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Iridium-Catalyzed Enantioselective C(sp^3)–H Amidation Controlled by Attractive Noncovalent Interactions

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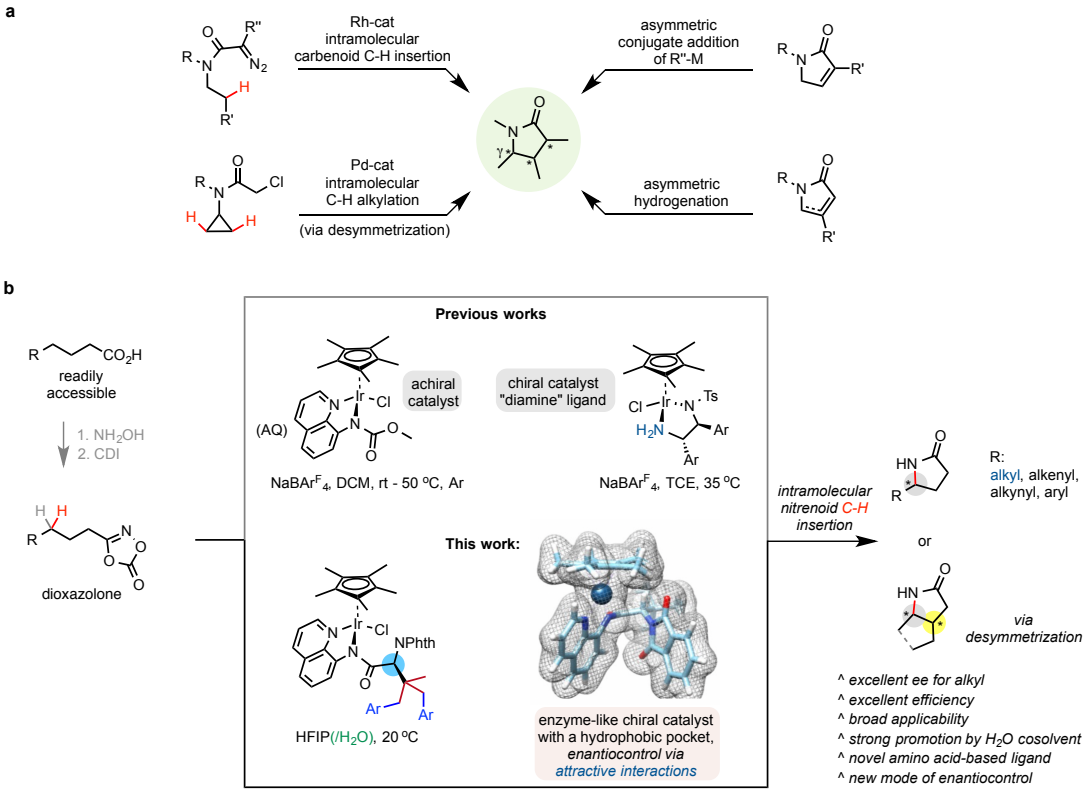
ABSTRACT: While remarkable progress has been made over the past decade, new design strategies for chiral catalysts in enantioselective C(sp^3)–H functionalization reactions are still highly desirable. In particular, the ability to use attractive non-covalent interactions for rate acceleration and enantiocontrol would significantly expand the current arsenal for asymmetric metal catalysis. Herein, we report the development of a highly enantioselective Ir(III)-catalyzed intramolecular C(sp^3)–H amidation reaction of dioxazolone substrates for synthesis of optically enriched γ-lactams using a newly designed α-amino acid-based chiral ligand. This Ir-catalyzed reaction proceeds with excellent efficiency and with outstanding enantioselectivity for both activated and unactivated alkyl C(sp^3)–H bonds under very mild conditions. It offers the first general route for asymmetric synthesis of γ-alkyl γ-lactams. Water was found to be a unique co-solvent to achieve excellent enantioselectivity for γ-aryl lactam production. Mechanistic studies revealed that the ligands form a well-defined groove-type chiral pocket around the Ir center. The hydrophobic effect of this pocket allows facile stereo-controlled binding of substrates in polar or aqueous media. Instead of capitalizing on steric repulsions as in the conventional approaches, this new Ir catalyst operates through an unprecedented enantiocontrol mechanism for intramolecular nitrenoid C–H insertion featuring multiple attractive non-covalent interactions.

INTRODUCTION

Development of enantioselective transformations is at the forefront of research in the transition metal-catalyzed functionalization of carbon-hydrogen (C–H) bonds, which can greatly augment its synthetic utility with more precise stereocontrol.[1-3] While remarkable progress has been made over the past decade, significant challenges remain unaddressed and new strategies for designing more effective chiral catalysts is highly desirable.[4-6] In general, the vast majority of the current strategies for enantiocontrol in asymmetric metal catalysis relies on the "blocking" mechanism, in which repulsive steric interactions are employed as a key element to destabilize the transition states, thereby minimizing the undesired stereoisomer.[7] In contrast, enzymes typically adopt the "promoting" mechanism via attractive non-covalent interactions (e.g. hydrogen bonding, electrostatic effect, π interactions, hydrophobic effect, and van der Waals forces) to stabilize the viable transition states, thus maximizing the desired stereochemical pathway under mild conditions.[7,8] However, due to the relatively weak strength and directionality, multiple non-covalent interactions need to work in concert to exert strong conformational constraint, rendering it much harder to realize for small molecule asymmetric catalysis.[7,9] While elements of attractive non-covalent interactions such as H-bonding and ion pair interactions have been utilized in metal-catalyzed C–H functionalization reactions,[10,11] design of enzyme-like metal catalysts for highly enantioselective C–H functionalization invoking cooperative non-covalent interactions has yet to be demonstrated.

