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Ligand Controlled Ir-Catalyzed Regiodivergent Oxyamination of Unactivated Alkenes

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Supporting Information

ABSTRACT: An intramolecular Ir(III)-catalyzed regiodivergent oxyamination of unactivated alkenes provides valuable γ-lactams, γ-lactones and δ-lactams. The regioselectivity is controlled by the electronically tunable cyclopentadienyl Ir(III)-complexes enabling oxyamination via either 5-exo or 6-endo pathways. With respect to the mechanism, we propose a highly reactive [3.1.0] bicycle intermediate derived from Ir(V) nitrene-mediated aziridination to be a key intermediate toward the synthesis of γ-lactams.

Regio- and stereoselective alkene oxyamination is attractive as a strategic synthetic disconnect[1] because of the abundance of vicinal N, O motifs in biologically active natural products and pharmaceuticals and the wide availability of alkene precursors. Inspired by Sharpless' pioneering asymmetric amino-hydroxylation reaction,[2] extensive effort has been made using transition-metal catalysis involving Os,[3] Cu,[4] Pd,[5] Rh,[6] Fe,[7] Au[8] and Mn,[9] among other strategies.[10] In cases where the alkene is not electronically biased, regioselective oxyamination remains challenging. Intramolecular oxyamination wherein the alkene is tethered with a N- or O-containing group has been developed to overcome this limitation, providing access to 5-exo and 6-endo products selectively (Scheme 1a). For example, Donohoe[3b] has shown the utility of Os-catalyzed 5-exo aminohydroxylation of alkene tethered carbamates for the synthesis of all syn amino-diol motifs. Sorensen[5b] and Liu[5e] have reported intramolecular 5-exo/6-exo oxyaminations of alkenes via combination of a Pd(II)-catalyst with $PhI(OAc)_2$ or H_2O_2 as the oxidant and oxygen source. More recently, the 5-exo cyclization was realized through Fe(IV)-nitrene mediated amino-benzoxylation reported by Xu.[7c] In contrast, 6-endo oxyamination is relatively less explored, and the Thorpe−Ingold effect is usually required to increase 6-endo selectivity. For example, Liu[5g] reported asymmetric 6-endo aminoacetoxylation of unactivated alkenes by Pd(II/IV) catalysis, with high regioselectivities only accomplished when a significant Thorpe−Ingold effect was used. A general catalytic system which can enable oxyamination with either regioselectivity (5-exo and 6-endo) as well as with reversed sense of oxyamination remains unknown.

Our group has recently described a regiodivergent diamination of terminal alkenes,[11] wherein the regioselectivity is controlled by the reaction solvent. With relatively acidic hexafluoroisopropanol (HFIP) as the reaction medium, γ-lactams are obtained selectively, while the selectivity could be switched by employing basic TFE/2 M $KHCO_3$ cosolvent system leading to δ-lactams selectively. However, expanding this transformation for substrates tethered with internal alkenes or weaker nucleophiles like carboxylic acids proved problematic. On the basis of our continuing interest in investigation of Cp ligand effects for Rh- and Ir-catalysis,[12] we speculated that ligand manipulation could potentially provide a more general solution. Herein, we report a regiodivergent oxyamination of unactivated alkenes controlled by the Cp ligand on Ir with more electron-deficient systems leading to 6-endo selectivity compared to high 5-exo selectivity for Cp* (Scheme 1b). The use of exogenous nitrenoid precursor on alkenyl acid substrates leads to inverted regioselectivity. Finally, stereoselective *trans*-addition of N, O-motifs to the 1,2-dialkyl alkene enables access to either *syn* or *anti* isomers by simply switching the alkene geometry (Z/E). In contrast, the E styrenyl alkene delivers *syn*-addition product in good yield.

We commenced our study by coupling the alkene tethered N-pivaloylhydroxamate **1a** with propionic acid **2a** as the nucleophile (Table 1). Unlike previous studies where the O-

