ORGANIC CHEMISTRY

Selective formation of γ-lactams via C–H amidation enabled by tailored iridium catalysts

Seung Youn Hong,* Yoonsu Park,* Yeongyu Hwang, Yeong Bum Kim, Mu-Hyun Baik,† Sukbok Chang†

Intramolecular insertion of metal nitrenes into carbon-hydrogen bonds to form γ-lactam rings has traditionally been hindered by competing isocyanate formation. We report the application of theory and mechanism studies to optimize a class of pentamethylcyclopentadienyl iridium(III) catalysts for suppression of this competing pathway. Modulation of the stereoelectronic properties of the auxiliary bidentate ligands to be more electron-donating was suggested by density functional theory calculations to lower the C–H insertion barrier favoring the desired reaction. These catalysts transform a wide range of 1,4,2-dioxazol-5-ones, carbonylnitrene precursors easily accessible from carboxylic acids, into the corresponding γ-lactams via sp^3 and sp^2 C–H amidation with exceptional selectivity. The power of this method was further demonstrated by the successful late-stage functionalization of amino acid derivatives and other bioactive molecules.

The catalytic oxidation of C–H bonds is the most desirable way of converting readily available raw feedstocks to useful, value-added commodity chemicals. One such reaction highly sought after in pharmaceutical as well as materials chemistry is the direct nitrogenation of aliphatic C–H bonds (*1*–*4*). An effective general method for carrying out these C–N coupling reactions is to first convert the nucleophilic amino functionalities to more reactive, electrophilic nitrene precursors that are subsequently used as reaction partners in metal-catalyzed C–H amination reactions (Fig. 1A). The initial demonstration of this chemistry was reported by Breslow in 1983 (*5*), wherein reactive hypervalent ylides acted as sulfonylnitrene precursors in the Fe(III)- or Rh(II)-catalyzed oxathiazolidine synthesis. Major advances were achieved in the early 2000s when Du Bois and others found elegant ways of generating reactive nitrogen ylide species (*6*–*9*), which could be used to prepare a variety of amide products of high synthetic utility (*7*). In addition, organic azides have been identified as productive nitrene precursors to indoles (*10*, *11*), indolines (*12*), and pyrrolidines (*13*). Recently, hydroxylamine derivatives were elegantly used as an effective handle for synthesizing aza-arenes in N-unprotected form (*14*). Despite these advances, cyclic amides such as lactams that are valuable scaffolds in synthetic and medicinal applications could not be obtained directly through a C–H amidation strategy. Considering how successful C–N coupling techniques have been in general, the absence of such a method for preparing lactams is puzzling. In principle, carbonylnitrenes generated in situ might allow for direct construction of a cyclic amide scaffold.

As shown in Fig. 1B, catalytic reactions are believed to proceed through a key metal-nitrenoid species, which inserts into aliphatic C–H bonds to generate the corresponding azaheterocyclic products. The main reason that C–H amidation is ineffective for lactam synthesis lies in the intrinsic instability of the putative carbonylnitrene intermediate, which may easily decompose and form isocyanates via a Curtius-type rearrangement (Fig. 1C, left). This instability is well documented for acyl azides that were explored as synthetic precursors under photolytic, thermolytic (*15*), and transition-metal catalysis conditions (*16*, *17*). As a result, the general consensus is that acyl nitrenes are unfit to serve as amide sources in C–H insertion processes (*18*).

We envisioned that this paradigm might be challenged if the decomposition pathway could be blocked and the desired C–H amidation of the nitrenoid could be engineered to be faster (Fig. 1C, right). Previously, we discovered that 1,4,2-dioxazol-5-ones, which can be readily obtained from abundant carboxylic acids, are versatile substitutes for acyl azides in related C–N coupling reactions (*19*); thus, we imagined that these substrates may provide a nitrene-based route to lactam synthesis (*20*). Seeking to develop a catalyst capable of C–H activation and acylnitrene formation while suppressing the Curtius-type degradation, we were drawn to an iridium complex stabilized by an electron-donating cyclopentadienyl ligand. Cyclometallated Cp*Ir(III) complexes are widely known to facilitate C–H activation under ambient conditions. These reactions proceed via an inner-sphere imido insertion into an iridium-carbon bond, where acyl azides or analogous dioxazoles serve as the nitrogen source (*21*, *22*). The key intermediate is thought to be a high-valent Ir(V)-carbonylimido species (*22*), which undergoes a reductive C–N coupling to deliver the corresponding Ir(III)-acylamido product. We hypothesized that the half-sandwich Ir(III) complex may be able to form the acylnitrenes and promote C–H insertion via an outer-sphere mechanism (Fig. 1D), envisioning that catalytic C–N coupling in these systems need not be limited to inner-sphere mechanisms. We were encouraged by the fact that the Cp*Ir(III) platform did not produce detectable amounts of isocyanates during other C–N coupling processes; hence, we anticipated that the competitive decomposition pathway might be controlled by proper tuning of the catalyst.

