CHEMISTRY
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201702397

Link to VoR: http://dx.doi.org/10.1002/chem.201702397

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Mechanism-Driven Approach to Develop a Mild and Versatile C–H Amidation via Ir(III) Catalysis

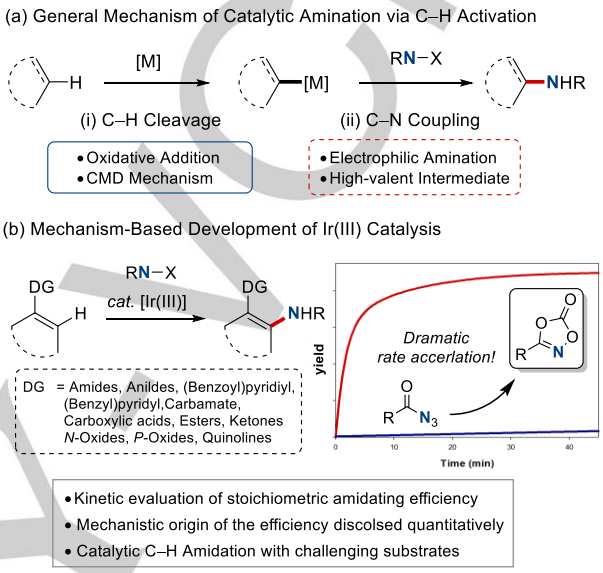
Yeongyu Hwang,[+] Yoonsu Park,[+] and Sukbok Chang*

Abstract: Described herein is a mechanism-based approach to develop a versatile C–H amidation protocol under Ir(III) catalysis. Reaction kinetics of a key C–N coupling step with acyl azide and 1,4,2-dioxazol-5-one led us to conclude that dioxazolones are much more efficient in mediating the formation of carbon–nitrogen bond from an iridacyclic intermediate. Computational analysis unraveled that the origin of higher reactivity is placed on asynchronous decarboxylation motion, which may facilitate the formation of Ir-imido species. Importantly, stoichiometric reactivity was successfully translated into the catalytic activity with a broad range of substrates (18 different types of substrates), many of which were regarded as challenging to functionalize. Applying the new method enables the late-stage functionalization of drug molecules.

Introduction

Catalytic C–H activation mediated by transition metals enables diverse functionalization of unactivated hydrocarbons in a straightforward manner.[1] Growing demands of utilizing the technique in multiple disciplines[2] promote the development of efficient catalysts capable of selectively targeting specific C–H bonds. From a fundamental perspective, understanding the mechanistic details of the catalysis may provide a solution to properly modulate the performance of the catalysts. Indeed, seminal mechanistic studies have provided valuable insights to drive further directions, thus triggering the improvement in catalytic performance.[3]

Among various C–H functionalization reactions, C–H amination constitutes a valuable route to introduce an amino functionality into hydrocarbon substrates.[4] Challenges in achieving efficient C–H amination catalysis mainly lie on facilitating two key steps depicted in Scheme 1a. A number of strategies, such as oxidative addition or concerted-metalation deporotonation (CMD) mechanism, have been devised to facilitate C–H bond cleavage to afford a metallacyclic intermediate.[5] Another challenge is to retain facile C–N coupling in reactions with an aminating agent. In constrat to the C–H cleavage, only few of understandings on the C–N couplings were revealed to date with Cu,[6] Pd,[7] and Rh[8] catalysis. Consequently, lack of principles on the C–N formation prevents a rational design of effective reagents and catalysts. In essence, which factors can affect the stoichiometric formation of carbon–nitrogen bond? How can we rationally improve efficiency of the catalytic systems? By addressing those fundamental issues, mild and versatile amination could be rationally achieved.



Scheme 1. Mechanism-based development of C–H amidation. DG= directing group.

Herein, we described such a study to develop a new amidation protocol with Ir(III) catalyst, which was guided by insights gained from the study of stoichiometric C–N coupling. Integrated kinetic and computational analysis unraveled the secret underlying the formation of high-valent Ir species, and such implications enabled us to disclose versatile catalyst system applicable to a broad range of challenging substrates, including those not reactive with previously reported procedures.