γ-Lactams are a "privileged scaffold" widely present in drug molecules and natural products.[12,13] While a variety of methods for the γ-lactams synthesis have been reported, broadly applicable strategies for enantioselective synthesis of γ-lactams are surprisingly underdeveloped (Scheme 1**a**).[14-19] Furthermore, in contrast to the high enantiomeric excess value (up to 99% ee) obtained for aryl substituted γ-lactams, enantiocontrol for the synthesis of γ-lactams bearing alkyl substituents remains poorly addressed.[13] Recently, one of authors reported a powerful method for synthesis of NH-free γ-lactams via iridium-catalyzed intramolecular C–H amidation of 1,4,2-dioxazol-5-one substrates (Scheme 1**b**).[20] These dioxazolones can easily be prepared from the corresponding readily available alkyl carboxylic acids in high yields. This method represents the first γ-lactam synthesis via intramolecular nitrenoid C–H insertion. The Ir(III) catalyst features strong electron-donating pentamethylcyclopentadienyl and *N*-methyloxycarbonyl or acyl 8-aminoquinoline ligands. More recently, an asymmetric variant of this reaction of Ir[21] and Ru catalysis[22] has also been achieved by using Noyori-type chiral 1,2-diamine ligands, affording optically active γ-lactams. The enantioselectivity is attributed to the transient intramolecular hydrogen bonding between the carbonyl of the substrate amide moiety and the NH_2 group of the diamine ligand. While an excellent level of enantioselectivity was attained for the benzylic C–H amidation, the asymmetric reaction of more demanding unactivated alkyl substituted substrates is still challenging.[23-27] The insufficient enantiocontrol might be attributed to the distant single point interaction between the chiral induction site of the ligand and the approaching substrate. Herein, we report the development of new chiral Ir catalysts that possess a well-defined enzyme-like chiral pocket, resulting in a more intimate dioxazolone substrate/catalyst interaction. Instead of relying on steric repulsion for enantiocontrol, this Ir asymmetric catalysis operates through multiple non-covalent interactions including hydrophobic effect, π-π stacking and C–H/π interactions. Remarkably, the enantioselectivity was

Scheme 1. Enantioselective synthesis of γ-lactams.



a) Representative methods for enantioselective synthesis of γ-lactams. **b)** Enantioselective synthesis of γ-lactams via Ir-catalyzed intramolecular C(sp^3)–H amidation of dioxazolones.

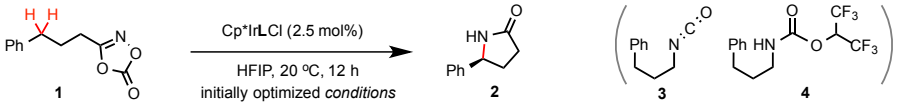
found to be significantly increased in aqueous cosolvent for γ-aryl substituted substrates. This new chiral Ir catalyst system exhibits a broad substrate scope and gives outstanding efficiency and enantioselectivity with both activated and unactivated alkyl C(sp^3)–H amidation reactions. Notably, it offers the first general route for the asymmetric synthesis of γ-alkyl γ-lactams.

RESULTS AND DISCUSSION

In the previous studies, one of authors showed that 1,4,2-dioxazol-5-ones[28] can serve as a convenient and effective precursor of *N*-acyl nitrenes via a decarboxylation process to undergo directed intermolecular C–H amidation reaction through an inner-sphere pathway under Rh(III) or Ir(III) catalysis.[29,30] Subsequently, it was discovered that the reactivity of acyl nitrenoid intermediate can be tuned by the ligand on Ir catalyst to undergo an intramolecular C–H insertion through an outer-sphere mechanism, forming γ-lactams in high yield.[20] Mechanistic studies revealed that the strongly electron-donating Cp* and *N,N*-bidentate aminoquinoline ligands (AQ) are crucial to achieve a highly chemoselective C–H insertion process by suppressing the competing Curtius rearrangement pathway of Ir-carbonylnitrenoid intermediate, which gives rise to isocyanate side products. Inspired by the pioneering works of Davies, Hashimoto, Du Bois and others on bi-metallic rhodium and ruthenium-catalyzed enantioselective nitrenoid and carbenoid C(sp^3)–H insertion reactions using carboxylic and amino acid-derived chiral ligands,[31-35] we wondered whether AQ-coupled derivatives of chiral carboxylic acids might give useful level of enantiocontrol and maintain sufficient reactivity in this monometallic Ir-catalyzed nitrenoid C–H insertion system.

