) and 5.1 ppm (doublet, J = 5.9 Hz) in CD_2Cl_2, respectively. This observation suggested that the olefin geometry critically influences on the product configuration.

Solid state structure of **II** and **III** was subsequently obtained by an X-ray crystallographic analysis to reveal that indeed they are diastereomers each other (Figure 1b and 1c). While the benzylic proton of **II** was shown to be more shielded by quinolinyl and lactam moieties, this anisotropic effect is reduced in **III**. The Ir–N2 bond length increases from 2.107(2) Å (**I**[10f]) to 2.283(3) Å in **II** and 2.323(3) Å in **III**, suggesting that putative Ir-nitrenoid transfer was accompanied with the addition of the ligand *N2* atom into double bonds in both cases. Most importantly, the structure of **II** and **III** clearly indicates that the presupposed 1,3-dipole of (amino)Ir-nitrenoid inserts into the pendant double bond in a *syn* manner.

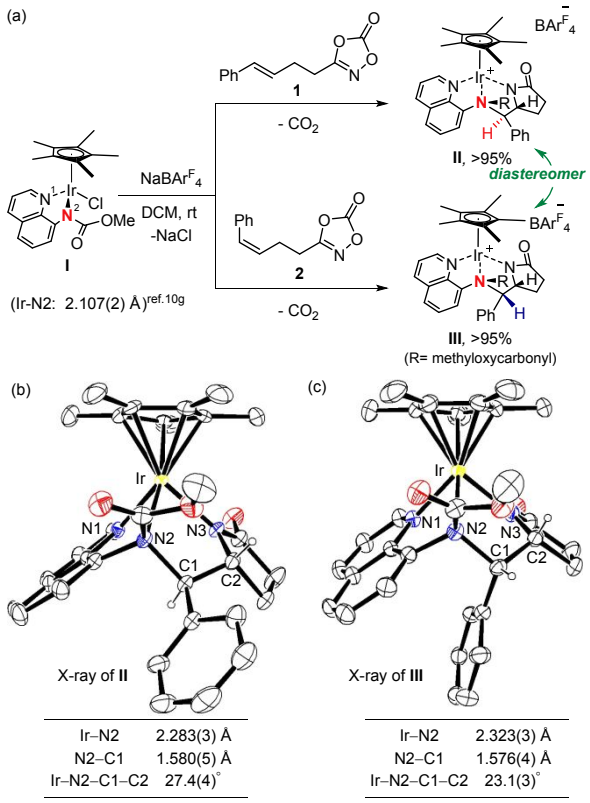


Figure 1. (a) Stoichiometric olefin diamination. Solid state structure of (b) **II** and (c) **III** with selected data.

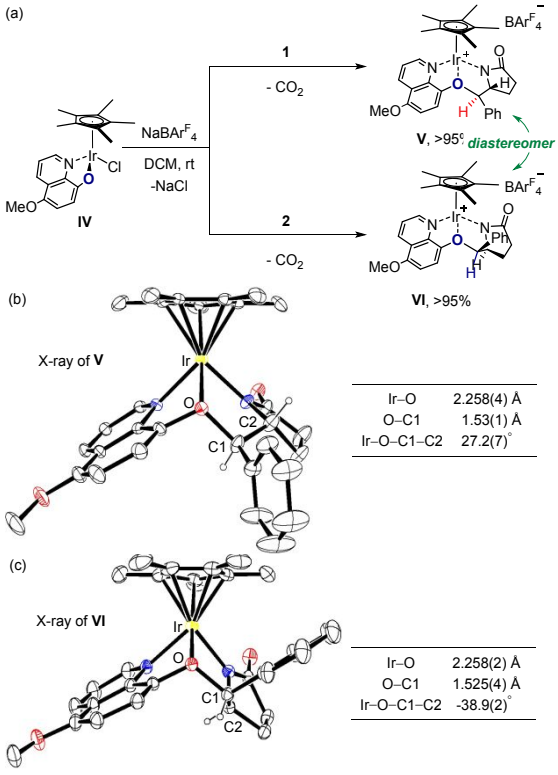


Figure 2. (a) Stoichiometric olefin oxyamidation. Solid state structure of (b) **V** and (c) **VI** with selected data.