Our group has recently elucidated mechanistic details on the C–N coupling process with group 9 Cp*M(III)-based catalysts with various aminating agents.[8a] We demonstrated that a rhodacyclic complex was successfully coupled with sulfonyl azides, affording C–N coupled Rh-amido complex at elevated temperature.[8b] Our continued efforts to develop mild C–H amination enabled us to scrutinize a new type of amidating agents 1,4,2-dioxazol-5-ones,[9] which display superior ability in mediating C–N coupling reactions. Detailed mechanistic studies strongly corroborated the involvement of organometallic Rh(V) and Ir(V)-imido species as the key intermediates.[8d] This notable outcome ignited extensive subsequent studies with dioxazolones as the amide source, especially focusing on the development of Rh(III),[10] Ru(II),[11] or Co(III)[12] catalysts, leading to broad applications in the facile preparation of synthetic valuables.[13]

Although dioxazolones have been taken much spotlights recently, the origin of high catalytic activity is underexplored. For instance, it is intriguing to see whether the effectiveness of dioxazolone can also be applicable to other systems. In this regards, we wondered if the superior reactivity of dioxazolones in the C–N coupling would still be conserved in the isolobal Ir(III)-based system. As the Ir(III) catalysts were continuously proven to be effective for activating *ortho* C–H bonds of

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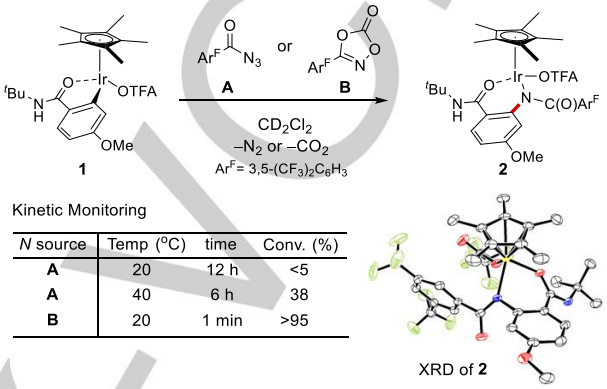
substrates bearing various directing groups including synthetically useful functional moieties,[14] a valuable amidating protocol would be anticipated if appropriate amidating agents were employed. It should be noted that recent studies on the Rh(III) and Co(III)-catalyzed C–H amidation with dioxazolones are mostly limited to nitrogen-based directing groups, which are laborious for the post-functionalization.[8c,10a,12-13,15]

Results and Discussion

To test the hypothesis, we commenced our study by designing a stoichiometric model reaction to evaluate the kinetics of the C–N coupling. A well-defined iridacycle **1**, known as an intermediate in catalytic C–H amination,[16] was subjected to the key C–N bond formation (Scheme 2). When iridacycle **1** was exposed to acyl azide **A** at ambient temperature, no detectable conversion was observed by ^{1}H NMR spectroscopy in 12 h. Upon heating the reaction mixture to 40 °C for 6 h, 38% of **1** was converted to a new iridium species. Surprisingly, the same transformation was completed within one minute at 20 °C by replacing the azide by 1,4,2-dioxazol-5-one **B**. Indeed, composition of the emerging iridium complex was characterized as a C–N coupled Ir-amido complex **2**: the solid-state structure of **2** was confirmed by a single crystal XRD analysis.[17]