Scheme 1. Alkene Oxyamination

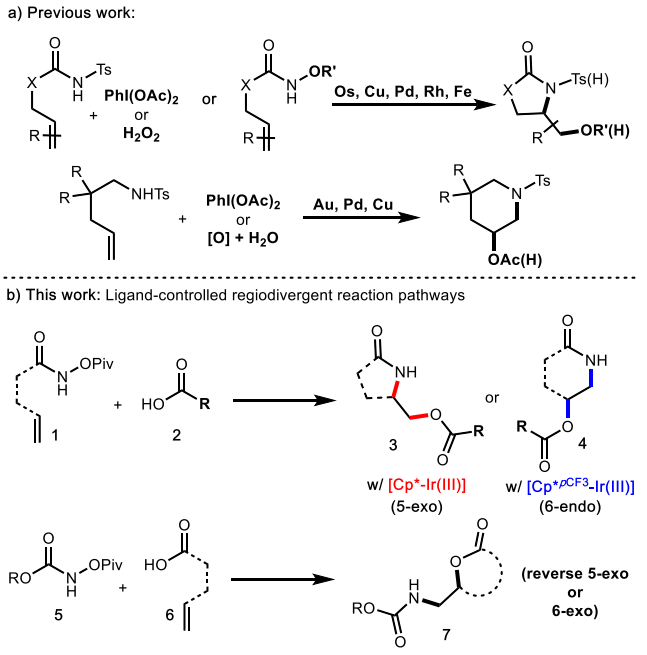

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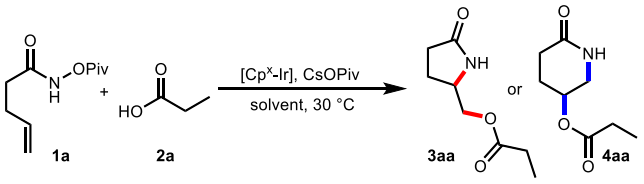
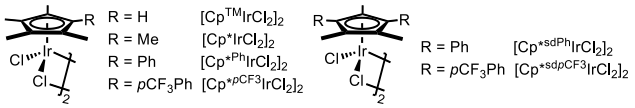
Table 1. Reaction Optimization[a]



entry	catalyst	solvent	yield (%)[b]	rr (γ:δ)[c]
1[d]	$[Cp^*IrCl_2]_2$	HFIP	47	6.7:1
2	$\mathbf{[Cp^*Ir(CH_3CN)_3](SbF_6)_2}$	**HFIP**	**68**	**8.5:1**
3[e]	$\mathbf{[Cp^*Ir(CH_3CN)_3](SbF_6)_2}$	**HFIP**	**71(68)**[f]	**8.2:1**
4	$[Cp^*IrCl_2]_2$	TFE/2M $KHCO_3$	trace	--
5	$[Cp^{TM}IrCl_2]_2$	HFIP	trace	--
6	$[Cp^{*Ph}IrCl_2]_2$	HFIP	28	1.1:1
7	$[Cp^{*sdPh}IrCl_2]_2$	HFIP	27	1:3.9
8	$[Cp^{*pCF3}IrCl_2]_2$	HFIP	65	1:9.3
9	$[Cp^{*sdpCF3}IrCl_2]_2$	HFIP	61	<1:20
10	$[Cp^{*pCF3}Ir(CH_3CN)_3](SbF_6)_2$	HFIP	75	1:11
11[g]	$\mathbf{[Cp^{*pCF3}Ir(CH_3CN)_3](SbF_6)_2}$	**HFIP**	**75(70)**[f]	**<1:20**



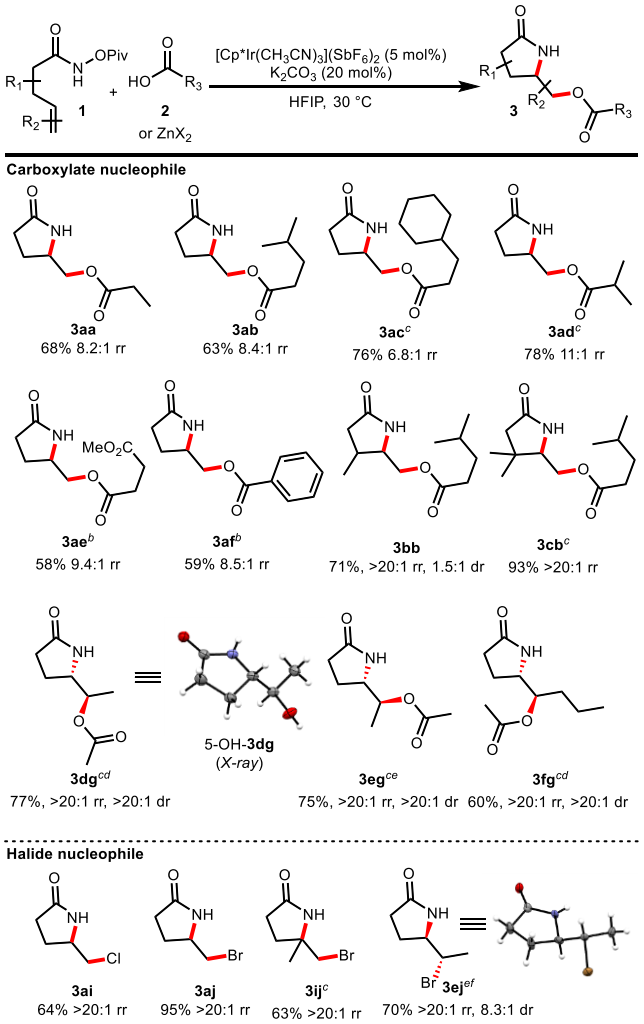
[a]Reactions were conducted on a 0.06 mmol scale using **1a** (1.0 equiv), **2a** (2.5 equiv), [Cp[x]-Ir] (5.0 mol % Ir-monomer), CsOPiv (20 mol %). [b]Yield of major isomer as determined by ^{1}H nuclear magnetic resonance (NMR). [c]Determined by analysis of ^{1}H NMR of the unpurified reaction mixture. [d]1.0 equiv CsOPiv. [e]20 mol % K_2CO_3 instead of CsOPiv. [f]Isolated yield of major isomer. [g]24 °C instead of 30 °C.

