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Ir(III)-Catalyzed Mild C−H Amidation of Arenes and Alkenes: An Efficient Usage of Acyl Azides as the Nitrogen Source

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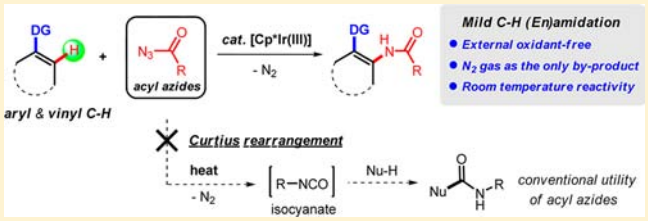
Supporting Information

ABSTRACT: Reported herein is the development of the Ir(III)-catalyzed direct C−H amidation of arenes and alkenes using acyl azides as the nitrogen source. This procedure utilizes an in situ generated cationic half-sandwich iridium complex as a catalyst. The reaction takes place under very mild conditions, and a broad range of sp^2 C−H bonds of chelate group-containing arenes and olefins are smoothly amidated with acyl azides without the intervention of the Curtius rearrangement. Significantly, a wide range of reactants of aryl-, aliphatic-, and olefinic acyl azides were all efficiently amidated with high functional group tolerance. Using the developed approach, *Z*-enamides were readily accessed with a complete control of regio- and stereoselectivity. The developed direct amidation proceeds in the absence of external oxidants and releases molecular nitrogen as a single byproduct, thus offering an environmentally benign process with wide potential applications in organic synthesis and medicinal chemistry.



INTRODUCTION

Among a broad range of transition metal systems investigated for the direct C−H functionalizations, iridium has received special attention due to its high activity in the C−H bond activation.[1] Indeed, the first example of photolytic cleavage of alkanes was achieved by a phosphine-bound cyclopentadienyl iridium complex.[2] This remarkable finding, albeit in a stoichiometric manner, led to subsequent investigations of alkane activation operating at the Ir(III) metal center.[3] However, the procedure has not been developed into efficient catalytic C−H functionalizations; rather, it was used mainly for an interchange process to generate swapped metal alkyl complexes and alkanes. Along with the archetypal C−H activation of alkanes, stoichiometric reactions based on a cyclometalation pathway employing a half-sandwich iridium have also been actively studied.[4] In this regard, certain chelate group-containing arenes was known to be able to work as a supporting ligand (η^2-C,Y bidentate) to form robust iridacycles,[5] which exhibit notable catalytic activities in a wide range of organic transformations (Scheme 1A).[5,6] Because of the inherent stability of half-sandwich iridacycles, the catalytic C−H bond functionalization of chelate group-containing arenes or alkenes has not been much investigated.

On the other hand, significant advances have been made recently in the direct C−H amination reactions, thus improving substrate scope and reaction conditions.[7−10] In this context, we succeeded in the direct installation of amines in heteroarene C−H bonds.[11] More recently, we explored the Rh- and Ru-catalyzed intermolecular C−H amination of arenes using sulfonyl, aryl, or alkyl azides at temperatures higher than 80 °C.[12] The developed procedure does not require external oxidants and releases N_2 as a single byproduct.[13−15] Since our reports, several examples of the arene C−H amidation with sulfonyl azides have also been revealed using Rh or Ru catalysts.[16] While *intramolecular* amination of various types of sp^2 or sp^3 C−H bonds using azides was established with certain catalytic systems[13c,14] such as (MeO)Ir(I)[14b] and Ir(III)-salen,[14f] the corresponding *intermolecular* reaction has been limited mainly to allylic and benzylic sp^3 C−H bonds.[13,15]

Scheme 1

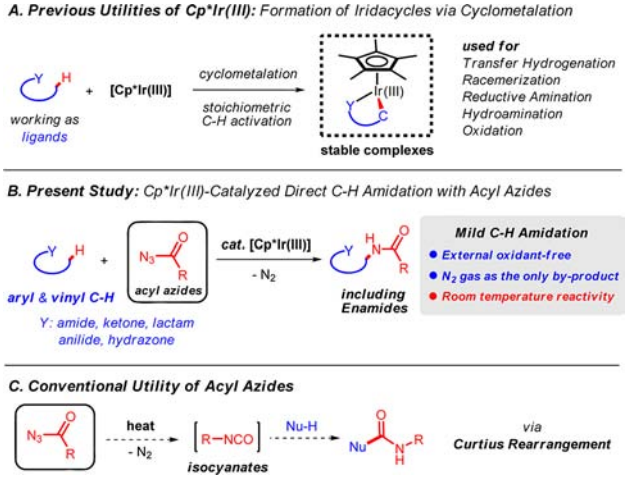


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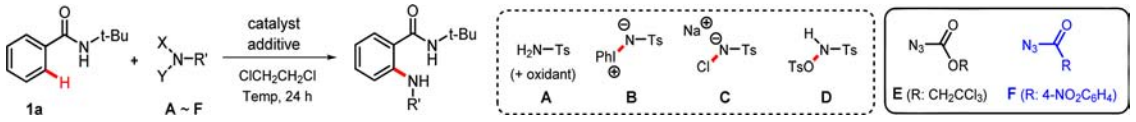
Table 1. Optimization of Direct C−H Amidation of Benzamide[a]