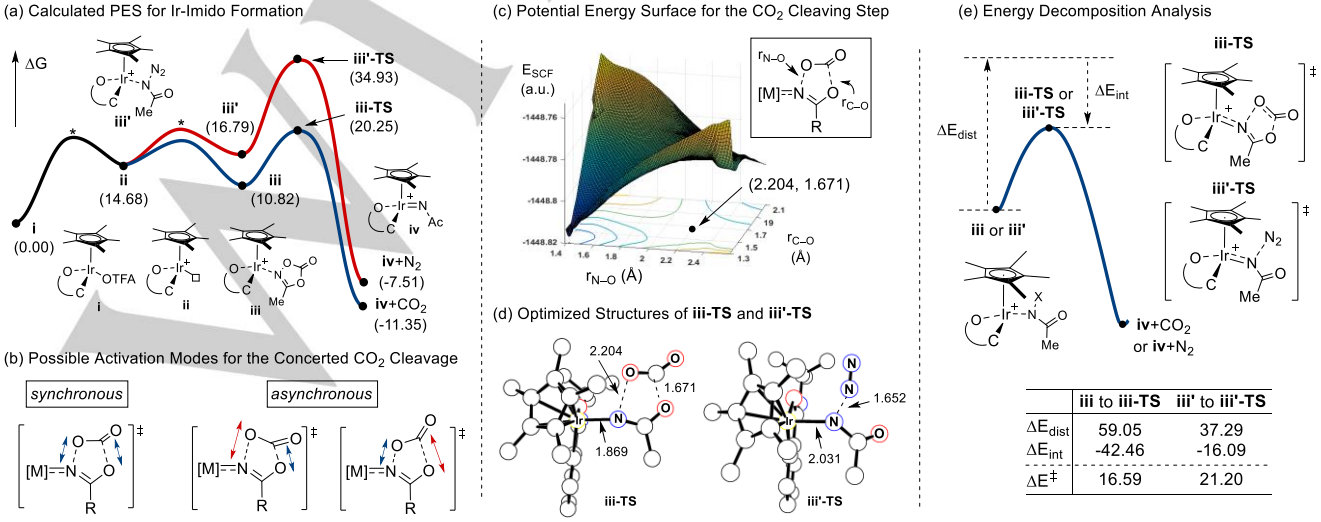
To understand the significant kinetic difference induced by the type of amidating agents, a series of theoretical studies were conducted. First, reaction energy profile was evaluated with two amidating agents based on the widely-accepted mechanism (Figure 1a).[8c,d] The mechanism constitutes three key steps: ligand exchange with an amidating agent, oxidative formation of a metal–imido species, and subsequent C–N reductive elimination. Dissociation of OTFA anion in complex **i** yields a coordinatively-unsaturated cationic species **ii**. Subsequent coordination of azide to form **iii'** requires 2.1 kcal/mol, whereas dioxazolone coordination to form **iii** is favored by 3.9 kcal/mol. Importantly, adduct species **iii** and **iii'** are able to form the same Ir-imido species **iv** by extruding CO_2 and N_2, respectively, and despite the similar oxidative processes, computed reaction barriers displayed notable differences in energy: the CO_2 liberation easily takes place by traversing **iii-TS** with only 9.5 kcal/mol of kinetic barrier, whereas the transition state for N_2 dissociation from azide adduct **iii'** lies at 18.1 kcal/mol higher in energy. In consequence, the net reaction barriers to form Ir-imido species from complex **i** are 20.3 and 34.9 kcal/mol with dioxazolone and acyl azide, respectively. These computed values are in qualitative agreement with experimentally observed reactivity in Scheme 2.



N source	Temp (°C)	time	Conv. (%)
A	20	12 h	<5
A	40	6 h	38
B	20	1 min	>95

Scheme 2. Stoichiometric C–N coupling with acyl azide and dioxazolone.

Analyzing the differences in the Ir-imido formation, we noted that cleaving motions of N_2 and CO_2 are fundamentally different. A two-bond cleaving event for CO_2 liberation has the higher structural degree of freedom than a single-bond dissociation step for the N_2 clevage. Whereas the monotonic N–N_2 elongation is the only possible movement in the dediazotization of acyl azides, a few distinctive modes can be considered in the decarboxylation process of dioxazolones: concerted and stepwise cleavages of N–O and C–O bonds. Because we were unable to locate any physically meaningful intermediates for stepwise mechanism, that cleaving motion was excluded for further considerations. On the other hand, another classification can be made within the concerted mechanism. The N–O and C–O cleavages may take place either simultaneously (synchronously) or independently (asynchronously, Figure 1b).



	iii to iii-TS	iii' to iii'-TS
ΔE_{dist}	59.05	37.29
ΔE_{int}	-42.46	-16.09
$\Delta E^{\ddagger}$	16.59	21.20

Figure 1. Computational mechanistic investigation on the stoichiometric C–N coupling.

To carefully distinguish the translational motion, conformational searches by systematically varying the lengths of the N–O (r_{N-O}) and C–O (r_{C-O}) bonds were performed, as described in Figure 1c.[17] The resulting PES and its contour plot clearly indicated that the concerted cleaving motion is asynchronous: the saddle point on the PES is placed on around 2.2 Å of N–O and 1.7 Å of C–O bonds, similar to that of optimized **iii-TS** in Figure 1d. Any other critical points were not found on other locations, corroborating the singularity of concerted asynchronous TS in decarboxylation process.