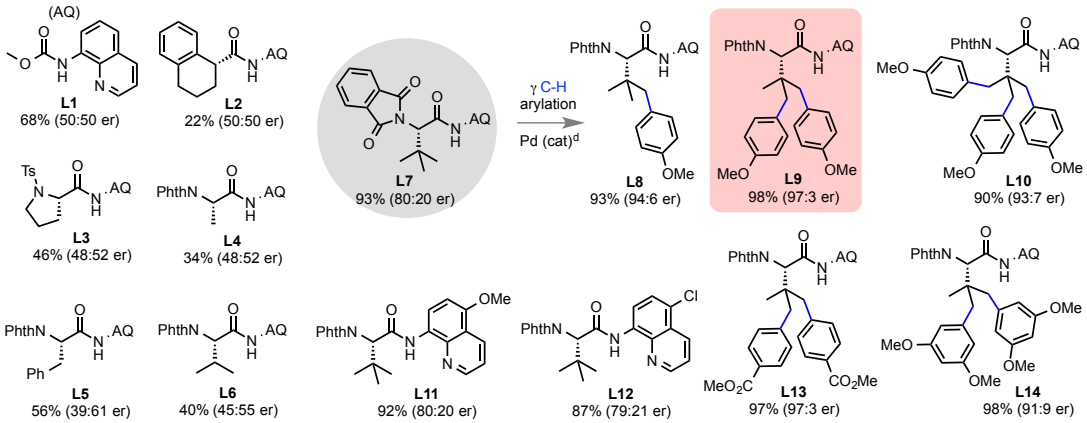
As shown in Scheme 2, the benzylic C–H amidation reaction of a model substrate **1** was investigated in the initial catalyst development. Various AQ-based chiral iridium catalysts were readily prepared by reacting stoichiometric mixture of $[Cp^*IrCl_2]_2$ and AQ-coupled ligands (**L**) with Na_2CO_3 in dichloromethane at room temperature (rt). We were pleased to observe that the desired C–H amidation reaction of **1** proceeded smoothly in hexafluoroisopropanol (HFIP) at rt with 2.5 mol% of Ir catalyst containing the AQ-coupled Phth-protected L-*tert*-leucine (Tle) ligand **L7**, giving γ-lactam **2** in 93% yield and 80:20 er along with 7% of carbamate **4** (entry 1). Side product **4** was presumably formed via the addition of *in situ* generated isocyanate **3** with HFIP. Of note, the catalyst system did not require any additives, and the addition of $NaBAr^F_4$ had little impact to the reactivity in HFIP (entry 2). Use of trifluoroethanol solvent gave slightly higher er but formed more isocyanate side product (entry 9). In comparison, reactions in less polar solvents such as dichloromethane or 1,1,2,2-tetrachloroethane (TCE) showed significantly reduced reactivity using 2.5 mol% of catalyst. In consistent with the previous observations,[20-21] the reaction in TCE did not proceed in the absence of sodium organoborate (entry 6), and moderate yield of **2** (62%) along with considerable amount of isocyanate side product **3** (37%) was obtained using higher loading of Ir catalyst (10 mol%) and 10 mol% of $NaBAr^F_4$ (entry 8) in TCE solvent. Most other solvents such as acetone or toluene gave poor results irrespective of the presence of $NaBAr^F_4$ additive (see SI for details). As shown in entries 10-14, surprisingly, the addition of water as a co-solvent increased the reaction rate and also improved enantioselectivity (entry 1 vs 12). Mixture of HFIP/H_2O in ratios of 1:1 to 1:5 gave similar results. A 1:2 ratio of HFIP/H_2O offered the optimal balance of reactivity and solubilizing ability (entry 12).

Scheme 2. Development of AQ-coupled chiral carboxylic acid-based ligands for Ir-catalyzed enantioselective C–H amidation of **1**.



Entry	Change from initially optimized conditions reagents (equiv)	Product[a] 2 [% (er)]	4 [%]
1	Ir-**L7**	93 (80:20)	7
2	Ir-**L7**; + 2.5 mol% of $NaBAr^F_4$	91 (80:20)	9
3	Ir-**L7**: 2.5 → 5 mol%	95 (83:17)	5
4	Ir-**L7**: 2.5 → 1 mol%	90 (78:22)	10
5	Cat: **L7** + Cp^*IrCl_2 (mixed *in situ*)	89 (58:42)	11
6	Ir-**L7**, HFIP → TCE	3	(>90 % of **1**)
7	Ir-**L7**, HFIP → TCE; + 2.5 mol% of $NaBAr^F_4$	5	50[b] (42% of **1**)
8	Ir-**L7**: 2.5 → 10 mol%; + 10 mol% of $NaBAr^F_4$; HFIP → TCE	62 (93:7)	37[b]
9	Ir-**L7**, HFIP → trifluoroethanol	85 (88:12)	15[c]
10	Ir-**L7**, HFIP → HFIP/H_2O (10/1)	96 (90:10)	3
11	Ir-**L7**, HFIP → HFIP/H_2O (1/1)	96 (95:5)	3
12	Ir-**L7**, HFIP → HFIP/H_2O (1/2)	97 (96:4)	3
13	Ir-**L7**, HFIP → HFIP/H_2O (1/5)	96 (93:7)	3
14	Ir-**L7**, HFIP → HFIP/H_2O (1/10)	65 (86:14)	15
15	Ir-**L7**: 2.5 → 1 mol%; HFIP/H_2O (1/2)	91 (96:4)	9
16	Ir-**L7**: 2.5 → 5 mol%; HFIP/H_2O (1/2)	97 (96.5:3.5)	3
17	Ir-**L7**, 25 °C → 10 °C; HFIP/H_2O (1/2)	95 (97:3)	3
18	Ir-**L7**, 25 °C → 50 °C; HFIP/H_2O (1/2)	91 (91:9)	7
19	Ir-**L9**[d]: 2.5 mol%; HFIP/H_2O (1/2)	98 [96[e]] (99:1)	<1
20	Ir-**L9**[d]: 1 mol%; HFIP/H_2O (1/2)	95 (98.6:1.4)	3