motif is mostly from either an external oxidant (e.g., $PhIOAc_2$)[5b,c,g] or an internal oxidant (e.g., RNH-OBz),[4a,7c] our method incorporates readily available carboxylic acids. Using $[Cp^*IrCl_2]_2$ in combination with CsOPiv in HFIP, we were pleased to find that the desired oxyamination product **3aa** was formed in 47% yield and 6.7:1 regioselectivity favoring γ-lactam (5-exo). The competitive coupling with pivalate was detected in negligible yield (<5%), but the coupling with chloride was observed with 10% yield from 2.5 mol % of $[Cp^*IrCl_2]_2$. Therefore, the employment of a preformed cationic iridium catalyst was utilized to avoid amino-chlorination byproduct formation, improving the yield to 68% (entry 2). K_2CO_3 was chosen as the optimal base for 5-exoselectivity, as it was found to be more general during substrate scope study. In order to obtain δ-lactams (6-endo selectivity), the use of our previous conditions (TFE/2 M $KHCO_3$) led to trace amount of oxyamination product (entry 4). We speculated that the failure arose from the weaker nucleophilicity of carboxylates compared to secondary amines. Thus, a more electron-deficient Cp ligand may be able to increase π-acidity of the Ir-catalyst and therefore promote the nucleophilic attack by carboxylates.

In the event, we found a significant improvement in reactivity and selectivity toward δ-lactam **4aa** by applying more electron-deficient Cp ligands (entries 5–9). Although $Cp^{*sdpCF3}$ delivers the best regioselectivity for δ-lactams, Cp^{*pCF3} was selected as optimal for further development due to its higher reactivity and ease of preparation. The corresponding cationic iridium complex was also successfully used to increase reactivity (entry 10), while selectivity was further improved when the reaction was conducted at ambient temperature (entry 11).

With optimized reaction conditions in hand, we turned to evaluate the scope of γ-lactam formation (5-exo). The reaction tolerates both aliphatic and aromatic acids (**3aa**–**3af**, Scheme 2). When benzoic acids are used, a stoichiometric amount of

Scheme 2. γ-Lactam Scope[a]



[a]Conditions: **1** (0.1 mmol, 1.0 equiv), **2** or ZnX_2 (2.5 equiv), $[Cp^*Ir(CH_3CN)_3](SbF_6)_2$ (5 mol %), K_2CO_3 (20 mol %), HFIP (0.3 M), 30 °C for 16 h. [b]1.0 equiv K_2CO_3. [c]40 °C. [d]From *E*-olefin; [e]From *Z*-olefin; [f]4 °C.

base is required for good yield (**3af**). The influence of substituents at the α- and β-position of the alkenyl hydroxamate was explored. Substituents at the α-position caused significant Lossen rearrangement, whereas substrates containing β-substitution participated smoothly, even when containing a more sterically hindered β dimethyl moiety (**3bb**, **3cb**). More importantly, in addition to terminal olefins, substrates bearing an internal alkene are also compatible, with complementary diastereomers formed from *cis* and *trans* 1,2-dialkyl alkenes reflective of a stereoselective *anti*-addition of N- and O-groups to the double bond (**3dg**, **3eg**, **3fg**).[13] The