entry	catalyst (mol %)	additive (mol %)	N source	1a:A−F	temp (°C)	yield (%)[b]
1	$[IrCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)/*tert*-butyl peroxybenzoate (100)	**A**	1:1.5	80	6
2	$[IrCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)/$K_2S_2O_8$ (100)	**A**	1:1.5	80	<1
3	$[IrCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)/$Cu(OAc)_2$ (100)	**A**	1:1.5	80	<1
4	$[IrCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)	**B**	1:1.5	80	<1
5	$[IrCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)	**C**	1:1.5	80	<1
6	$[IrCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)	**D**	1:1.5	80	<1
7	$[IrCp^*Cl_2]_2$ (4)	$AgNTf_2$ (16)	**E**	1:1.1	80	23
8	$[IrCp^*Cl_2]_2$ (2)	$AgNTf_2$ (8)	**F**	1:1.1	25	95 (93)
9[c]	$[IrCp^*Cl_2]_2$ (2)	$AgNTf_2$ (8)	**F**	1:1.1	25	90
10	$[IrCp^*Cl_2]_2$ (1)	$AgNTf_2$ (4)	**F**	1:1.1	25	78
11	$[IrCp^*Cl_2]_2$ (2)	$AgBF_4$ (8)	**F**	1:1.1	25	48
12	$[IrCp^*Cl_2]_2$ (2)	$AgPF_6$ (8)	**F**	1:1.1	25	76
13	$[Ir(cod)Cl]_2$ (2)	$AgNTf_2$ (8)	**F**	1:1.1	25	<1
14	$Ir(acac)_3$ (2)		**F**	1:1.1	25	<1
15	$[RhCp^*Cl_2]_2$ (2)	$AgNTf_2$ (8)	**F**	1:1.1	25	8
16[d]	$[RhCp^*Cl_2]_2$ (4)	$AgNTf_2$ (16)	**F**	1:1.1	80	<5
17[d]	$[RhCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)	**F**	1:1.1	80	<5
18	$[RhCp^*(MeCN)_3](SbF_6)_2$ (4)		**F**	1:1.1	80	<1
19[d]	$[Ru(p\text{-cymene})Cl_2]_2$ (4)	$AgNTf_2$ (16)	**F**	1:1.1	80	24
20	$Pd(OAc)_2$ (4)	$PhI(OAc)_2$ (100)	**F**	1:1.1	80	<1
21	$Pd(OAc)_2$ (4)		**F**	1:1.1	80	<1

[a] **1a** (0.2 mmol), **A**−**F**, catalyst, additive, and 1,2-dichloroethane (0.5 mL) at the indicated temperature. [b] NMR yield (isolated yield in parentheses). [c] Ran for 10 min. [d] A side product resulting from reaction of **1a** with isocyanate generated in situ from **F** was formed in ca. 10%.[21]

Described herein is a new achievement of the (Cp*)Ir(III)-catalyzed direct C−H amidation of arenes and alkenes using acyl azides (Scheme 1B), in which the facile cyclometalating power of Cp*Ir(III) is combined with an additional role of acyl azides, working also as an internal oxidant to enable the catalytic cycle. A wide range of carbonyl azides bearing aryl, aliphatic, and olefinic groups could readily be employed at ambient conditions. In addition, our developed catalytic system was successfully applied to the olefinic C−H amidation to obtain *Z*-enamides.

Since acyl azides have been known to be *a facile carbon donor to furnish an amide group* upon conversion to isocyanates (Curtius rearrangement, Scheme 1C),[17] our present mild and selective catalytic protocol opens a novel methodology to utilize acyl azides as *the nitrogen donor of an acyl amino group*.