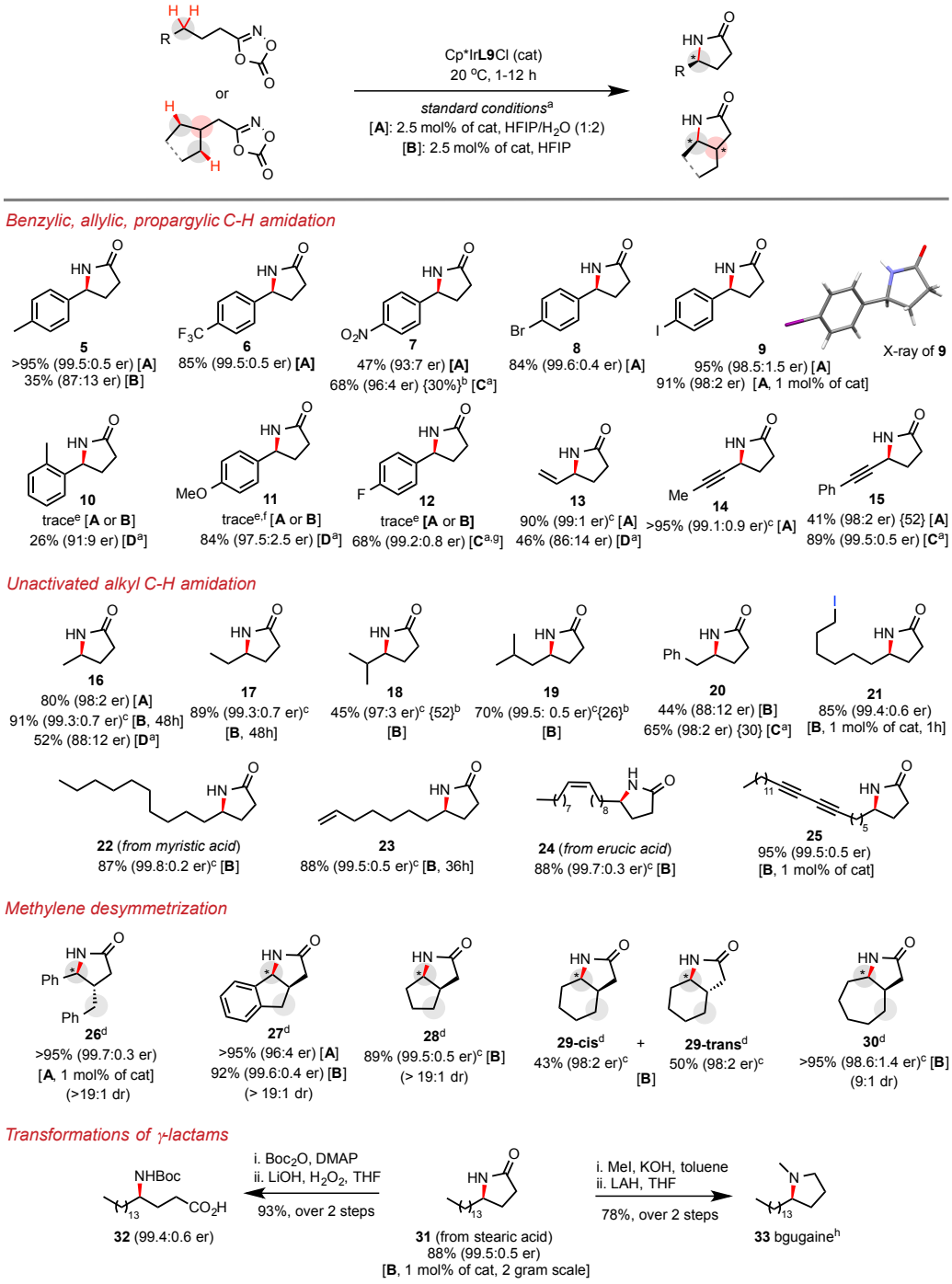
Results with ligands under the initially optimized conditions (entry 1)[f]



a) Yields are based on ^{1}H-NMR analysis of reaction mixture on a 0.2 mmol scale. Er was determined by HPLC using a chiral column. HFIP of 99.7% purity was used. b) Instead of **4**, isocyanate **3** was obtained. c) Carbamate of TFE was obtained. d) Cp*Ir**L9**Cl > 99% ee. See SI for the synthesis of **L8**-**L10**, **L13** and **L14** via Pd-catalyzed C–H arylation of **L7** with aryl iodides. e) Isolated yield. f) Slightly higher yield and er were obtained for selected ligands using 5 mol% of Ir catalyst. See SI for results under other reaction conditions.