Encouraged by the above promising result of the stereodefined diamination, we also examined oxyamidation as another entry of olefin difunctionalization. In this context, Cp*Ir(III)(κ^2-*N,O*-chelate) species was first considered, and iridium complexes bearing 5-methoxy-8-hydroxyquinoline ligands were accordingly applied.[10g] When a representative complex **IV** was reacted with γ-alkenyl dioxazolones (**1** and **2**), the expected oxyamidation took place readily to give single diastereomers **V** and **VI** in excellent yields, respectively (Figure 2a). Their structures were again unambiguously confirmed by X-ray analysis to reveal that an oxyamidated product **V** is a structural analogue of the diaminated complex **II** (Figure 2b). On the other hand, the structural feature of **VI** is distinctive to that of **III** in that the dihedral angles of Ir–X–C1–C2 are quite differed: 23.1° for **III** (X= N2) and -38.9° for **VI** (X= O). It should be noted that, irrespective of structural discrepancy between two sets of complexes obtained from diamination and oxyamidation, both types of olefin difunctionalization were found to proceed in a *syn*-selective manner to afford diastereoisomeric products depending on the olefin geometry.

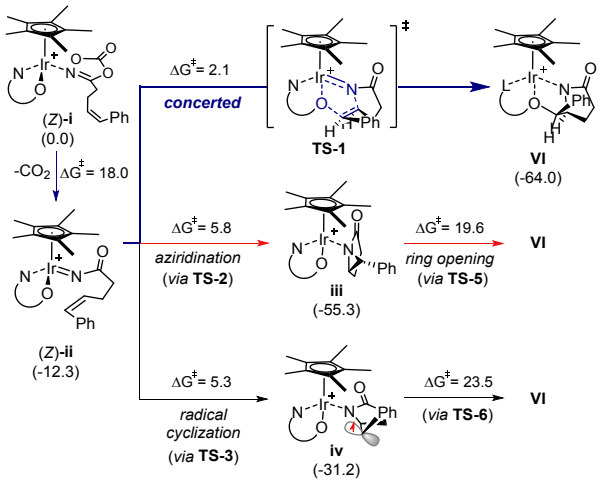


Figure 3. Plausible working modes of a putative Ir-nitrenoid (*Z*)-**ii**. Energy profiles for the proposed pathways were calculated at PCM(dichloromethane)-M06/SDD+6-311++G**//M06/Lanl2dz+6-31G** level of theory.

To better understand the underlying origin of the observed excellent stereoselectivity in the olefin insertion, putative intermediates were evaluated by DFT calculation under the plausible working modes (Figure 3). Representatively, Ir complex **IV** and *Z*-alkenyl dioxazalone **2** were selected for this theoretical study (for others, see Supporting Information). The reaction will be initiated by an oxidative decarboxylation of an Ir complex-substrate adduct (*Z*)-**i**.[10f] It requires 18.0 kcal/mol of energy to generate a key Ir-imido intermediate (*Z*)-**ii**. Based on the literature regarding the reactivity of presupposed metal-nitrenes toward olefins,[14] we evaluated three plausible pathways in our case to lead to an oxyamidation product **VI** from (*Z*)-**ii**: concerted cycloaddition, aziridination-ring opening, and radical cyclization. Among those, the concerted [3+2] cyclizative pathway (blue line) was calculated to be energetically most downhill by 51.7 kcal/mol, and it was also found to be kinetically favorable with only negligible barrier of 2.1 kcal/mol.[15]

On the other hand, a two-step path involving an aziridine intermediate **iii** was found to require higher barrier by 3.7 kcal/mol. Moreover, the subsequent ring-opening process was calculated to be kinetically demanding ($\Delta G^{\ddagger}$ = 19.6 kcal/mol, red line). In addition, a radical cyclization was found to kinetically less favorable at 5.3 kcal/mol (black line) when compared to the concerted pathway, and the resulting alkyl radical **iv** traverses **TS-6** with activation barrier of 23.5 kcal/mol via the interception with an oxygen atom embedded in ligand.[16] Moreover, the concerted pathway was also calculated to be most accessible when a less nucleophilic alkene was employed (see Supporting Information for details).

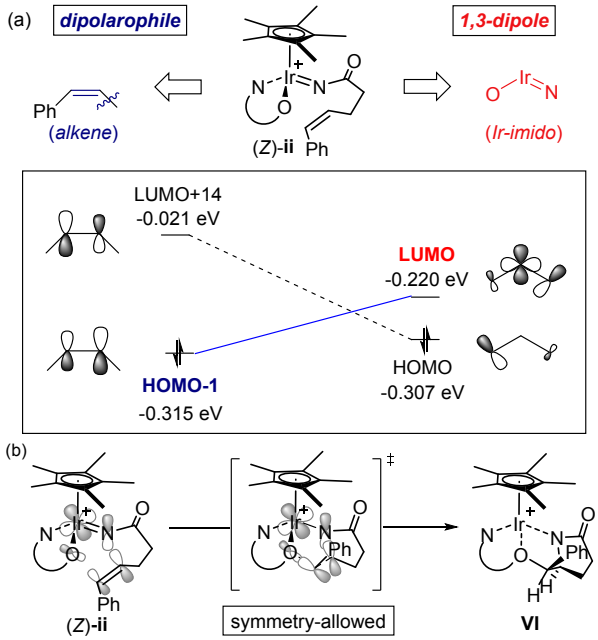


Figure 4. (a) Quantitative FMO analysis of Ir-nitrenoid (*Z*)-**ii**. (b) Conceptual MO interaction describing the proposed concerted pathway.