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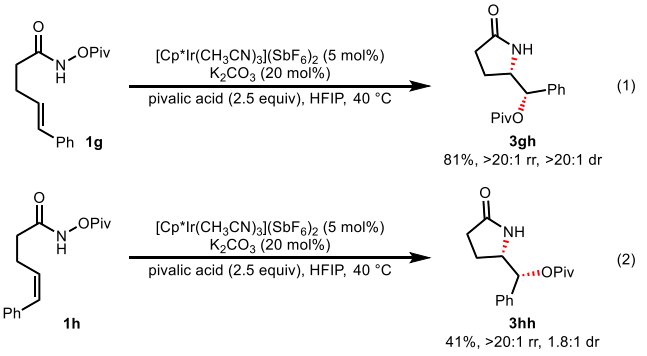
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

relative stereochemistry of **3dg** was confirmed by X-ray crystallography of the corresponding alcohol.

To further extend this method, chloride and bromide were also tested as an external nucleophile (**3ai**, **3aj**). Zinc halides were found to be the optimal halide source, providing amino-chlorination and -bromination products in good yields. Gratifyingly sterically hindered 1,1-disubstituted alkene was successfully transformed to the desired γ-lactam containing a quaternary carbon center (**3ij**). Internal alkenes are also suitable substrates; *cis*-alkene delivers **3ej** with excellent diastereoselectivity and good yield. In contrast to oxy-amination, however, the *E* olefin delivers the same diastereoisomer as the major product (**3ej**), albeit with lower diastereoselectivity (1.8:1 dr).

Interestingly, styrenyl systems participate well but deliver products with different selectivity. Substrate **1g** provides *syn*-addition product with excellent selectivity (eq 1). On the other

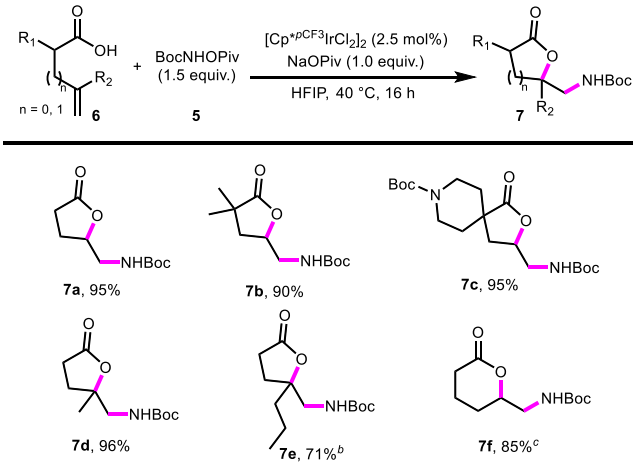


hand, diastereomeric **1h** provides a mixture of *syn* and *anti* addition product in poor selectivity (eq 2). The former is consistent with a recent report by Chang[14] implicating a [3+2]-type mechanism. We view the latter result as evidence that in some cases, the two mechanisms are competitive.

Given that it would be enabling to deliver the amino alcohols with reversed regioselectivity about the alkene, we wondered whether alkenoic acids[4h,i,n] could be engaged with exogenous hydroxamate ester by a presumably mechanistically related manifold. Thus, we decided to test this transformation by simply switching the positions of carboxylic acids and pivaloylhydroxamate tethering the acid nucleophile to the alkene. We were delighted to find the reaction proceeds smoothly with electron-deficient $[Cp^{*pCF3}IrCl_2]_2$ producing desired amino lactones in almost quantitative yield (**7a**–**7c**, Scheme 3). Additionally, 4,4-disubstituted alkenes are successfully applied, leading to amino lactones bearing a congested quaternary center (**7d**, **7e**). More importantly, a 6-exo cyclization process can also be realized in high yield promoted by a more electron-deficient $Cp^{*sdpCF3}Ir(III)$-catalyst.[15]