To test these design ideas, we examined a series of stoichiometric reactions with acylnitrene precursors (Fig. 2A), using the iridacycle **I** and phenyl-1,4,2-dioxazole derivatives as reactants. According to the proposed reaction mechanism, the Ir-nitrenoid intermediate should be formed, and if an appropriate C–H bond were offered in close proximity, an insertion might occur more readily than the unproductive decomposition. Thus, dioxazoles bearing ortho-isopropyl substituents were presumed to be ideal, as the weak tertiary benzylic C–H bond of the isopropyl group may readily undergo C–H insertion. When (*o*-isopropyl)phenyldioxazole **1** was treated with a mixture of iridium species **I** and $NaBAr^F_4$, the Ir-dioxazole adduct **III** was formed quantitatively, as confirmed by nuclear magnetic resonance (NMR) and x-ray diffraction analysis. At slightly elevated temperature (50°C) in the presence of excess nitrile, **III** was fully converted to the C–H insertion product isoindolinone **3** with the concomitant release of a cationic iridacycle **II** and molecular acetone. With analogous 1,4,2-dioxazol-5-one (**2**), which was previously found to be a much more reactive substrate in other C–N forming reactions (*19*), the identical lactam **3** was rapidly produced even at room temperature in 5 min with CO_2 extrusion. More important, a catalytic amount of **II** was found to mediate this C–H insertion with excellent reactivity (see fig. S4), and the formation of the lactam **3** strongly supports our proposal that the postulated Ir-nitrenoid species is indeed the active intermediate and is capable of rapidly activating the relatively weak C–H bond while the undesired Curtius decomposition pathway is suppressed effectively. In contrast, when a dioxazolone bearing a flexible aliphatic chain (**4**) was used, a distinctively different result was obtained under the same conditions, leading to a six-membered Ir(III)-amido species **IV**. Although the substrate has two benzylic C–H bonds at the γ-position, the C–H insertion pathway was completely suppressed, thus highlighting that the C–N coupling and C–H insertion pathways are in competition and that the chemoselectivity is dependent on the choice of the dioxazolone substrate.

To better understand the reactivity of the Ir-nitrenoid species for the subsequent optimization of the catalysis, we carried out computer simulations on the three most plausible reaction pathways:

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C–N coupling, Curtius-type rearrangement, and C–H insertion (Fig. 2B). Starting from the Ir(V)-imido intermediate **VI**, transition state calculations revealed that the C–N coupling is most facile, with a barrier of only 9.1 kcal/mol. Barriers for the Curtius-type rearrangement and C–H insertion were slightly higher in energy: 9.6 kcal/mol for **VI-TS2** and 12.0 kcal/mol for **VI-TS3**, respectively. These results encouraged us to devise further strategies to avoid side reactions. As shown in Fig. 2C, we hypothesized that replacing the phenylpyridine ligand with monoanionic LX-donor ligands (X = O or N) might shut down the inner-sphere X–N coupling: Because N–N bonds [average bond dissociation energy (BDE) of ~39 kcal/mol] and O–N bonds (~50 kcal/mol) are weaker than the C–N bond (BDE of ~73 kcal/mol) (*23*), the new ligands would reduce the thermodynamic driving force for this undesired pathway. Inhibiting the Curtius-type degradation pathway in favor of the desired amidation was much more challenging. Our detailed analysis of the computer simulations revealed one potentially exploitable feature: The partial charge of the iridium center in the three transition states is remarkably different (Fig. 2B). Whereas our calculations assign a partial charge of 0.40 to the metal in the intermediate **VI**, remarkable reduction of that positive partial charge is seen for the Curtius-type rearrangement (**VI-TS2**, natural bond orbital NBO_{Ir} = 0.27). The C–H insertion is not accompanied by any notable change of partial charge, with a metal charge of 0.39 in the transition state **VI-TS3**. Hence, we can conclude that the Curtius rearrangement transition state should be much more sensitive to changes of the partial charge of the metal center than the C–H insertion, and that electron-donating ligands may increase the Curtius-rearrangement barrier to a larger extent than the C–H insertion barrier.