Having identified the energy landscape of the reaction progress, another theoretical insight was obtained by an FMO analysis to see how Ir-nitrenoids engage in the kinetically most accessible concerted [3+2] cyclization pathway.[17] Figure 4a shows a MO diagram partitioned into two fragments as a function. The carbon-carbon double bond in substrate is denoted as an olefinic dipolarophile, and its π molecular orbitals pertain to HOMO-1 at -0.315 eV and LUMO+14 at -0.021 eV. On the other hand, the fragment of Ir-nitrenoid species reveals a 1,3-dipole character as seen by the three-centered LUMO and HOMO at -0.220 and -0.327 eV, respectively. Indeed, as shown in Figure 4b, LUMO of Ir-imido and HOMO-1 of the olefin moiety overlap in a symmetry-allowed manner. Although an inverse electron-demand combination between HOMO and LUMO+16 can also be considered (dashed line), the former interaction is predicted to be dominant in that a smaller energy gap of 0.095 eV is involved in this combination between LUMO and HOMO-1. Moreover, the corresponding

intermediates derived from Cp*Ir(III)(κ^2-*N,N'*-chelate) also showed a similar behavior as a three-centered LUMO according to the analogous FMO analysis (see Supporting Information for details).

Transition state analysis offered an additional information on the working mode of the putative Ir-imido in the concerted process. As enumerated in Figure 5a, the transition state **TS-1** reveals that formation of the C–N bond (2.47 Å) takes place early whereas C–O bond remains to be developed at 3.02 Å. Considering that the bond lengths of C–N and C–O bond in **VI** are 2.258(2) Å and 1.525(4) Å, respectively (see Figure 2c), the cyclization is rationalized to be concerted but asynchronous. This aspect may be reflected in the nature of LUMO of **ii** that is mainly composed of Ir–N π^* orbital whereas contribution of the oxygen *p* orbital is relatively small (Figure 5b). Once again, this orbital analysis strongly supports that the putative Ir-nitrenoids will behave as a motif of LUMO-controlled dipoles to participate in the olefin difunctionalization being mechanically reminiscent of 1,3-dipolar cycloaddition reactions.[18] In fact, certain electrophilic dipoles such as ozone (O_3) and nitrous oxide (N_2O) were shown to display analogous molecular orbital interactions, referred as a Sustmann type III.[17b,19] While the synthetic utility of metal-involved [3+2] cycloadditions have been reported,[20] to our best knowledge, our current study represents the first example how FMOs of metal-nitrenoids govern their reactivity and selectivity toward the olefin difunctionalization.

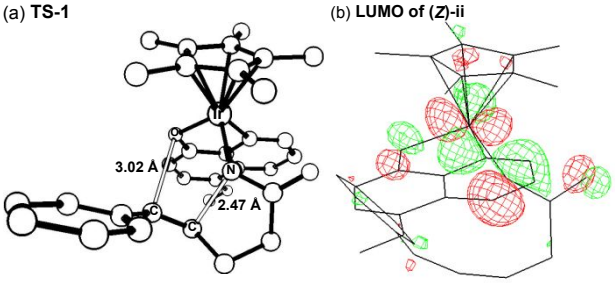


Figure 5. (a) DFT-computed structures of **TS-1** and (b) LUMO of (*Z*)-**ii** (isovalue: 0.05).

On the basis of the above rationale, we next wondered whether the mechanistic motif of 1,3-dipolar cycloaddition can be developed into a *catalytic* version as depicted in Scheme 2. A deliberate combination of pre-catalyst $[Cp^*IrCl_2]_2$ and nucleophile $(L)X^-$ is anticipated to form an active species **v** that can bind to an alkenyl dioxazolone (**1** or **2**) leading to an adduct **vi**. A putative Ir-nitrenoid **vii**, generated upon the oxidative coupling of **vi** to release CO_2, will undergo the postulated concerted cycloaddition onto tethered double bond to give an iridium-lactam species **viii**. It should be noted that this cyclization will be a stereodefined process affording diastereomeric isomers **viii** depending on the olefin geometry. The final protonation with a concomitant ligand exchange from **viii** was predicted to be also crucial for the overall catalytic performance.