In contrast to **L7**, ligands based on Pro (**L3**), Ala (**L4**), Phe (**L5**) and Val (**L6**) gave significantly lower yields and er under the initially optimized conditions (entry 1). As shown with **L11** and **L12**, substitution on the AQ moiety of **L7** displayed little impact. Considering that AQ is a well-known bidentate auxiliary in the palladium-catalyzed β or γ C–H bond functionalization reactions,[36,37] we further leveraged sp^3 C–H arylation technology to modify ligand **L7**. Reaction of PhthTle-AQ **L7** with 4-iodoanisole with $Pd(OAc)_2$ catalyst and AgOAc additive in PhCl at 110 °C gave a separable mixture of mono-, di-, and tri-γ-arylated products **L8**, **L9**, and **L10**. Di-arylated ligand **L9** gave further improved C–H amidation results (98% yield, 99:1 er) in HFIP/H_2O mixed solvents (entry 19). Lowering the loading of catalyst Ir-**L9** to 1 mol% also worked well (entry 20). Several other observations are noteworthy: 1) The reaction proceeded well at further decreased temperature (10 °C) albeit at slightly lower reaction rate (entry 17); reaction at 50 °C forms more side products and with lower er (entry 18). 2) Use of *in situ* mixed $[Cp^*IrCl_2]_2$ with **L7** gave lower yield and er (entry 5). 3) An air atmosphere is tolerated. 4) Different C–H arylated analogs of **L7** gave variable results (see **L13**, **L14**). 5) Higher loading of catalyst gave slightly higher er. 6) More notable improvement of performance of **L9** over **L7** in terms of reactivity and enantioselectivity was observed for certain challenging substrates (*vide infra*).

Scheme 3. Substrate scope of Ir-catalyzed enantioselective methylene C–H amidation and desymmetrization..



a) Yields are based on isolated yields on a 0.2 mmol scale reaction under standard conditions **A**, **B** under ambient air atmosphere. Additional conditions **C**: 5 mol% of catalyst, HFIP, **D**: 10 mol% of catalyst, 10 mol% of $NaBAr^F_4$ in TCE solvent. er values were based on chiral HPLC analysis. b) Yield of carbamate side product in {} for selected reactions. c) er was measured based on the *N*-Cbz protected derivatives. d) Absolute stereochemistry was not determined. e) Poor conversion of starting material was observed. f) The reaction solution changed from colorless to bright yellow upon mixing starting material with catalyst. g) 5 mol% of $NaBAr^F_4$ was added. h) a 99:1 er was obtained for its N-benzyl analog. See SI for details..

Substrate scope. With the optimized conditions (**A**, 2.5 mol% of Ir-**L9** in HFIP/H_2O) for benzylic C–H amidation in hand, we next examined the scope of this chiral γ-lactam synthesis with various dioxazolone substrates (Scheme **3**). As exemplified by **5**, the use of HFIP/H_2O (1:2) solvents consistently gave better yield and enantioselectivity than HFIP solvent alone (conditions **B**, 2.5 mol% of Ir-**L9** in HFIP). Functional groups such as CF_3 (**6**), NO_2 (**7**) and halogens (**8**, **9**) on phenyl ring were tolerated. The absolute stereochemistry of iodo-containing product **9** was confirmed by X-crystallographic analysis. Certain electron-withdrawing/polar groups such as NO_2 (**7**) on phenyl ring significantly reduced the reactivity. For these substrates, 5 mol% of catalyst in HFIP solvent (conditions **C**) was required to obtain reasonable yield of γ-lactam products along with the increased amount of carbamate side product while enantioselectivity of the reactions was

largely unaffected. Notably, product **11** carrying a methoxyphenyl group was formed in poor yield under the standard conditions in either HFIP or HFIP/H_2O solvents. In contrast, switching the solvent to TCE, increasing the loading of Ir (10 mol%), and adding $NaBAr^F_4$ (conditions **D**) afforded 84% yield and 97:3 er. Not surprisingly, steric congestion around the reactive center resulted in decreased reactivity and enantioselectivity, as seen in the formation of **10**. As shown in the formation of **13** and **14**, allylic or propargylic substrates challenging to diamine-Ir catalyst system[21] gave γ-vinyl or alkynyl γ-lactams in excellent yield and outstanding er in HFIP/H_2O solvents. Synthesis of **15** bearing a phenyl alkynyl substituent required higher loading of catalyst (5 mol%) and HFIP solvent.

As shown by **16**-**25**, we were pleased to observe that cyclization at the unactivated aliphatic C–H bonds proceeded with excellent yield and enantioselectivity in HFIP solvent under conditions **B**, thus forming various γ-lactams carrying aliphatic γ-alkyl substituents. Similar to the reactions of γ-alkynyl substituted substrates, substrates bearing short γ-alkyl group (e.g. **16**) worked well in HFIP/H_2O solvents whereas longer alkyl groups showed diminished reactivity and worked better in HFIP. It is worth mentioning that highly enantioselective synthesis of such γ-lactams (>95% ee) remains challenging using existing methods.[13] Many of these substrates can be easily prepared from readily available aliphatic carboxylic acids. Functional groups such as iodo (**21**), terminal and internal alkenes (**23**, **24**) and alkynes (**25**) were tolerated. A simplest γ-alkyl γ-lactam product **16** was prepared in 91% yield and 99.3:0.7 er. Product **22,** derived from a natural compound *myristic acid*, was prepared in 87% yield and with 99.6% ee. Products **21** and **25** were prepared in excellent yield and with excellent er using 1 mol% of catalyst.