On the basis of this computer-aided design idea, a series of new iridium catalysts were synthesized; the catalytic reactivities of selected complexes are summarized in Fig. 2D (*24*). All iridium complexes were easy to prepare, stable in air, and convenient to handle without special precautions. To our delight, alkoxypyridyl iridium complex **VII**, which is a known precatalyst for water-oxidation chemistry (*25*), displayed some catalytic activity for the desired amination: A mixture of the lactam ***5*** and isocyanate ***6*** was obtained in 29% and 33% yield, respectively, while no N–O coupled product was observed. This result suggested that LX-type ligands can indeed prevent undesired ligand deconstruction and mediate C–H insertion chemistry. At the same time, however, formation of a large amount of isocyanate indicated that extensive ligand manipulation was necessary. The use of another N,O-chelating ligand, 8-alkoxyquinoline (**VIII**), gave rise to a notable improvement in the reaction efficiency, furnishing 73% of ***5*** at 40°C. Because the nature of the contact atom of the ligand may alter the electronic property of the metal center, we paid special attention to the influence of the X-chelating ligand component and envisioned the use of an amino group in lieu of the alkoxide. Whereas the reaction was sluggish when the alkoxy moiety was substituted with tosylamide group (**IX**), *N*-acetyl–protected aminoquinoline (**X**) showed a similar reactivity and selectivity even at room temperature. Although the *tert*-butyloxycarbonyl (Boc) group resulted in only a slight improvement (**XI**), a methyloxycarbonyl group (**XII**) further suppressed Curtius-type decomposition. At last, methoxy substitution on the ligand (5-OMe: **XIII** and 4-OMe: **XIV**) exclusively gave ***5*** in excellent yield within 6 hours and 2 hours at room temperature, respectively. This result is fully consistent with our assumption that electron-donating groups would facilitate the C–H insertion product while suppressing the formation of isocyanate. The highly active nature of catalyst **XIV** enabled a gram-scalable synthesis, and the product ***5*** was obtained in excellent yield using only 1 mole percent (mol %) of the catalyst (see fig. S1). Well-known catalytic systems for related C–H amidation, such as Ru(II)-porphyrin and dirhodium(II) complexes, were completely ineffective for the production of the lactam scaffold (*7*, *26*, *27*). These observations highlight that the iridium catalyst is particularly effective in leveraging the reactivity of acylnitrene. The present system does not require in situ protection of newly formed lactam N–H bonds to maintain catalyst activity, whereas a number of related known catalyst systems suffered from