Along with our previous work on the Ir-catalyzed haloamidation of alkynes,[12] the above described mechanistic rationale on the olefin difunctionalization led us to screen reaction parameters by using an alkenyl dioxazolone substrate **1** (Table 1). When NaCl was employed as a chloride source in the presence of 15-crown-5 (1.5 equiv each), (α-chlorobenzyl)lactam **3** was obtained (11%) in hexafluoroisopropanol (HFIP) solvent by the action of $[Cp^*IrCl_2]_2$ (2.5 mol %) catalyst (entry 1). Subsequently, an acid additive was found to have significant influence on the reaction efficiency. For instance, acetic acid, benzoic acid, or binaphthyl-2,2′-diyl hydrogen phosphate (BNDHP) displayed significant improvements (entries 2–4). While the use of *p*-toluenesulfonic acid (*p*-TsOH) or HCl were found to have more pronounced effects (entries 5–6), a slight erosion in diastereoselectivity was accompanied in these cases mainly due to the olefin isomerization induced by the acid.[21] Pleasingly, product **3** was obtained quantitatively with excellent diastereoselectivity when HCl was added in dichloromethane/trifluoroethanol (DCM/TFE, 1:1) co-solvent (entry 7).[22] Significantly, an almost same outcome was obtained when HCl was employed alone in the absence of NaCl/15-crown-5 (entry 8), suggesting that HCl can serve as a source of both proton and chloride.

Scheme 2. Proposed catalytic cycle

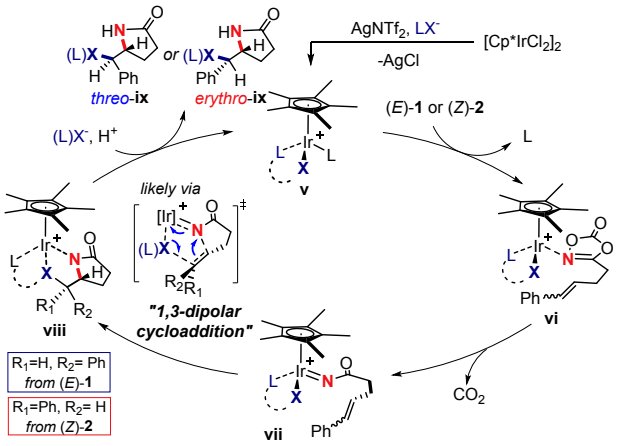
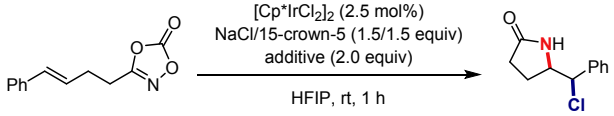


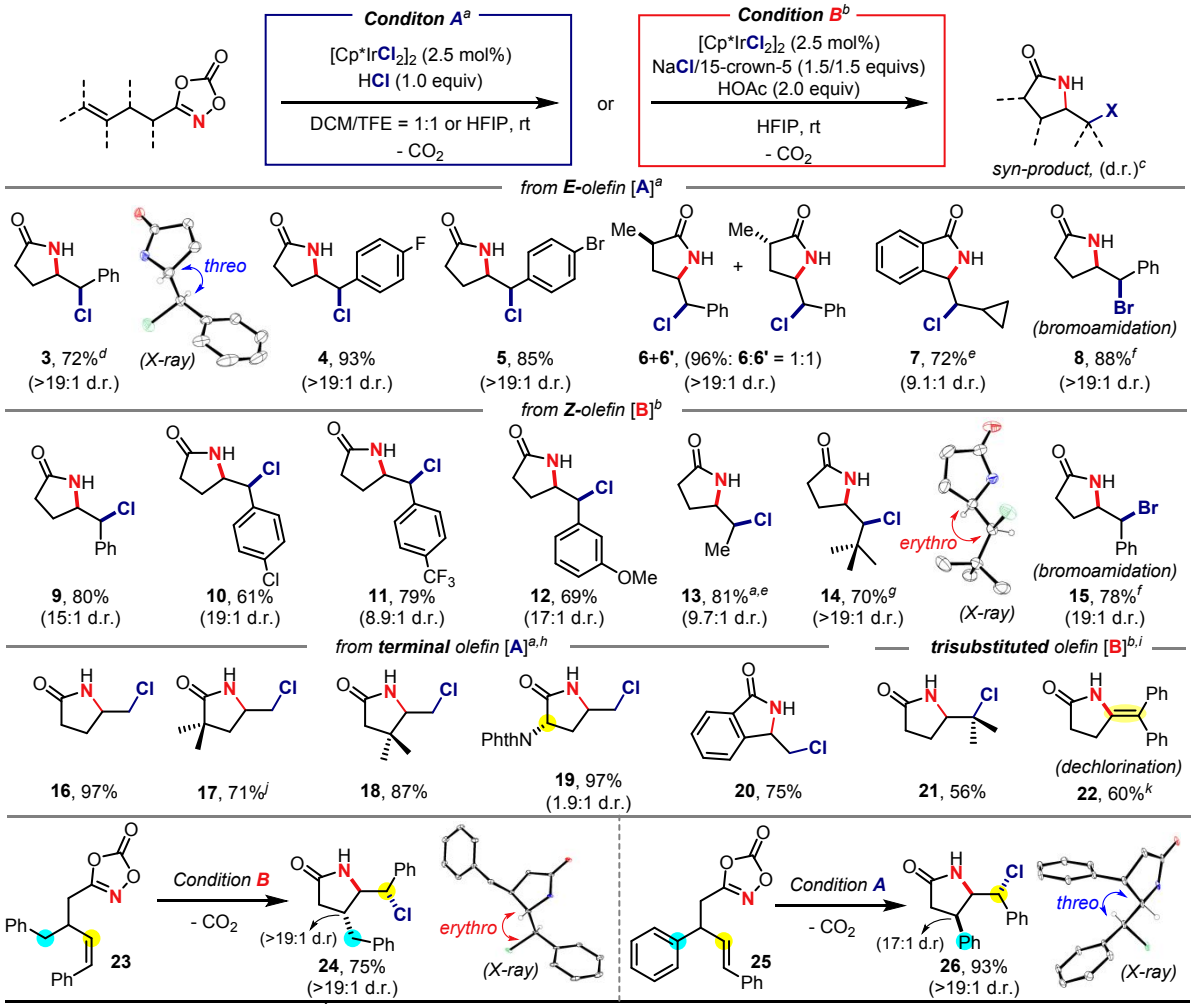
Table 1. Selected reaction parameters in chloroamidation