RESULTS AND DISCUSSION

Optimization of Reaction Condition. We first investigated the amidation activity of a dimeric cyclopentadienyl iridium complex $[Cp^*Ir(III)Cl_2]_2$, which was known to display high activity in a *stoichiometric cyclometalation* reaction with chelating group-containing arenes.[4,5] Benzamide **1a** was chosen as a test substrate to react with various types of amino sources (Table 1). *p*-Toluenesulfonamide (**A**) was not reacted with **1a** using $[Cp^*IrCl_2]_2$ in the presence of various oxidants such as *t*-butyl peroxybenzoate (entry 1), $K_2S_2O_8$ (entry 2), $Cu(OAc)_2$ (entry 3), $PhI(OAc)_2$, V_2O_5, $FeCl_3$, or $Ce(SO_4)_2$ (see Table S1 in the Supporting Information for details).[18] This result implies that the examined catalytic amination system is incompatible with *external oxidants*. As a result, we turned our attention to different nitrogen sources, potentially working also as an *internal oxidant* through a cleavage process, thereby avoiding the requirement of external oxidants for the catalytic turnover.

Among others examined, *N*-halogenated amines such as iminoiodinane (**B**) and chloramine-T (**C**), which were known to be facile nitrene sources,[19] did not show any reactivity under the employed catalytic system (entries 4−5). An additional attempt to initiate the desired catalytic cycle by cleaving N−O bond of *N*-sulfonyloxyamine (**D**) was not successful (entry 6). In contrast, we were pleased to see that acyl azides could readily be involved in the Ir-catalyzed C−H activation by reductive cleavage of their N−N bonds to give the desired C−H amidated products upon release of N_2. Whereas the use of an alkyloxycarbonyl azide **E** resulted in low yield (entry 7), benzoyl azide **F** was smoothly reacted at room temperature leading to *N*-acylaminobenzamide in excellent yield (entry 8).

The reaction was found to be highly facile even in a short period of time (10 min at 25 °C) or with a reduced amount of iridium catalyst (1 mol %), both of which provided satisfactory yields (entries 9−10). It should be addressed that the high reaction efficiency was maintained under the conditions using two reactants in an almost equimolar ratio (**1a**/**F**, 1:1.1). Silver additives convert the neutral metal precursor to its cationic species, and $AgNTf_2$ was observed to be most effective. It needs to be mentioned that benzoyl azides were not rearranged to the corresponding isocyanates under the present mild conditions, thus not allowing a side reaction to form a C−C bond.[20,21]

Other previously reported catalytic systems enabling a facile C−H cyclometalation process, in particular $[RhCp^*Cl_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$, were much less effective in this case (entries 15−19) even though they were shown to be active for the amination of arenes with sulfonyl, aryl, or alkyl azides at above 80 °C.[12] It was reasoned that more forcing conditions led

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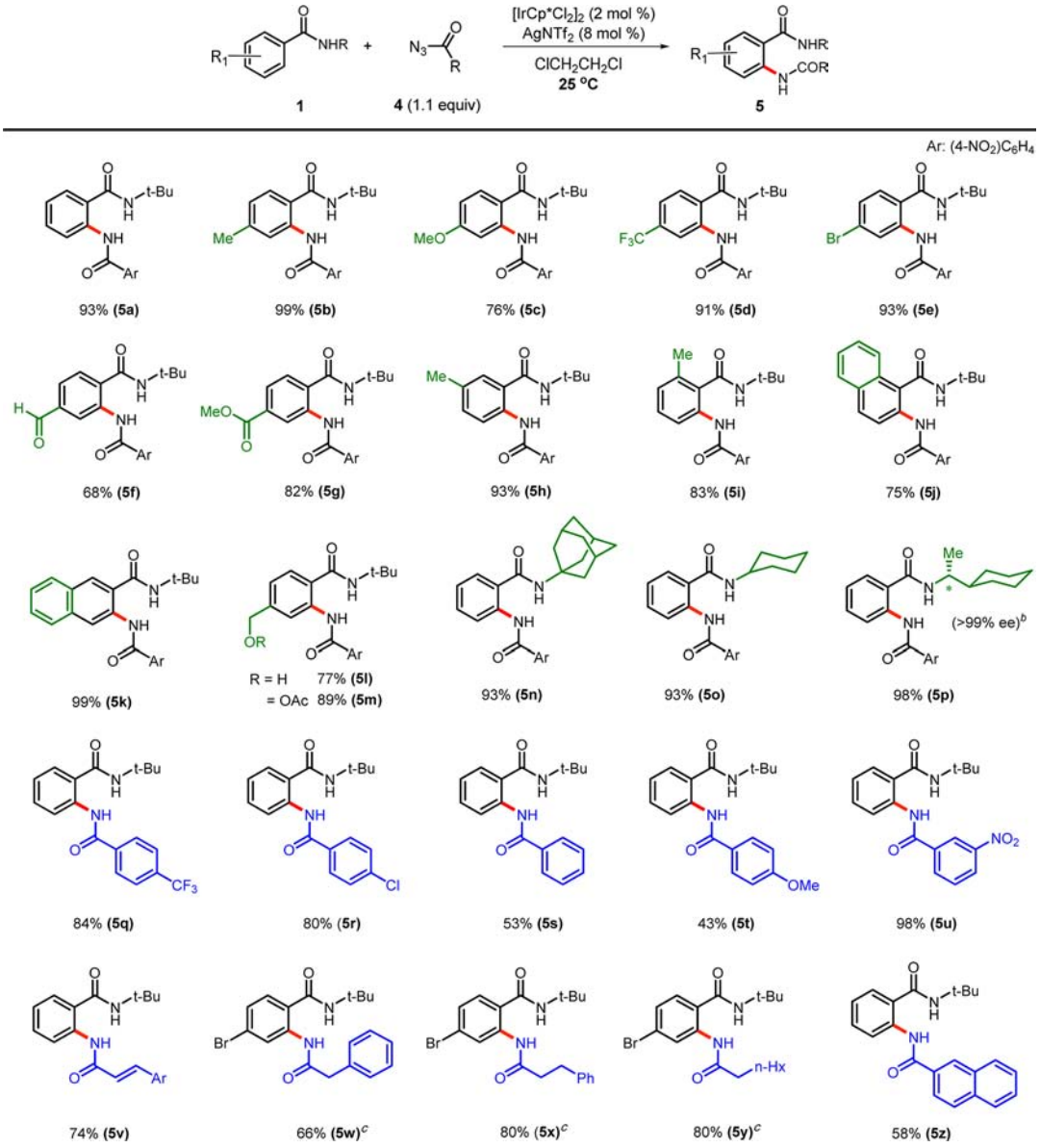
Table 2. Substrate Scope of the Ir-Catalyzed C−H Amidation of Benzamides[a]