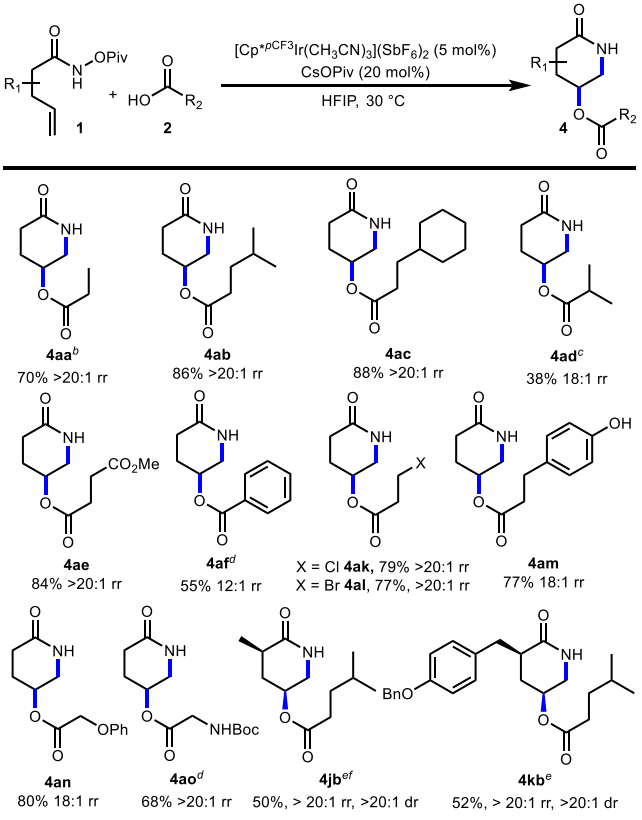
Next, we sought to investigate the scope of δ-lactams (6-exo selectivity). This reaction was found to be compatible with various aliphatic and aromatic acids (**4aa**–**4ao**, Scheme 4). Different substitutions such as β-halides or α-heteroatoms are well tolerated. Additionally, unlike the synthesis of γ-lactams, α-substituted substrates are converted to δ-lactams with excellent diastereoselectivity (**4jb**, **4kb**).[16] This is most likely attributed to the electron-deficient $Cp^{*pCF3}Ir$-catalyst suppressing Ir-nitrene formation and concomitantly initiating the other reaction pathway via its π-Lewis acidity.

Scheme 3. Amino Lactone Scope[a]



[a]Conditions: **6** (0.1 mmol, 1.0 equiv), BocNHOPiv (1.5 equiv), $[Cp^{*pCF3}IrCl_2]_2$ (2.5 mol %), NaOPiv (1.0 equiv), HFIP (0.3 M), 40 °C for 16 h. [b]5 mol % of $[Cp^{*pCF3}IrCl_2]_2$. [c]5 mol % of $[Cp^{*sdpCF3}IrCl_2]_2$.

Scheme 4. δ-Lactam Scope[a]



[a]Conditions: **1** (0.1 mmol, 1.0 equiv), **2** (2.5 equiv), $[Cp^{*pCF3}Ir(CH_3CN)_3](SbF_6)_2$ (5 mol %), CsOPiv (20 mol %), HFIP (0.3 M), 30 °C for 16 h. [b]24 °C. [c]2.5 mol % $[Cp^{*sdpCF3}IrCl_2]_2$ used. [d]1.0 equiv CsOPiv used. [e]40 °C. [f]The relative stereochemistry was determined via nuclear Overhauser spectroscopy analysis.

In the course of these studies, we made a serendipitous observation that we postulate sheds light on the mechanism of oxyamination. We isolated aziridine containing intermediate **11** when conducting the reaction in the presence of **10** (Scheme 5). We hypothesize that this reaction proceeds via the