We sought to understand how the asynchronicity affects the reaction barrier. For this purpose, energy decomposition analysis was performed to elucidate underlying electronic influence (Figure 1e). The electronic energy difference between **iii** and **iii-TS** was 4.6 kcal/mol lower than the transformation from **iii'** to **iii'-TS**, implying that electronic reorganizations in transition states gave rise to the differences in the activation barriers. While total distortion energy (ΔE_{dist}) is more required for liberating CO_2 (59.1 kcal/mol) than that for dediazotization (37.3 kcal/mol), total interaction energy (ΔE_{int}) between the Cp*Ir fragment and dioxazolone moiety is much stronger (-42.5 kcal/mol) than that between analogous fragments for **iii'-TS** (-16.1 kcal/mol), thus making the net electronic barrier lower in energy. These energetic components, for the first time, suggested that the electronic communication between Ir–N(dioxazolone) is much developed on the **iii-TS** than that of Ir–N(azide) on the **iii'-TS**. We rationalized that such strong interaction is only possible with dioxazolone because asynchronous CO_2 cleavage maximizes the formation of empty *p*-orbital in nitrogen, thus making stronger overlap between Ir(d_π)–N(p*).[8d] As shown in Figure 1d, shorter Ir–N(dioxazolone) (1.87 Å) than Ir–N(azide) (2.03 Å) further supports the stronger Ir–N bonding.

Having the importance of synchronicity in the amidating agent, we speculated that utilizing dioxazolones in catalytic reaction possibly reduce the energetic span, thus leading to a more efficient and robust C–H amidation procedure. To overview general trends, four representative substrates, quinoline *N*-oxide, enamide, enone, and acetophenone, were selected and subjected to catalytic conditions (Figure 2). Significantly, the catalytic amidations of the first three substrates were much faster in reaction with dioxazolone.[18] When quinoline *N*-oxide was monitered, it was readily amidated with dioxazolone **B** while the azide analogue **A** was not reacted at all. (Figure 2a). In a reaction of enamide substrate (Figure 2b), more pronounced rate acceleration was observed: the initial rate with dioxazolone **B** was at least ~367 times faster. As another notable example, enone substrate was reacted almost exclusively with dioxazolone while amidation with **A** did not proceed (Figure 2c). In sharp contrast, reaction rates of acetophenone substrate were rather similar with both amidating sources. It suggested that lowering the C–N coupling barrier did not affect kinetic performance of the catalytic reaction. The similar kinetics observed from **A** and **B** suggested that C–N coupling may not be involved in the turnover-limiting stage. A primary kinetic isotope effect (KIE; k_H/k_D = 2.1) corroborated that C–H bond cleavage is likely involved in a rate-limiting step. (Figure S5)