[a]**1** (0.2 mmol) in 1,2-dichloroethane (0.5 mL) at 25 °C for 24 h (isolated yields). [b]Optical purity was checked by HPLC. [c]At 50 °C.

to the undesired thermal decomposition of acyl azides (Curtius rearrangement). The observation that a pregenerated cationic rhodium species $[RhCp^*(MeCN)_3](SbF_6)_2$ was also ineffective (entry 18) proved the unique catalytic activity of the present iridium system especially when acyl azides were used.

Reaction Scope. With the optimized conditions in hand, we next explored the substrate scope of benzamides bearing various substituents in reaction with various acyl azides to obtain structurally versatile 2-acylaminobenzamides (Table 2). It was observed that the reaction efficiency was maintained to be high irrespective of the electronic variation at the arene substituents of benzamides (**5a**−**5e**). Rather, product yields were more influenced by the substituents of benzoyl azides; electron-withdrawing groups afforded higher product yields (**5q**−**5u**). In addition, functional groups commonly used in organic synthesis were found to be compatible with the present Ir-catalyzed amination conditions. For instance, substrates bearing bromo (**5e**), aldehyde (**5f**) or ester (**5g**) moiety were smoothly amidated without difficulty. It is again worthwhile mentioning that this amination protocol is highly benign in that two reactants are employed almost in an equimolar ratio at ambient temperature to release N_2 as a single byproduct.

The position of substituents (*meta*- or *ortho*-) in benzamides did not influence the reaction efficiency (**5h** and **5i**, respectively). The reaction of naphthamides was highly regioselective favoring sterically more accessible sites (**5j**, **5k**). While an unmasked hydroxyl group was compatible with the present conditions (**5l**), an acetyl-protected derivative underwent the amidation in good yield (**5m**). Notably, the reaction efficiency was not diminished by the variation at the *N*-substituents of secondary amides (**5n**, **5o**), and a stereogenic center alpha to the amido nitrogen was completely conserved during the amidation process (**5p**). To our delight, we observed that not only benzoyl azides with variable substituents, but also different types of carbonyl analogues such as cinnamoyl (**5v**) and aliphatic acyl azides (**5w**−**5y**) were readily reacted in good yields albeit at slightly higher temperatures (50 °C), hence

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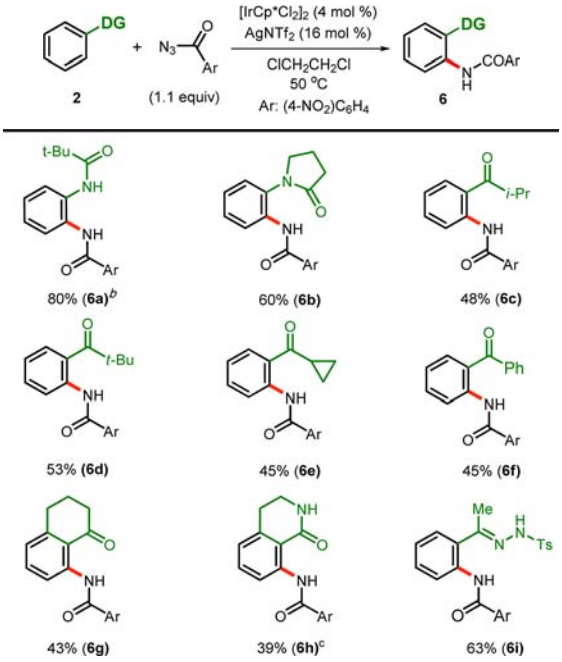
significantly extending the synthetic utility of the present direct C−H amidation approach.