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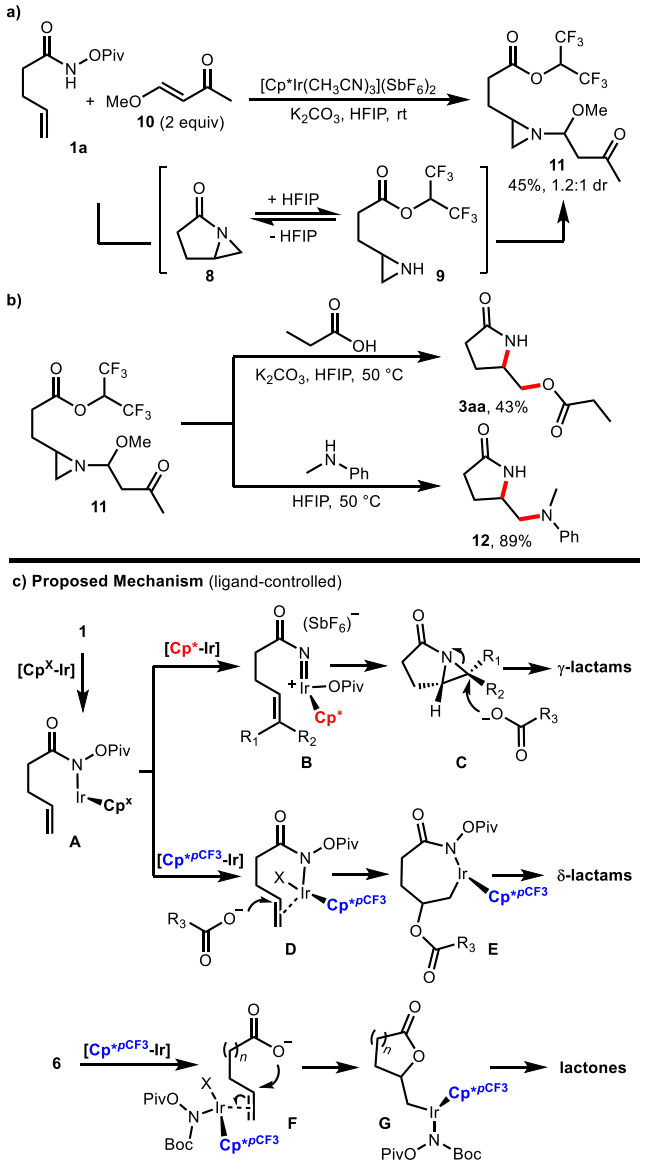
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 5. Mechanistic Studies



strained azabicyclo[3.1.0] intermediate **8**, formed via an Ir(V)-nitrene-mediated aziridination, which is intercepted by the solvent (hexafluoro-2-propanol) through cleavage of the strained amide bond instead of opening the aziridine ring.[17] To further support the proposed mechanism, aminal **11** was isolated and subjected to propionic acid or methylaniline in HFIP. The corresponding oxyamination (**3aa**) and diamination (**12**) products are formed in good yields, which is likely through retro-Michael addition/cyclization to reform the key intermediate **8** and subsequent irreversible quenching by the external nucleophile.

These findings lead us to propose the following mechanisms to account for each product. The observed strong ligand effect is consistent with our previous proposed reaction pathways.[11] Accordingly, the divergent syntheses of γ- and δ-lactams are dependent on the electronic nature of the Cp ligand. When applying an electron-rich Cp*, γ-lactams are formed via an Ir(V)-nitrene intermediate. In contrast, when electron-deficient Cp*^{pCF3} is subjected to the reaction conditions, δ-lactams are synthesized via a proposed nucleophilic attack on the activated alkene prior to Ir nitrene formation (**D** in Scheme 5). Last, regiocomplementary products result from carboxylate trapping of an activated Ir-nitrene alkene complex leading to the aminolactone product (**F** in Scheme 5).[18]

In conclusion, we have successfully developed a regiodivergent and stereoselective oxyamination of unactivated alkenes. The regioselectivity is controlled by tuning the electronics of the Cp ligands. Value-added structures such as γ-lactams, γ-lactones and δ-lactams can be rapidly assembled from readily available starting materials. Importantly, the experimental evidence strongly suggests the existence of a highly electrophilic azabicyclo[3.1.0] intermediate, which unveils the mechanistic details of stereoselective γ-lactam formation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b06366.

Detailed experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR spectra for all isolated compounds (PDF)
Data for $C_6H_{10}BrNO$ (CIF)
Data for $1(C_{16}H_{21}NO_3)$ (CIF)
Data for $C_6H_{11}NO_2$ (CIF)

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Notes

The authors declare no competing financial interest.

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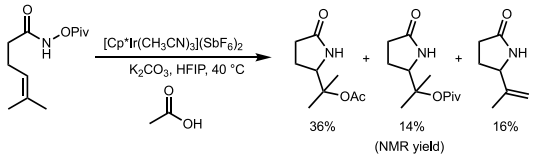
(13) Trisubstituted alkenes also participate but give mixtures of products; for example:



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(15) Internal alkenes do not provide product under these conditions.

(16) Internal alkenes lead to γ-lactam products under these optimized conditions.

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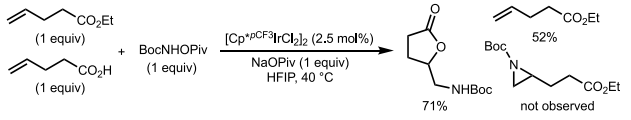
(18) A competition reaction between enoic acid and enoate ester shows exclusive reaction of the acid. If the reaction proceeds via aziridination/ring-opening, one would expect no selectivity.



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