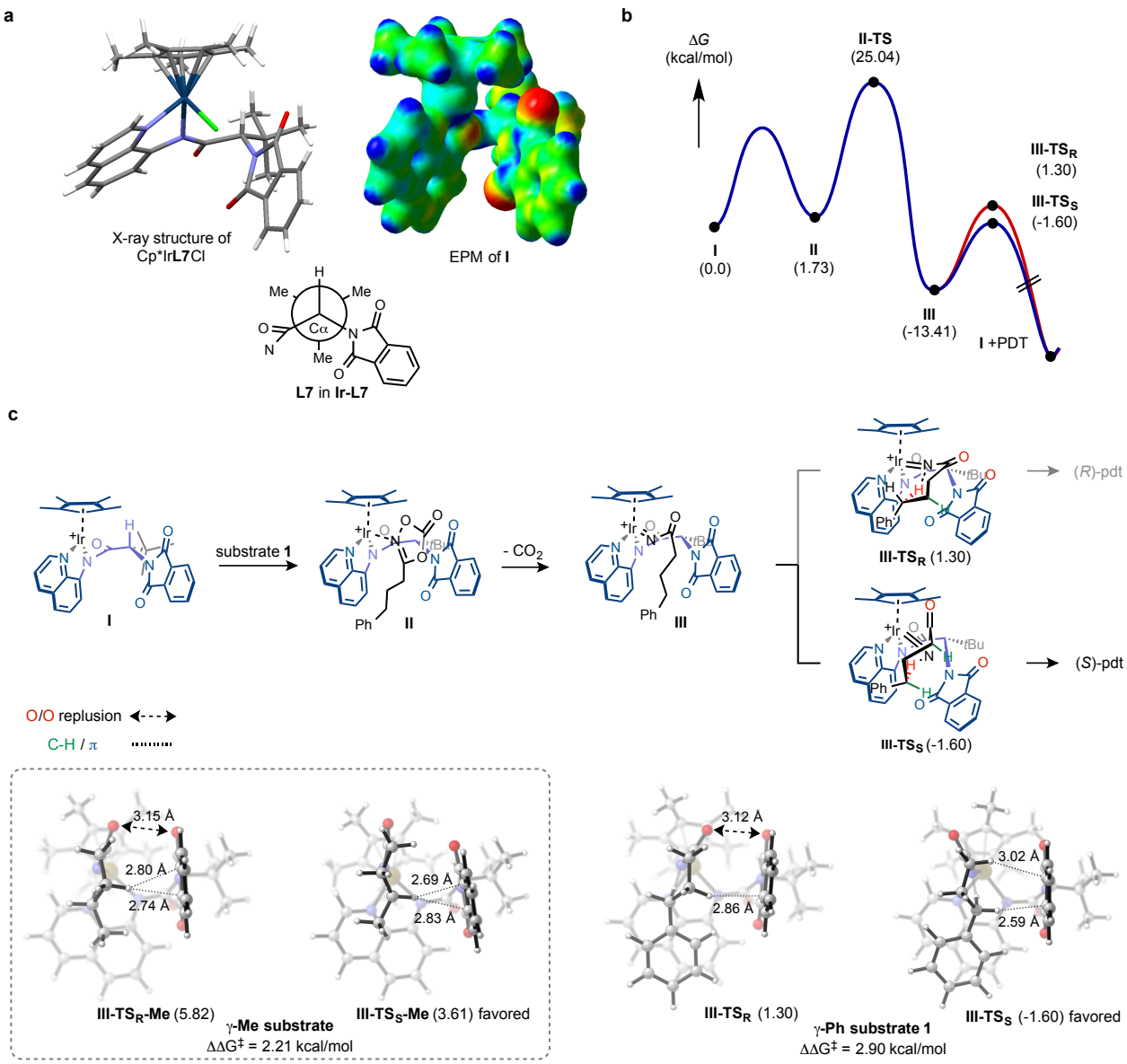
In addition to the above enantioselective methylene C–H amidation, desymmetrization of substrates carrying two symmetric methylene groups also worked well to form more complex γ-lactams carrying consecutive stereogenic centers. For instance, desymmetrization of benzylic methylenes of either acyclic or cyclic substrates gave products **26** and **27** in high yield, and excellent er and dr under the conditions **A** or **B**. Reaction of cyclopentylmethyl dioxazolone gave a *cis*-fused product **28** in 76% yield, 99% ee, and >19:1 dr. Reaction of cyclohexylmethyl dioxazolone gave a diastereomeric mixture of **29-cis** and **29-trans** in excellent er. A gram-scale reaction of stearic acid-derived dioxazolone gave **31** in 88% yield and 99% ee under the conditions **B** with 1 mol% of catalyst. Boc activation of **31** followed by the treatment with LiOH provided Boc-protected γ-amino stearic acid **32** in 93% yield. A two-step sequence of *N*-methylation of **31** with MeI and reduction with lithium aluminum hydride (LAH) gave enantioenriched natural product bgugaine **33** in four steps and 66% overall yield from commercially available stearic acid.