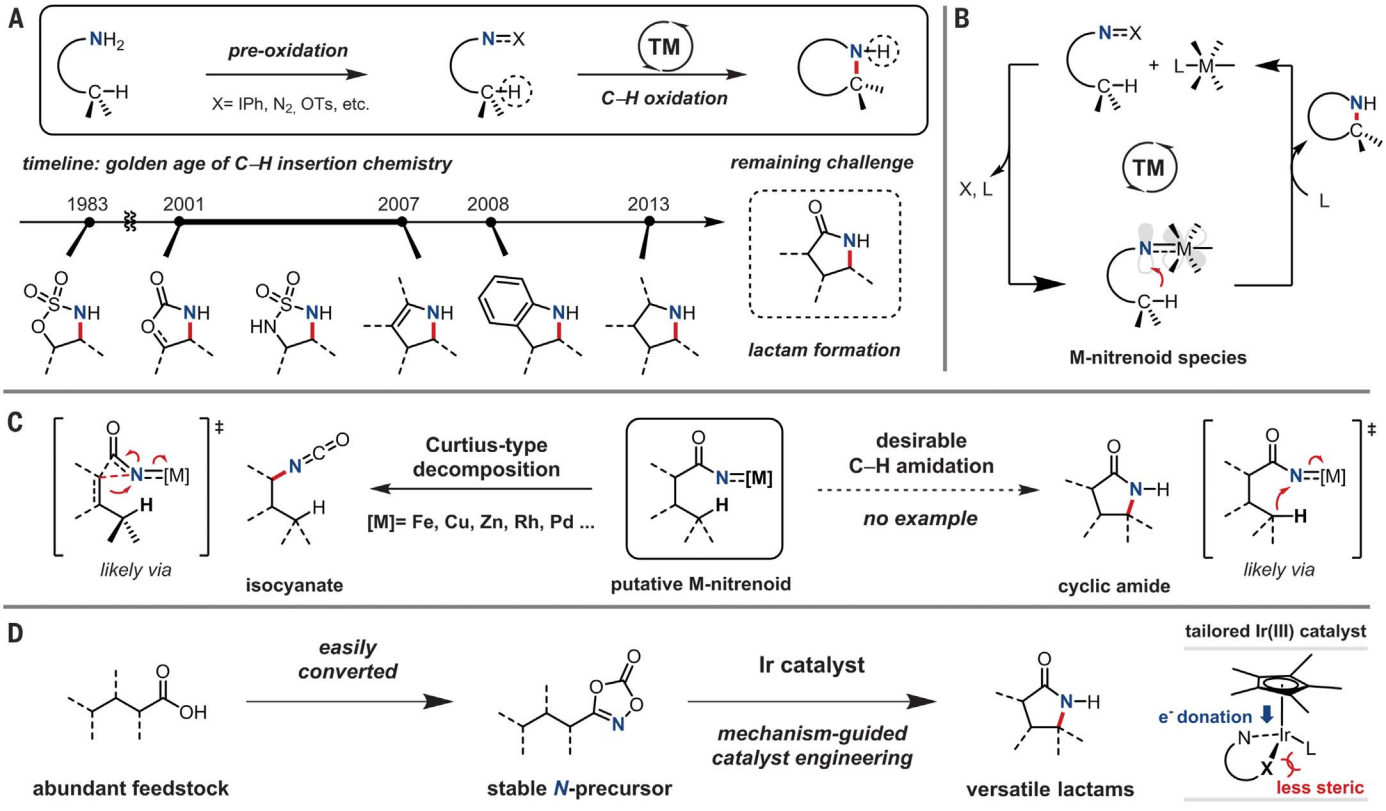

Fig. 1. A strategy for applying carbonylnitrene precursors in catalytic C–H amidation. (**A**) Examples of intramolecular C–H amination. (**B**) General catalytic mechanism. (**C**) Competitive decomposition pathway from the reactive intermediate. (**D**) Our approach with rational design of Cp*Ir(III) catalyst for γ-lactam synthesis.