We also found that that *the present catalytic system displayed a general applicability toward various directing groups* (Table 3).

Table 3. Direct C−H Amidation of Other Chelate Group-Containing Substrates[a]

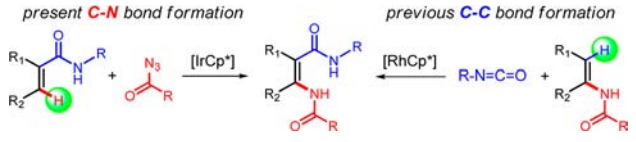


[a]**2** (0.2 mmol) in DCE (0.5 mL) at 50 °C for 24 h (isolated yields). [b]Substrate (1.8 equiv) and azide (0.2 mmol) were used. [c]$[IrCp^*Cl_2]_2$ (2 mol %) and $AgNTf_2$ (8 mol %) were used.

This aspect is significant in that the scope of chelate groups in the previously reported amination reactions was often limited or highly specified, thus narrowing the synthetic utility of known procedures.[9,10] In the present study, substrates bearing diverse chelate groups such as acylamido (**6a**), pyrrolidone (**6b**), acyclic- or cyclic ketones (**6c**−**6f** and **6g**, respectively), lactam (**6h**), and hydrazone (**6i**) moieties all underwent the *ortho*-amidation in acceptable yields under slightly more forcing conditions (4 mol % of catalyst at 50 °C).

Synthetic Utilities. The conventional usage of acyl azides is mostly based on the Curtius rearrangement under thermal conditions leading to isocyanates which are subsequently allowed to react with nucleophiles to produce *N*-substituted amides (*carbon source*). In addition, it was recently demonstrated that isocyanates could be utilized in the metal-mediated direct C−H functionalization of arenes or alkenes.[21] On the other hand, our current chemistry offers a new synthetic utility of acyl azides to furnish acylamino molecules (*nitrogen source*). It is also interesting to note that the two approaches are complementary to each other leading to the almost identical products by employing different starting materials (Scheme 2).

Scheme 2



Amino-containing compounds directly accessible through our method have versatile utilities in such areas as organic synthesis, coordination chemistry, and pharmaceutical industry.[22] The *ortho*-relationship between the pre-existing chelate-group and a newly introduced acyl amido moiety gives an additional opportunity to synthesize various privileged nitrogen-containing heterocycles according to the previously known cyclization procedures (Figure 1a).[23] In addition, synthetic

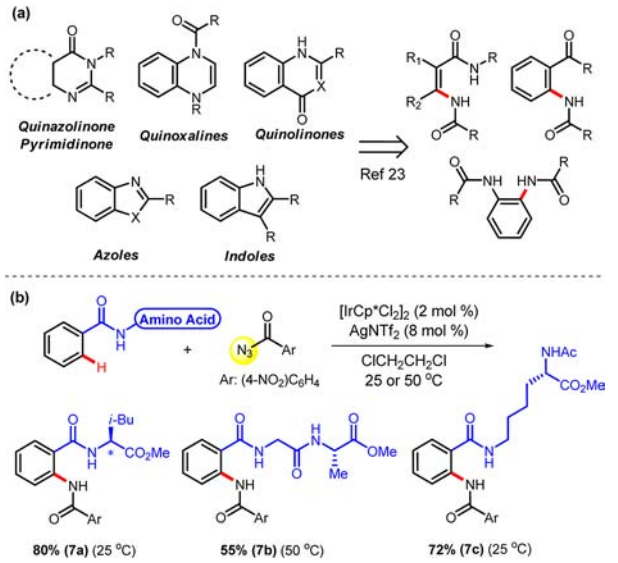


Figure 1. (a) Potential utilities of the amidated products obtained in this study. (b) Synthesis of benzanilides bearing peptides using the present Ir-catalyzed C−H amidation.

modulations through the transformation of chelate groups (e.g., amide and ketone) after the desired C−H functionalization have been established.[12b,c,24] For instance, a tosylhydrazone, which was found to be an efficient directing group in our reaction (Table 2, **6i**), is a versatile precursor for various functional groups.[24d]

As a notable synthetic application of our current approach, a series of *N*-acylaminobenzamides bearing peptides was readily synthesized by the Ir-catalyzed amidation reactions, thereby demonstrating feasibility of the present procedure with potential applicability in peptide chemistry (Figure 1b).