entry	additive [$pK_a(H_2O)$][23]	**3** (%)[a]	d.r.[b]
1	none (HFIP= 9.3)[24]	11	>19:1
2	acetic acid (4.8)	50	>19:1
3	*o*-nitrobenzoic acid (2.2)	41	>19:1
4	BNDHP (-)	60	>19:1
5	*p*-TsOH[c] (-2.8)	90	9.0:1
6	HCl (-8.0)	>95	7.1:1
7[d]	HCl	>95	>19:1
8[d,e]	HCl	>95	>19:1

[a]^{1}H NMR yields using 1,1,2,2,-tetrachloroehtane as an internal standard. [b]Diastereomeric ratio (d.r.), determined by ^{1}H NMR of the crude mixture. [c]Monohydrate form was used. [d]Run in DCM/TFE (1:1) co-solvent. [e]1.0 equiv of HCl was used without NaCl/15-crown-5.

Table 2. Substrate scope in the haloamidation of alkenyl dioxazolones



[a]Substrate (0.2 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol%) and HCl (1.0 equiv) in DCM/TFE (1:1) at 25 °C for 1 h. [b]Substrate (0.2 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol%), NaCl (1.5 equiv), 15-crown-5 (1.5 equiv) and acetic acid (2.0 equiv) in HFIP at 25 °C for 2 h. [c]Ratio of diastereoisomers, determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Conducted on 1.0 mmol scale. [e]5 mol% of $[Cp^*IrCl_2]_2$ was used. [f]Bromoamidation using NaBr as a bromide source (see Supporting Information for details). [g]Substrate was added using a syringe pump over 1 h. [h]HFIP was used as solvent. [i]HCl (1.0 equiv) was used instead of HOAc. [j]Run at 80 C. [k]Isolated as a dechlorinated product.

The Ir-catalyzed olefin haloamidation was found to have broad scope under mild conditions (Table 2). Dioxazolones bearing *E*-(aryl)alkenyl groups at the γ-position smoothly underwent the desired chloroamidation by using HCl (1.0 equiv) as both chloride and proton source to afford *threo*-lactams with excellent diastereoselectivity (**3**–**5**). The reaction was readily scaled up without difficulty, and the relative stereo stereochemistry of **3** was unambiguously determined based on the NMR and X-ray crystallographic analysis. Again, the observed selectivity can be rationalized as a consequence of the proposed [3+2] cycloaddition mode. The presence of a methyl group α to the dioxazolone moiety resulted in an equal mixture of two diastereoisomeric products (**6**/**6'**), but the relative stereochemistry of the newly formed neighboring C–N and C–Cl bonds were determined to be *threo* exclusively. When a cyclopropyl group is present at the alkenyl moiety, the corresponding lactam **7** was furnished with good diastereoselectivity. This protocol was successfully extended to the bromoamidation by using NaBr as the bromide source (**8**).