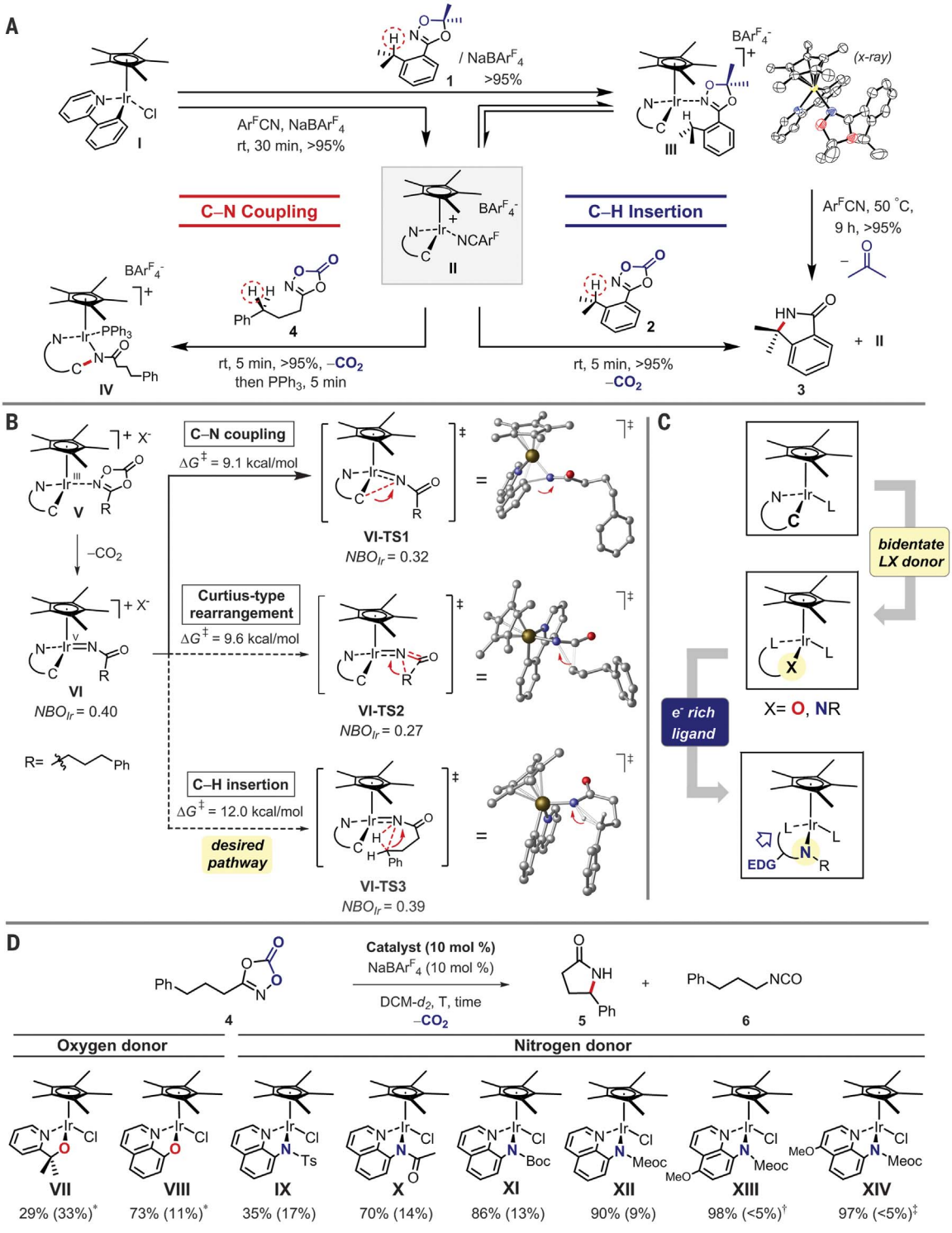

Fig. 2. Initial reaction development. (**A**) Stoichiometric studies: Viability of cyclometallated Cp*Ir(III) complex as a C–H insertion catalyst. (**B**) DFT-calculated competitive working modes from Ir(V)-acylimido species **VI**. (**C**) Principle of the catalyst design. (**D**) Catalyst optimization study. Unless otherwise indicated, reactions were run with 10 mol % of catalyst and NaBAr$^F_4$ in dichloromethane-d_2 at room temperature for 12 hours; the product yields were measured with ^{1}H NMR spectroscopy. Yields for side product **6** are indicated in parentheses. *Run at 40°C. †Run for 6 hours. ‡Run for 2 hours. Ar^F, 3,5-bis(trifluoromethyl) phenyl; rt, room temperature; Ts, *p*-toluenesulfonyl; Meoc, methyloxycarbonyl.

the deleterious inhibitory effect caused by strong coordination of the product to the catalyst (*11*, *13*), such that post-modification was necessary for catalytic turnover. Our methodology enables the direct preparation of unprotected γ-lactam products without any additional transformation.

Having identified the optimal catalysts, we investigated the generality of the iridium-catalyzed C–H amidation by exploring a wide range of substrates (Fig. 3). Various 1,4,2-dioxazol-5-ones were accessed from abundant carboxylic acid feedstock by two-step sequences consisting of acid activation/hydroxamic acid formation followed by carbonylative cyclization; both of these steps are highly efficient, and the dioxazolones can be easily prepared in excellent yields. The cyclization of substrates containing benzylic C–H bonds with catalyst **XIV** provided the corresponding γ-lactams in high yields (**5**, **7**–**10**), even in the presence of a Boc-protected free N–H group (**11**). The formation of 2,2-dimethyl lactam **12**, however, required slightly higher temperature (80°C), presumably as a result of the steric crowding adjacent to the dioxazolone moiety. Functionalization of a secondary benzylic C–H bond in the cyclopentyl ring resulted in *cis*-tricyclic γ-lactam (**13**) as a sole