Direct Enamide Synthesis. Enamides are present as a key structural motif in numerous natural products and drug candidates (Figure 2). They also serve as a versatile synthetic intermediate, especially in the formation of heterocycles or in asymmetric chemistry.[25]

As a result, various metal-catalyzed approaches complementary to the conventional methods have been extensively investigated (Scheme 3A).[26−29] However, broad substrate scope and mild reaction conditions have yet to be improved in most approaches. More critically, a high degree of stereoselectivity for the formation of thermodynamically unfavorable *Z*-enamides is not being fully addressed with the precedent procedures. Therefore, we envisioned that it would be highly desirable to synthesize stereodefined enamides via our current C−H amidation chemistry (Scheme 3B).

We were delighted to observe that the present iridium catalyst system allows *a direct access to Z-enamides with excellent regio- and stereoselectivity* presumably guided by the chelation-assisted olefinic C−H metalation (Table 4). Methacrylamides

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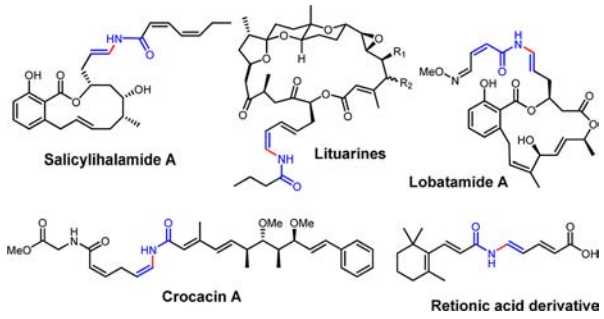
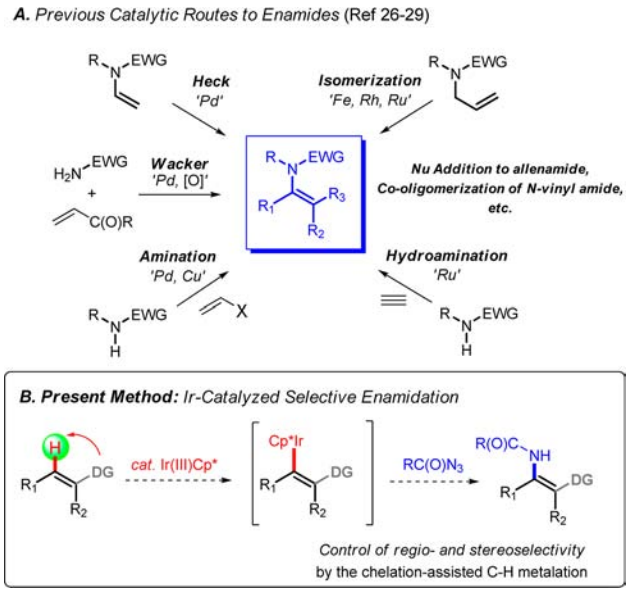


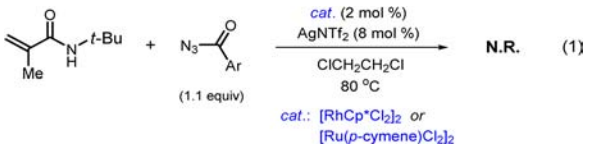
Figure 2. Some examples of natural and pharmaceutical products containing an enamide group.