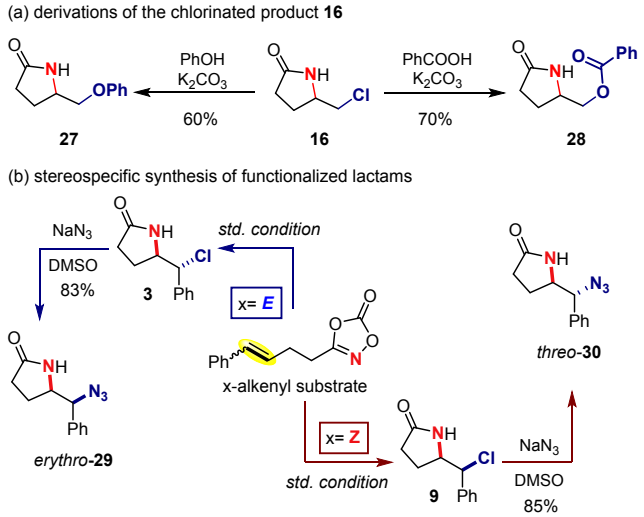
We were pleased to observe that, as anticipated, chloroamidation of *Z*-alkenyl dioxazolones provided *erythro*-products. However, when HCl alone was employed as in case of *E*-olefinic substrates, a decrease in diastereomeric ratio (4.8:1, major product **9**) was observed from a reaction of *Z*-alkene **2** (see Supporting Information for details). We assume that this is due to a partial isomerization of *Z*-olefin under these conditions.[25] In contrast, when NaCl and acetic acid were employed together as the chloride and proton sources respectively, excellent *erythro*-selectivity was obtained from *Z*-alkenyl dioxazolones (**9**–**12**). Dialkyl-substituted internal olefins were also readily chloroamidated in a *syn*-selective manner (**13** and **14**) as evidenced by the solid structure of **14**. Moreover, bromoamidation could also be achieved

by using NaBr instead of NaCl to afford *erythro*-(bromoalkyl)lactam (**15**).

The current procedure of Ir-catalyzed haloamidation was successfully applied to dioxazolones tethered with terminal olefins. For instance, 3-propenyldioxazolone was readily cyclized by the action with HCl (1.0 equiv) alone to afford the corresponding chlorinated lactam **16** in excellent yield.[26] The reaction efficiency was not much decreased by the presence of α- or β-dimethyl substituents between dioxazolone and terminal olefinic moieties (**17** and **18**). A reaction of L-allylglycine derivative was highly facile, but producing two diastereomers in low selectivity (**19**). Notably, (3-chloromethyl)isoindolinone (**20**) was synthesized in 3 steps starting from (*ortho*-vinyl)benzoic acid. On the other hand, the reaction efficiency became rather moderate when dioxazolone substrates bearing trisubstituted double bonds were subjected (**21** and **22**).

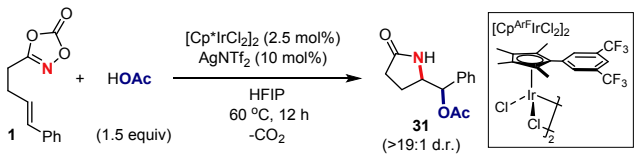
The fact that the presupposed Ir-nitrenoid was proven to efficiently insert into sp^3 γ C–H bonds[10f] or at γ arene carbons[10g] motivated us to interrogate plausible chemoselective reactivity in the presence of such competing reactive sites. Pleasingly, when a substrate **23** was subjected, chloroamidation occurred exclusively to afford *erythro*-lactam **24** in excellent diastereoselectivity confirmed by an X-ray crystallographic analysis. Notably, the corresponding insertion at the benzylic γ C–H bond (blue colored) did not occur at all. In addition, a substrate **25** smoothly underwent chloroamidation to furnish *threo*-lactam **26** exclusively (>19:1 *d.r.*). No spirocyclization at the *ipso* phenyl carbon (blue colored) was observed which is potentially competitive according to our previous study.[10g]

Scheme 3. Versatility of the product obtained in this study



We next briefly examined the synthetic utility of chloroamidated products as shown in Scheme 3. γ-(Chloromethyl)lactam **16** was readily converted to its oxygenated derivatives **27** or **28** in good yields when phenol and benzoic acid were reacted, respectively. By taking advantage of the current stereoselective chloroamidation, a set of diastereomeric derivatives could also be accessible. For instance, both *erythro*-azido γ-lactam **29** and *threo*-isomer **30** were easily obtained in two steps starting from alkenyl dioxazolone substrates in *E*- and *Z*-olefinic geometry, respectively. It needs to be mentioned that dioxazolone substrates can be prepared in high yields from the corresponding carboxylic acids in two steps: (i) conversion to hydoxamic acids with hydroxylamine, and (ii) carbonylation with carbodiimidazole (see Supporting Information for details).