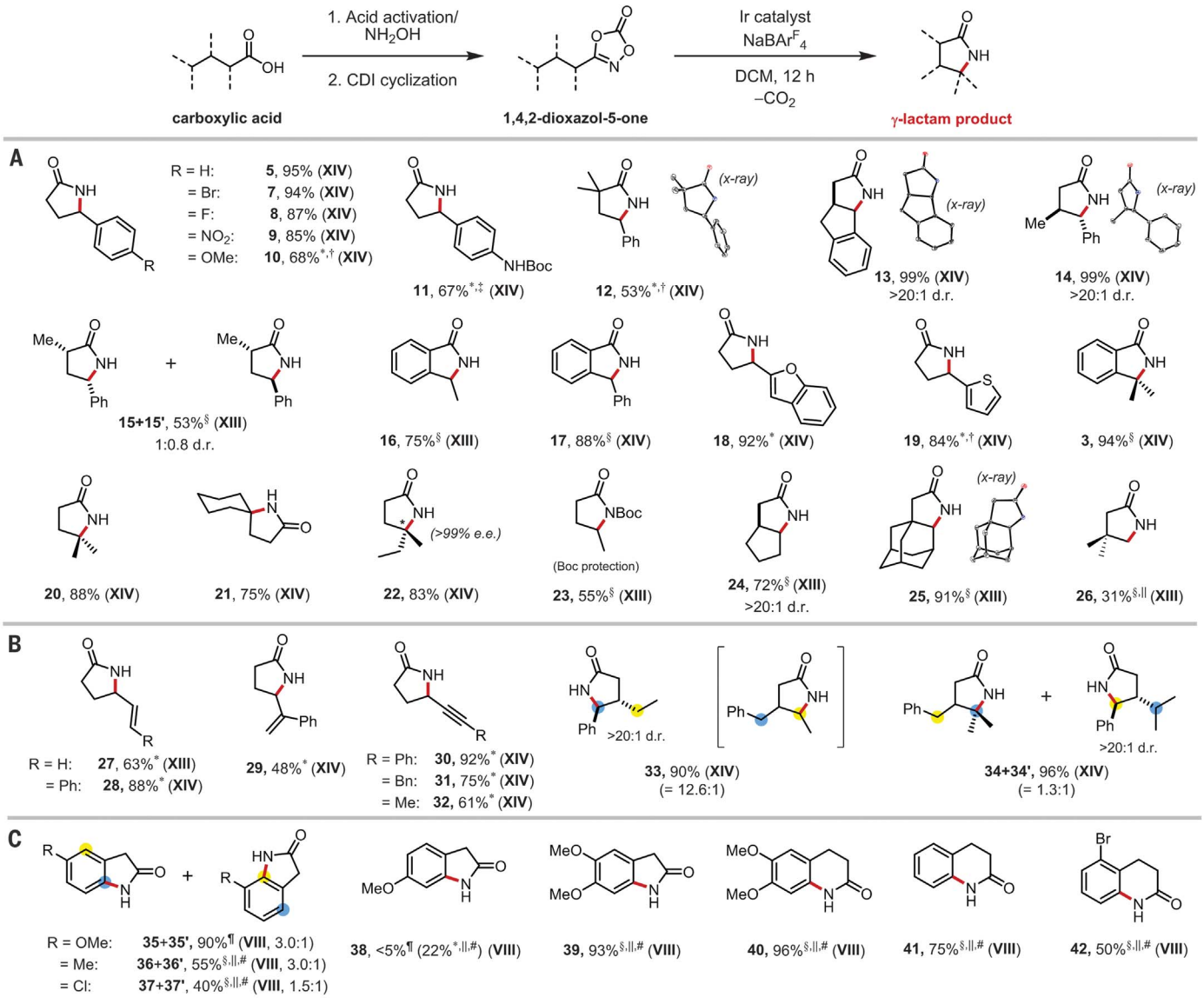

Fig. 3. Reaction scope of Ir(III)-catalyzed intramolecular amidation. (**A**) Functionalization of benzylic, tertiary, secondary, and primary C(sp^3)–H bonds. (**B**) Examination of chemo- and regioselectivity. (**C**) Functionalization of aromatic C(sp^2)–H bonds. Unless otherwise indicated, reactions were run with 2 mol % of catalyst and $NaBAr^F_4$ at 40°C for 12 hours. The Ir catalyst used is indicated in parentheses; the data are reported as percent isolated yields. *10 mol % catalyst was used. †Run at 80°C for 48 hours. ‡Run at 40°C for 12 hours followed by 80°C for 24 hours. §5 mol % catalyst was used. ||Hexafluoro-2-propanol was used as solvent. ¶Run at room temperature. #Run at 60°C. d.r., diastereomeric ratio; e.e., enantiomeric excess.

product in 99% yield. Whereas a β-methyl substituent gave rise to excellent reactivity and diastereoselectivity (**14**, >20:1), the amination of an α-substituted substrate gave a mixture of syn- and anti-inserted products without a bias (**15**, **15′**, 1:0.8). When dioxazolones prepared from benzoic acids were used, 3-substituted isoindolin-1-ones (**16**, **17**) were obtained in high yields. Heterocycles such as benzofuran (**18**) or thiophene (**19**) were also tolerated under the reaction conditions. The method also transformed tertiary C–H bonds, thereby introducing quaternary carbon centers (**3**, **20**) and an azaspirocyclic scaffold (**21**). The desired lactamization proceeded in a stereospecific manner when γ-chiral dioxazolone was used (**22**), providing a clue to the insertion mechanism (see below). Finally, amidation of nonactivated secondary C–H bonds of *n*-butyl (**23**), cyclopentyl (**24**), and adamantyl (**25**) groups was successful, and primary C(sp^3)–H bonds also underwent reaction, albeit in moderate yield (**26**).

The high reactivity of the Ir catalyst motivated us to examine the selectivity trends when multiple reactive sites were embedded in the same molecule (Fig. 3B). Preferential chemo- and regioselectivity patterns often provide clues to the reaction mechanism and have been widely used to understand microscopic insertion pathways (*28*). When γ-allylic C–H bonds that potentially undergo olefin aziridination were tested, insertion products were observed exclusively with no detectable sign of aziridine formation (**27**–**29**). Olefin isomerization was not observed during the formation of lactam **28**. Similarly, dioxazolones bearing γ-propargylic C–H bonds underwent lactamization in high yields (**30**–**32**), allowing for efficient access to key precursors in the total synthesis of (–)-stemoamide derivatives (*29*). Considering that intramolecular amidation has frequently suffered from related aziridination reactions caused by electron-rich π functionality (*28*, *30*, *31*), the remarkable chemoselectivity observed in this system is intriguing (*32*). Next, we designed substrates having nonequivalent γ and γ′ C–H bonds to qualitatively rank the reactivity toward distinctive C–H bonds. Benzylic C–H bonds were favored over nonactivated secondary C–H bonds (**33**, 12.6:1) but were