Scheme 3

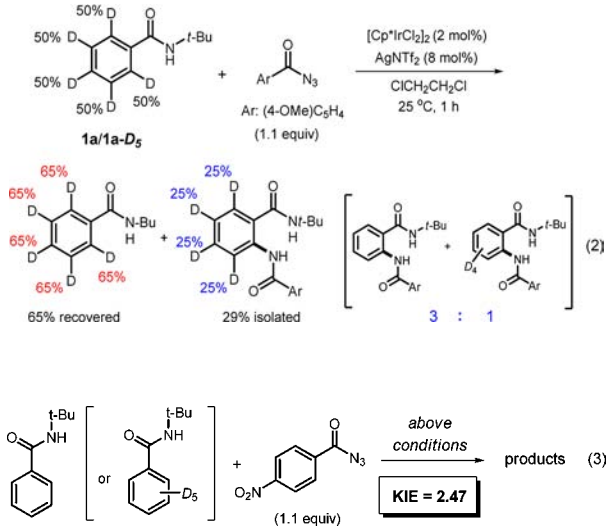


were reacted at 50 °C with benzoyl (**8a**), cinnamoyl (**8b**), and aliphatic acyl azides (**8c**). Electronically varied benzoyl azides gave slightly decreased product yields (**8d**, **8e**). Alpha-substituents other than a methyl group were also found to be effective (**8f**–**8j**). In particular, an ester moiety was tolerant to give a highly functionalized *Z*-enamide (**8g**). In addition, substrates bearing trisubstituted olefinic C–H bonds were selectively amidated (**8h**–**8j**). Variation at the *N*-alkyl amido moiety was also possible, even with the inclusion of a free hydroxyl group (**8k**–**8r**). *Z*-Enamides were formed exclusively in all cases, and their stereochemistry was unambiguously confirmed by H NMR and X-ray crystallographic analysis.

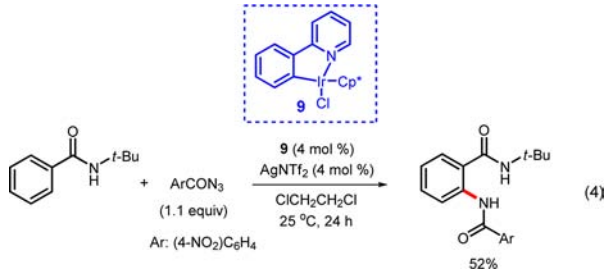
It was also noteworthy that the reactivity of acyl azides as the nitrogen source was special to the iridium catalyst system since both rhodium and ruthenium catalysts were not effective in the direct C–H enamidation of methacrylamides under otherwise similar conditions (eq 1).



Mechanistic Studies on the Present Reaction. To shed light on the mechanistic aspects of the Ir(III)-catalyzed direct C–H amidation, a series of preliminary mechanistic studies was carried out (see the Supporting Information for details). A competition reaction between equimolar amounts of *N*-*tert*-butylbenzamide (**1a**) and its deuterated analogue (**1a**-d_5) revealed that the C–H bond cleavage is irreversible in the presence of acyl azide since no H/D scrambling was observed (eq 2). A primary kinetic isotope effects (k_H/k_D = 2.47) was



observed from an intermolecular competition reaction (eq 3), suggesting that the C–H bond activation will likely be involved in the rate-limiting stage. Importantly, an isolated iridacyclic intermediate **9**,[5c] after treating it with a silver additive, catalyzed the direct amidation with benzoyl azide to indicate that the cationic metalacycle is indeed an active species during the course of catalysis (eq 4).



Based on the above experimental results and precedent literature,[5,30–32] a mechanistic proposal of the present Ir-catalyzed direct C–H amidation reaction is shown in Figure 3. Upon the initial generation of a cyclometalated intermediate **I**[5] with one vacant site accessible, azide will interact with the cationic metal center. It is now proposed that the formation of an iridium nitrenoid species **III** from azide-bound complex **II** occurs in an oxidative manner to release N_2 molecule.[30,31] Insertion of the nitrenoid moiety into iridacycle will follow to form a new C–N bond of **IV** that is finally protodemetalated to deliver an amidated product (**B**). Along with this consideration, a stoichiometric insertion of nitrenoid precursors into iridacyclic complexes was previously reported as leading to 6-membered imido metalacyclic species.[32] However, a concerted pathway generating **IV** directly from **II** without the intervention of **III** cannot be ruled out at the present stage. We suggest that the redox process in the reaction of azides with cyclometalated iridium species is quite feasible presumably due to the entropic