Table 3. Selected reaction parameters in oxyamidation[a]



entry	variation from entry 1	**31** (%)[a]
1	none	31
2[b]	AgOAc (additive, 1.0 equiv)	77
3[b]	AgOAc (additive, 40 mol%)	73
4	CsOAc (additive, 40 mol%)	68
5	NaOAc (additive, 40 mol%)	72
6[c]	$[Cp^{ArF}IrCl_2]_2$ (catalyst) + NaOAc	92
7[c]	$[Cp^*RhCl_2]_2$ (catalyst) + NaOAc	-
8[c]	$[Cp^*CoCl_2]_2$ (catalyst) + NaOAc	-

[a]^{1}H NMR yield using 1,1,2,2,-tetrachloroehtane as an internal standard. [b]Without $AgNTf_2$ (10 mol%). [c]40 mol% of NaOAc was used.

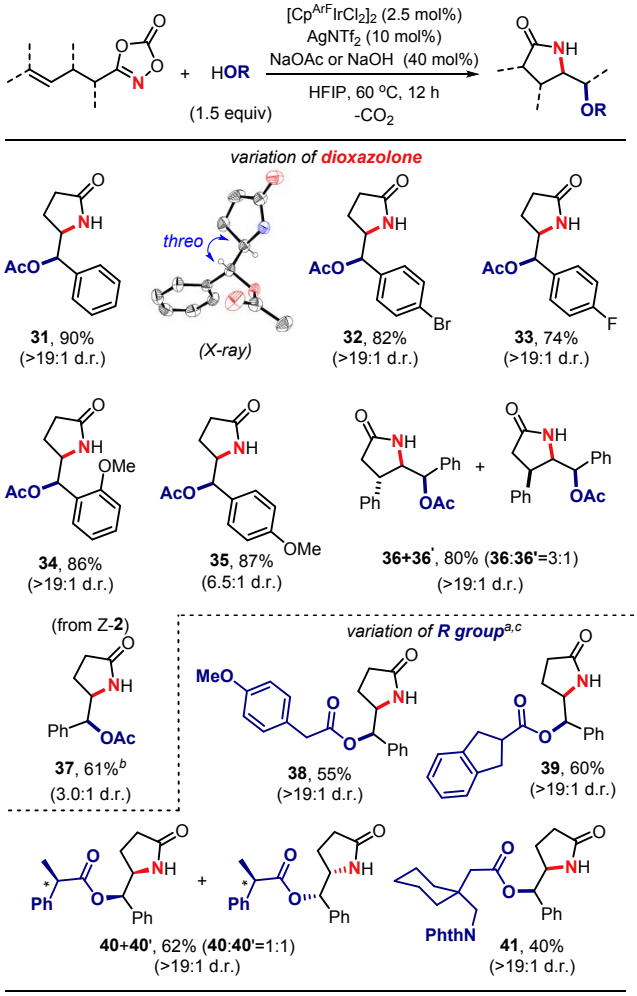
While (*α*-oxyalkyl)-*γ*-lactams could be obtained from chloroamidated compounds in an additional step (Scheme 3a), we wondered whether the current catalyst system could be applied to a *direct oxyamidation* by optimizing proper oxygen sources. Given that (*α*-oxyalkyl)-*γ*-lactams are broadly present in natural products and medicinal compounds as a bio-relevant pharmacophore,[27] the development of a catalytic route to this privileged scaffold is highly desirable. In this aspect, we first envisaged to use acetic acid as a convenient oxygen source for the following considerations: (i) the required catalytically active species $Cp^*Ir(OAc)^+$ (**v** in Scheme 2) was elucidated to be accessible according to our previous studies;[10c,28] and (ii) the olefin insertion will be benefited by the κ^2-chelate nature of acetate to lead to an oxyamidated intermediate more readily (**viii** in Scheme 2).

We accordingly examined optimal conditions for the envisioned catalytic oxyamidation of **1** by employing acetic acid (1.5 equiv) as an oxygen source (Table 3). To our delight, $[Cp^*IrCl_2]_2$ catalyst with $AgNTf_2$ displayed reactivity to some extents for the desired lactamization at 60 °C (entry 1). The use of silver acetate (1.0 equiv) resulted in a notable improvement in the reaction efficiency, giving the corresponding product **31** in 75% yield (entry 2). Moreover, a catalytic amount of AgOAc (40 mol%) was sufficient to obtain a similar level of reaction efficiency (entry 3). While CsOAc and NaOAc were also equally effective as an acetate additive (entries 4 and 5), further improvement was not achieved.