Mechanistic study. Intrigued by the superior performance of the new catalytic system in partially aqueous media, we sought to understand the origin of reactivity and enantioselectivity using the ligand Phth-Tle-AQ **L7**. The structure of the Ir catalyst carrying **L7** was confirmed by X-ray crystallography, as shown in Scheme **4a**. Interestingly, the planar phthalimide group of Phth-Tle-AQ is positioned in a close proximity to the AQ group with the C_α–H bond pointing toward the Cp* ring. In contrast to the existence of a diastereomeric mixture of Ir catalysts ligated by amino acid ligands carrying a sterically less demanding side chain such as Phth-Ala-AQ (**L4**, β-monosubstituted) and Phth-Val-AQ (**L6**, β-disubstituted), catalysts containing Tle (β-trisubstituted) or arylated Tle ligands, e.g. **L7** and **L9**, exist as a single diastereomer in solution phase, as confirmed by ^{1}H-NMR analysis (see SI for details). Such conformational stability of Tle-ligated catalysts can be explained by the rotational restriction of bonds connected to the C_α center due to the strongly favored staggered conformation between C_α and C_β. The high stability of Cp*Ir**L7**Cl catalyst in H_2O could be explained by the tight N,N-bidentate chelation of AQ to the Ir center. Starting from this experimentally-obtained conformation, density functional theory (DFT) calculations were carried out to estimate the relevant energetics and the enantiocontrol in a reaction of model substrate **1**.

As outlined in Scheme **4b** and **4c**, the reaction likely starts with an dissociation of chloride anion from neutral Cp*Ir**L7**Cl, forming a cationic Ir(III) species **I** with an open coordination site. Due to the high polarity and strong Cl^- solvating ability of HFIP[38] or H_2O, the dissociation takes place even in the absence of the Cl^- scavenger such as $NaBAr^F_4$.[20] The optimized structure of **I** is very similar to the Cl-bound Ir-**L7** catalyst. The electrostatic potential map (EPM) of **I** showed that the AQ, Cp* and Phth groups form a well-organized chiral pocket featuring a cationic Ir center buried in a hydrophobic groove with the top end blocked by the Cp* plane. Driven by the coordination of N of dioxazolone to the Ir center and the hydrophobic effect,[38] apolar substrate **1** dissolved in the polar reaction medium (HFIP or mixed HFIP/H_2O) readily enters the chiral pocket of **I** to form a substrate/catalyst complex **II**, which then undergoes decarboxylation to form an Ir-carbonylnitrenoid intermediate **III** with an energy barrier of 23.3 kcal/mol (Scheme **4b**). In comparison to **III**, its diastereomer **III'** with the alkyl group pointing toward Cp* is much less stable by 5.6 kcal/mol, possibly due to the steric clash with Cp* (see SI for the structure of **III'**). As the key stage, subsequent intramolecular C–H insertion of **III** takes place through a 6-membered chair-like transition state **III-TS$_R$** or **III-TS$_S$**, which is supposedly the enantioselectivity-determining step. Indeed, traversing **III-TS$_S$** that eventually gives (*S*)-configured lactam product is kinetically more favored than the process traversing **III-TS$_R$** by nearly 3 kcal/mol, which is consistent with the experimentally observed enantiomeric excess (94% ee, Scheme **4c**). Because of the high polarity of the amide group and its weaker complexation ability with Ir center, the final γ-lactam product can readily be released from the pocket, thus regenerating the catalytic species **I**.

Structural analysis of the transition state **III-TS** revealed that the γ-phenyl substrate **1** is fully confined in the chiral pocket of catalyst by multiple noncovalent interactions with the AQ and Phth planes. The phenyl group of **1** builds a π stacking interaction with the AQ plane in both **III-TS$_S$** and **III-TS$_R$**. The steric repulsion between the γ-Phe and Phth groups was found to be insignificant. In contrast, a $C_\gamma(sp^3)$–H/π attractive interaction between the aliphatic skeleton of substrate and Phth group is observed in both transition states with a H/π distance of 2.59 Å in **III-TS$_S$** and 2.86 Å in **III-TS$_R$**.[40-42] An extra $C_\alpha(sp^3)$–H/π interaction with a longer H/π distance of 3.02 Å is observed in **III-TS$_S$**. Noncovalent interaction (NCI) plot analysis revealed that a van der Waals repulsion between the carbonyl O of substrate and carbonyl O of Phth with an O-O distance of 3.12 Å also contributes to the destabilization of **III-TS$_R$**. Such interaction is absent in **III-TS$_S$**. As shown in Scheme **4c**, a $\Delta\Delta G^{\neq}$ of 2.21 kcal/mol was obtained for the corresponding transition states **III-TS$_S$-Me** and **III-TS$_R$-Me** of the reaction of γ-methyl substrate, offering similarly high enantioselectivity (product **16,** see SI for the details of DFT calculations). In comparison to **1**, the γ-methyl substrate does not form π-stacking interaction with the AQ group. However, the attractive C–H/π interactions with the Phth group remain operative likely leading to the enantiocontrol in the C–H insertion step.[43]

Scheme 4. Mechanistic studies of Ir-catalyzed enantioselective C–H amidation of **1** with Cp*Ir**L7**Cl.