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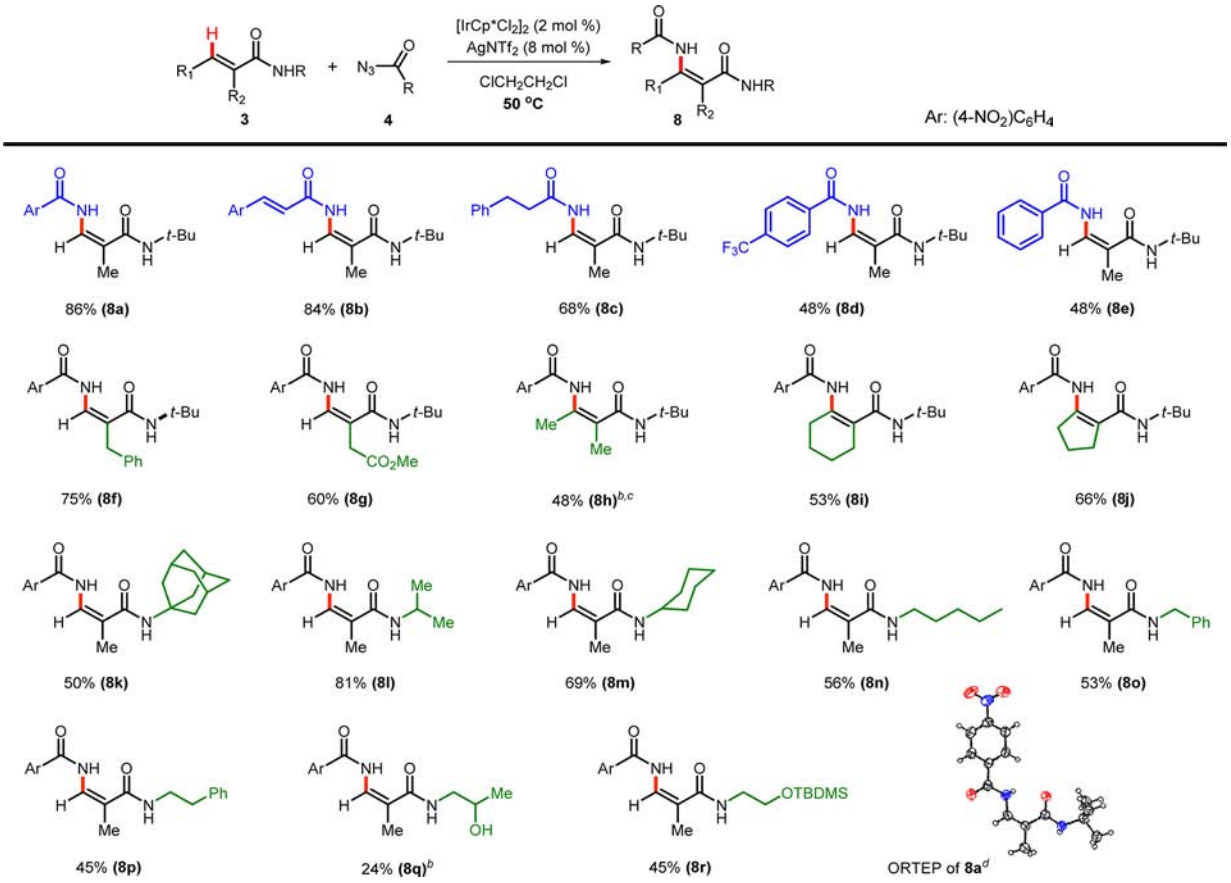
Table 4. Iridium Catalyzed Direct Amidation of Olefinic C−H Bonds[a]



[a]**3** (0.2 mmol) in DCE (0.5 mL) at 50 °C for 24 h (isolated yields). [b][IrCp*Cl_2]$_2$ (4 mol %) and $AgNTf_2$ (16 mol %) were used. [c]At 25 °C. [d]Ellipsoid displacement with 50% probability.

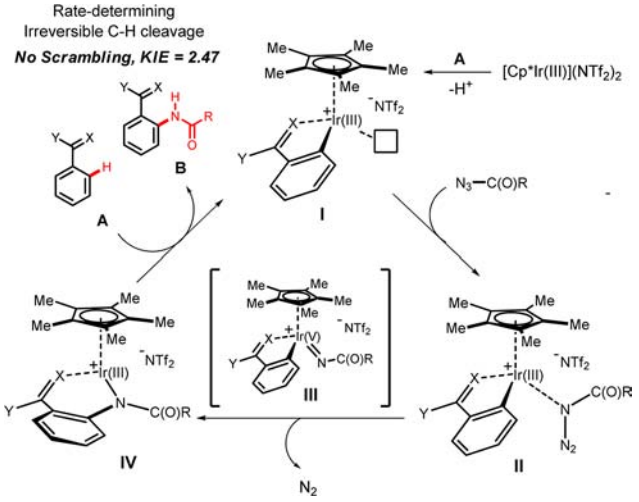


Figure 3. Simplified mechanistic proposal.

contribution upon the release of N_2, thereby driving the desired C−N bond formation with high efficiency.

CONCLUSIONS

In summary, we have developed the iridium-catalyzed direct C−H amidation of arenes and alkenes using acyl azides as the novel nitrogen source. The inherited power of cyclopentadienyl Ir(III) complexes toward the C−H bond activation was properly combined with the use of azides that additionally work as an internal oxidant leading to mild reaction conditions. This amidation approach does not require external oxidants and releases N_2 as its single byproduct, thus offering an environmentally benign procedure. The substrate scope of both arenes and acyl azides was found to be very broad, displaying high functional group tolerance. The present iridium catalyst system was also successfully applied to the direct C−H amidation of olefinic double bonds leading to *Z*-enamides with a complete control of regio- and streoselectivity. Further applications and mechanistic studies including DFT calculations are now underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H, ^{13}C NMR spectra, and X-ray analysis). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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