At this stage, we hypothesized that Cp* derivatives bearing electron-deficient substituents may provide lower-lying LUMOs on the corresponding metal center, thereby enhancing the catalytic

performance.[29] Indeed, excellent product yield of **31** could be obtained when $[Cp^{ArF}IrCl_2]_2$ was used as a catalyst (entry 6). In stark contrast, group 9 isoelectronic species such as Rh(III) and Co(III) were totally ineffective (entries 7 and 8).[30]

Table 4. Substrate scope in the oxyamidation of alkenyl dioxazolones[a]

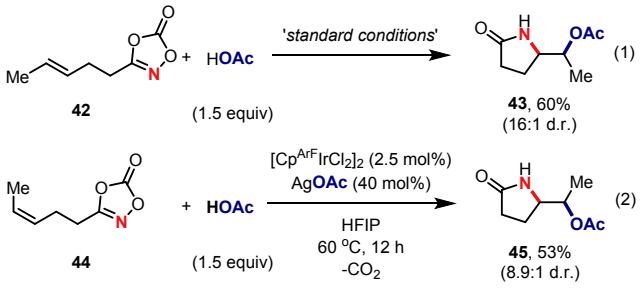


[a](*E*)-substrate (0.2 mmol), carboxylic acid (0.3 mmol), $[Cp^{ArF}IrCl_2]_2$ (2.5 mol%), $AgNTf_2$ (10 mol%), and NaOAc (40 mol%) in HFIP at 60 °C for 12 h; Ratio of diastereoisomers, determined by ^{1}H NMR analysis of the crude reaction mixture. [b](*Z*)-olefin was used with AgOAc (40 mol%) instead of $AgNTf_2$ and NaOAc. [c]NaOH (40 mol%) was used instead of NaOAc.

General applicability of the Ir-catalyzed olefin oxyamidation was subsequently scrutinized with $[Cp^{ArF}IrCl_2]_2$ catalyst (Table 4). *E*-(Aryl)alkenyl dioxazolones containing a range of substituents on the arene moiety readily underwent the desired oxyamidation in reaction with acetic acid to afford the corresponding lactams with excellent *syn*-selectivity (**31**–**33**). Interestingly, the position of substituents at the arene ring influenced the diasteoselectivity although the exact reason is not understood at the present stage. For instance, it proceeded in excellent *syn*-selective manner with a substrate bearing an *ortho*-methoxy group (**34**) whereas it was decreased a bit when the same substituent is at the *para*-position (**35**). While a reaction with *β*-phenyl-substituted substrate gave a mixture of **36** and **36'** (3:1), the oxyamidation proceeded with a *syn*-addition manner exclusively. It needs to be mentioned that the obtained compounds **36**/**36'** can serve as intermediates for the total synthesis of natural product clausenamide or its derivatives.[31] On the other hand, *Z*-olefinic substrates were found to furnish oxyamidated products with moderate diastereoselectivity. For instance, when **2** was subjected to the optimal conditions, lactam **37** was obtained as a major product (*erythro*/*threo*, 3.0:1).

In addition to acetic acid, a range of additional carboxylic acids were also successfully utilized for the olefin oxyamidation reaction. Not only primary but also secondary carboxylic acids could be applied to afford *thero*-lactams **38** and **39**, respectively. When a chiral carboxylic acid was employed, an equal mixture of two diastereomeric products (**40**/**40'**) was obtained while the oxyamidation took place with a complete *syn*-manner. In addition, *N*-protected gabapentin also participated in the reaction leading to **41** albeit in moderate yield.

Interestingly, dialkyl-olefinic substrates, prepared from (*E*)- or (*Z*)-4-hexenoic acids, underwent the oxyamidation to afford *erythro*-**43** and *threo*-**45**, respectively, with high diastereoselectivity (equations 1 and 2). This anti-addition revealed that a tandem process consisting of aziridination and ring-opening may also be operative in these cases although the exact reason is not clear at this stage.



■ CONCLUSION

In conclusion, we have proved that the intermediacy of metal nitrenoids can be harnessed as a mechanistic motif of LUMO-controlled 1,3-dipoles for the olefin difunctionalization. In parallel with a series of stoichiometric probes, DFT calculation suggested that our working hypothesis on the concerted [3+2] cycloaddition pathway is operative, wherein the postulated three-centered LUMO of Ir-nitrenoids dictates its selectivity and reactivity with olefins via symmetry-allowed orbital interactions. Our approach to utilize dipole character in the imido transfer was successfully applied toward the olefin difuctionalization of dioxazolones to furnish γ-lactams in excellent *syn*-selectivity. In this line, haloamidation and oxyamidation were able to achieve via Ir catalysis, and either *threo*- or *erythro*-products were obtained in a stereodefined manner where olefin geometry (*E*/*Z*) of substrates determines the stereochemistry of products. We anticipate that the present analysis of the reactivity of Ir-nitrenoids as a motif of 1,3-dipoles may serve as a general

platform for the development of additional stereoselective olefin difunctionalization reactions.

■ ASSOCIATED CONTENT

Supporting Information

Gibbs free energies for the optimized structures and transition states. Additional crystallographic and NMR data

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Notes

The authors declare no competing financial interest.

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Table of Contents