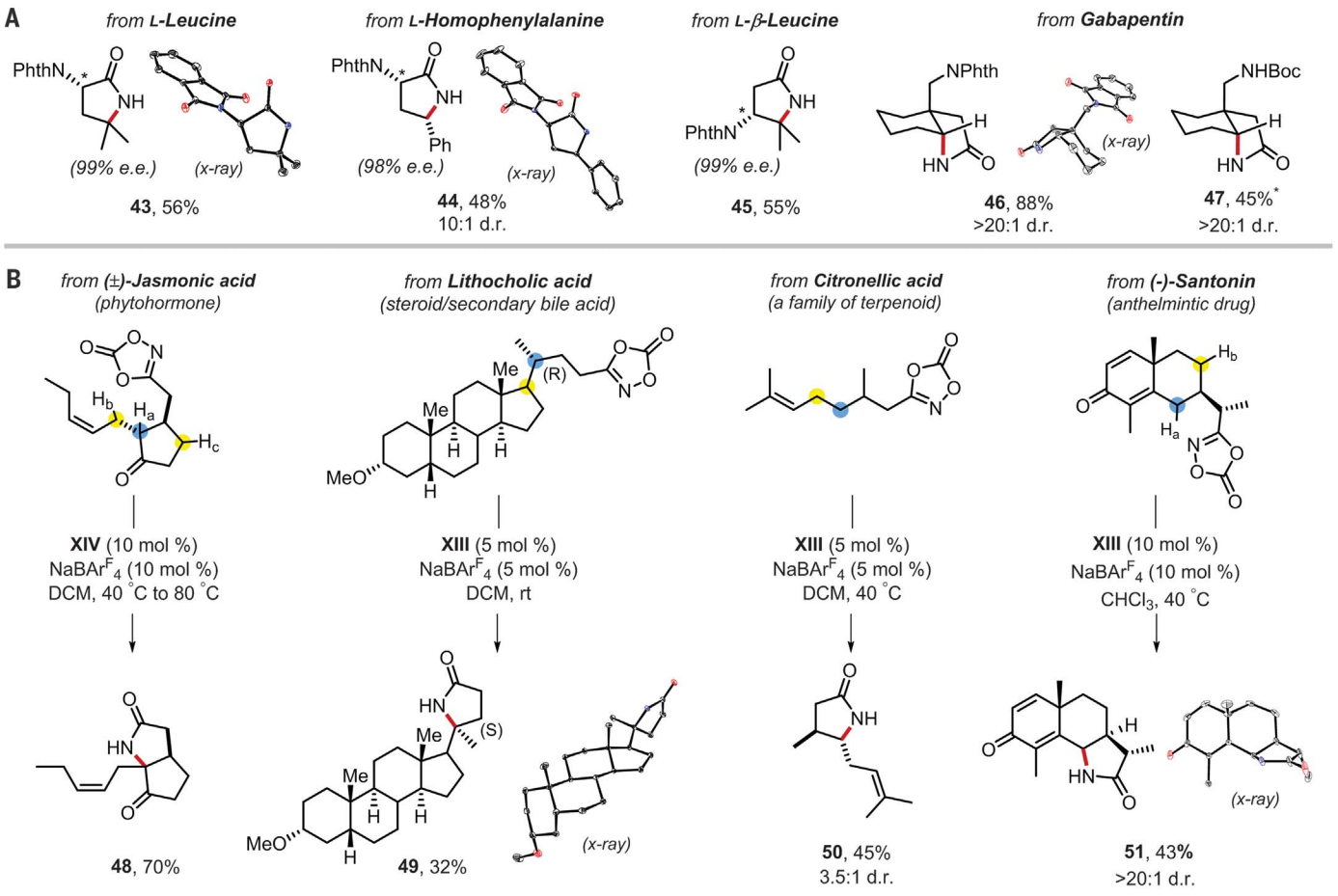

Fig. 4. Synthetic utility of the intramolecular C–H amidation. (**A**) Derivatization of amino acids to versatile γ-lactams. (**B**) Late-stage functionalization of complex molecules. Unless otherwise indicated, reactions were run with 5 mol % of catalyst **XIII** and $NaBAr^F_4$ at 40°C for 12 hours. *Hexafluoro-2-propanol was used as solvent.