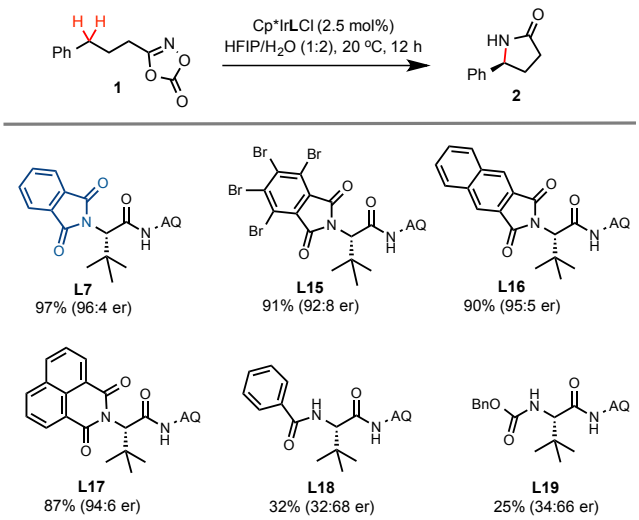


a, X-ray structure of catalyst Cp*Ir**L7**Cl and calculated structure (electrostatic potential map) of intermediate **I**. **b**, Calculated energy profiles for the reaction of **1**. DFT calculations were performed at the PCM (water) M06/{SDD, 6-311+G**}//B3LYP/{LANL2DZ, 6-31G**} level of theory, See SI for details. **c,** Proposed reaction pathways and stereochemical model with substrate **1** (γ-Phe) and calculated transition state structures for the enantiodetermining C–H insertion step for γ-Phe and γ-methyl substrates.

Having identified the critical stereo-steering role of Phth group, additional control experiments were designed to corroborate computational insights. As shown in Scheme **5**, analogous ligands of **L7** bearing different *N*-protecting groups were prepared and subjected to the reaction of **1** under standard conditions **A**. Replacing Phth group of **L7** with more flexible benzamide (Bz, **L18**) or carbamate (Cbz, **L19**) gave significantly diminished reactivity and enantioselectivity which favors the opposite direction possibly under the influence of the steric effect. In contrast, benzo-fused imide analogs with large arene moieties (**L15**-**L17**) gave comparable results to Phth. These results are in line with the stereoelectronic effect of the Phth group in the current enantiocontrol model.

Conclusion

In summary, we have developed a highly efficient and broadly applicable method for the asymmetric synthesis of γ-lactams via Ir-catalyzed enantioselective C(sp^3)–H amidation of dioxazolone substrates. The catalyst is equipped with a newly designed α-amino acid-based chiral ligand, and the Cp*, AQ and Phth groups were elucidated to form a well-defined chiral pocket around the Ir center. The hydrophobic effect of the pocket allows facile binding of substrates in polar or aqueous media. The new synthetic procedure is operationally simple under mild conditions, providing excellent yields with outstanding enantioselectivity for both activated and unactivated alkyl C(sp^3)–H bonds. It can effect both enantioselective methylene C–H amidation and point desymmetrization. Instead of capitalizing on steric repulsions , this new enzyme-like Ir catalyst operates through a rarely precedented enantiocontrol mechanism for C-H functionalization featuring



Scheme 5. Performance of **L7** analogs with different N-protecting groups. Yields are based on ^{1}H-NMR analysis of reaction mixture on a 0.2 mmol scale. Er was determined by HPLC using a chiral column.

multiple attractive non-covalent interactions.

ASSOCIATED CONTENT

Detailed synthetic procedures, compound characterization, NMR spectra, X-ray crystallographic data, and computational details are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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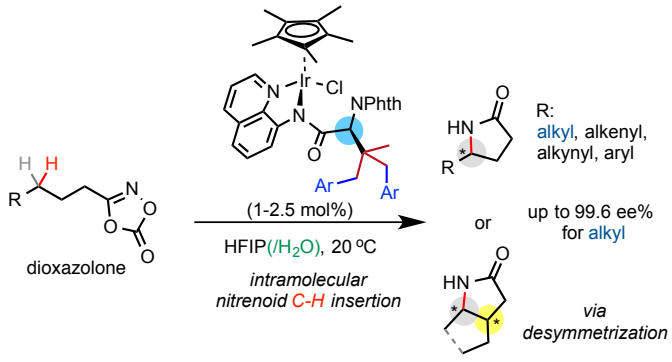
43. Bond distances between the γ C-H and the aminoquinoline of **III-TS$_R$-Me** and **III-TS$_S$-Me** were around 3.0 Å, implying weak C-H/π interactions between the substrate and the AQ plane. However, due to the similar intensity of the interactions, they are not expected to be critical in the energetics related to the enantio-determining step.


dioxazolone
(1-2.5 mol%)
HFIP(/H2O), 20 °C
intramolecular
nitrenoid C-H insertion
R:
alkyl, alkenyl,
alkynyl, aryl
up to 99.6 ee%
for alkyl
or
via
desymmetrization