disfavored relative to tertiary C–H bonds (**34**, **34′**, 1.3:1). The observed reactivity is not matched qualitatively with trends in homolytic bond cleavages, as the BDE of a secondary benzylic C–H bond (86 kcal/mol) is lower than that of a tertiary C–H bond (96 kcal/mol) (*33*). This finding implies that radical-type hydrogen atom abstraction may not be operative (*8*, *30*, *31*). In this context, intramolecular kinetic isotope experiment (KIE) results suggest a concerted C–H insertion mechanism. When deuterated dioxazolone (**4**-d_2) was subjected to the amidation, the intramolecular KIE value was found to be 1.51 ± 0.01 (table S3). This value is similar to the KIE obtained in the related Rh_2(II)-catalyzed amidation of sulfamates (*28*) and is lower than the values reported typically for H-atom abstraction mechanisms (*13*, *34*). In addition, the stereospecificity of the amination, which was demonstrated by the chiral lactam **22** in Fig. 3A, corroborated the concerted mechanism, although fast radical rebound cannot be ruled out. Density functional theory (DFT) calculations of the proposed mechanisms further indicated that the concerted insertion pathway from the singlet Ir-nitrenoid species is energetically more feasible than the involvement of a triplet nitrenoid traversing a radical abstraction pathway (reaction barrier $\Delta G^{\ddagger}$ = 6.5 and 14.2 kcal/mol, respectively). Detailed mechanistic descriptions including reaction energy profiles are shown in fig. S8.

We next extended the method to amidation of aromatic C(sp^2)–H bonds: 1,4,2-dioxazol-5-ones derived from 2-phenylacetic acids were successfully converted to the corresponding indolinones using catalyst **VIII** (Fig. 3C). Specifically, constitutional isomers of indolinone products **35** and **35′** were obtained in high yields with 3:1 regioselectivity, presumably due to steric hindrance at the meta position. Other meta-substituents such as methyl (**36**) and chloro (**37**) groups were also smoothly incorporated with similar selectivity. In contrast, a methoxy substituent in the para position significantly diminished reactivity (**38**), implying that an electrophilic aromatic substitution-type pathway might be operative (*14*). 3,4-Dimethoxy-bearing dioxazolone gave rise to a single product **39** in excellent yield. Six-membered dihydroquinolinones **40**–**42** were also produced by the same procedure. Catalysts **XIII** and **XIV**, which were efficient in the C(sp^3)–H amidation, were less active in this sp^2 C–H amidation, which suggests that the reactions have slightly different electronic demands (*24*).

Because 1,4,2-dioxazol-5-ones can be conveniently prepared in high yields from abundant carboxylic acids, we anticipated that the present amidation protocol would provide an efficient means of preparing valuable γ-lactams including biorelevant molecules. To our delight, a wide range of amino acids were readily converted to γ-lactams under the optimal conditions (Fig. 4A). For instance, the reaction of *N*-phthalimide–protected L-leucine derivatives provided the corresponding cyclic amide **43** in 56% yield without epimerization at the α-carbon center (99% enantiomeric excess). When a substrate derived from unnatural L-homophenylalanine was used, syn-addition of the amino group was found to occur more favorably over the formation of anti-inserted products (**44**, syn/anti = 10:1). Not only α- but also β- and γ-amino acids, such as L-β-leucine and gabapentin derivatives, were successfully converted to the corresponding lactams **45**–**47** in acceptable yields, respectively.

The amidation protocol was also highly effective in more complex molecules that possessed multiple reactive C–H bonds (Fig. 4B) (*35*). In a

reaction of a jasmonic acid derivative having three potentially reactive sites (tertiary, allylic, and secondary C–H bonds), tertiary C–H inserted product **48** was observed exclusively without any other detectable regioisomers. To further test the applicability of this method for late-stage functionalizations, we examined a family of bile acid and terpenoid substrates. Dioxazolones derived from lithocholic acid underwent the intramolecular amidation, leading to a steroid-type lactam scaffold (**49**). In addition, the amide moiety was selectively formed at the secondary γ-C–H bond of a citronellic acid derivative (**50**) even in the presence of activated C–H bonds at the δ-position. A lactam surrogate of (–)-α-santonin (**51**) was successfully synthesized under the optimal conditions, and the C–N bond formation took place selectively at the allylic position.

Our findings show that a mechanism-guided approach can be used to resolve a long-standing challenge in catalytic C–H amidation chemistry. Although this work falls short of definitively proving the existence of the Ir(V)-nitrenoid intermediate, all of the data and insights gained are fully consistent and strongly support its putative role.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/359/6379/1016/suppl/DC1
Materials and Methods
Figs. S1 to S11
Tables S1 to S19
NMR Spectra
HPLC Traces
References (*36*–*80*)

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Selective formation of γ-lactams via C–H amidation enabled by tailored iridium catalysts

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Guiding nitrenes away from a migration

Nitrogen conventionally shares its electrons in three bonds with one or more partners. A singly bonded nitrogen, or nitrene, is exceptionally reactive and can insert itself into normally inert C–H bonds. If the nitrene forms next to a carbonyl center, though, it tends to react with the C–C bond on the other side instead. Hong *et al.* used theory to guide the design of an iridium catalyst that inhibits this rearrangement, steering the nitrene toward C–H insertion to form a variety of useful lactam rings.

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