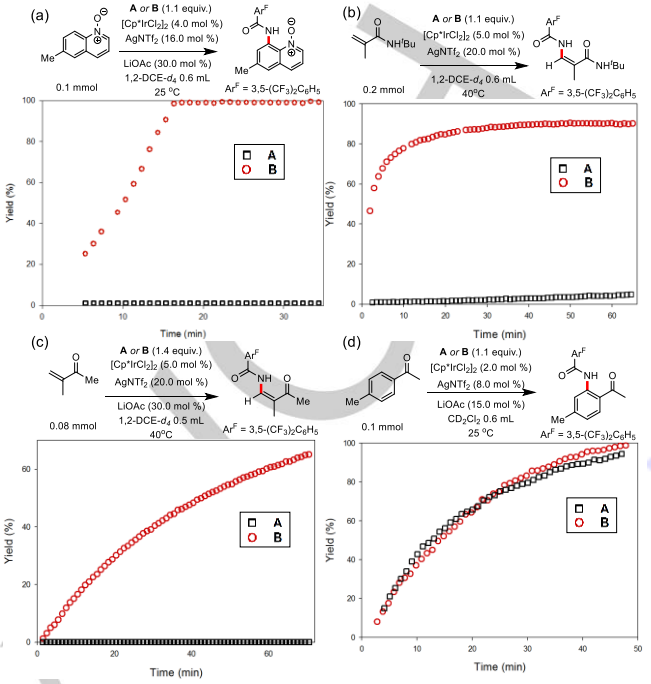
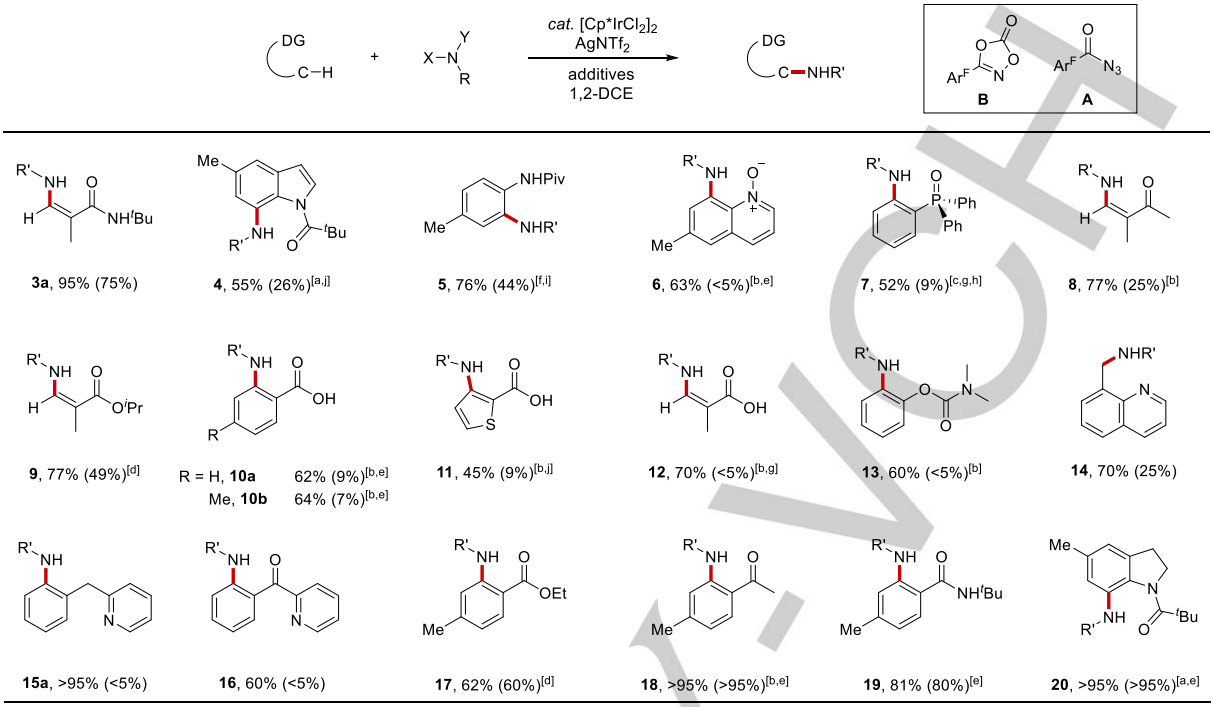


Figure 2. Comparative catalytic ^{1}H NMR reaction profiles with acyl azide and dioxazolone. R= C(O)Ar^F.

To test whether the efficiency of dioxazolone is maintained in general, various types of substrates were further subjected to the catalytic reactions with both dioxazolone and acyl azide (Scheme 3). To our delight, a truly diverse range of substrates, which displayed moderate to poor reactivity with acyl azides, were readily amidated with dioxazolone. Enamides were selectively amidated in satisfactory yields (**3a**) and *N*-pivaloylindole was amidated exclusively at the C-7 position in moderate yield (**4**). *N*-Pivaloylanilide was also efficiently amidated (**5**) and quinoline *N*-oxide was amidated at the C-8 position with dioxazolone only (**6**) while the corresponding benzoyl azide was not reacted at all. Triphenylphosphine oxide was amidated in moderate yield (**7**). Vinyl moiety in enone and methacrylate was amidated stereoselectively to furnish synthetically valuable *Z*-enamide products in good yields (**8**–**9**). Carboxylic acid was found to serve as an effective directing group in the current C–H amidation with dioxazolone. Indeed, benzoic acids, 2-thiophenecarboxylic acid, and methacrylic acid were all amidated in satisfactory yields (**10**–**12**). Again, the amidation efficiency in reactions of those carboxylic acids with azide was seen to be much poorer. In addition, an amidation of *N,N*-dimethylphenyl carbamate occurred smoothly (**13**).

Not only sp^2 but also sp^3 C–H bond was readily amidated in case of 8-methylquinoline (**14**). Interestingly, the reaction of 2-benzylpyridine was efficient (**15a**), where a 6-membered iridacycle intermediate will be formed *in situ*. In contrast, the same reaction with acyl azides was totally ineffective. 2-Benzoylpyridine was amidated in satisfactory yield (**16**). Interestingly, a few substrates displayed similar amidation efficiency between two amidating reagents. For instance, arene sp^2 C–H bonds of benzoate and acetophenone derivatives were amidated equally well (**17**–**18**). Likewise, benzamide and *N*-

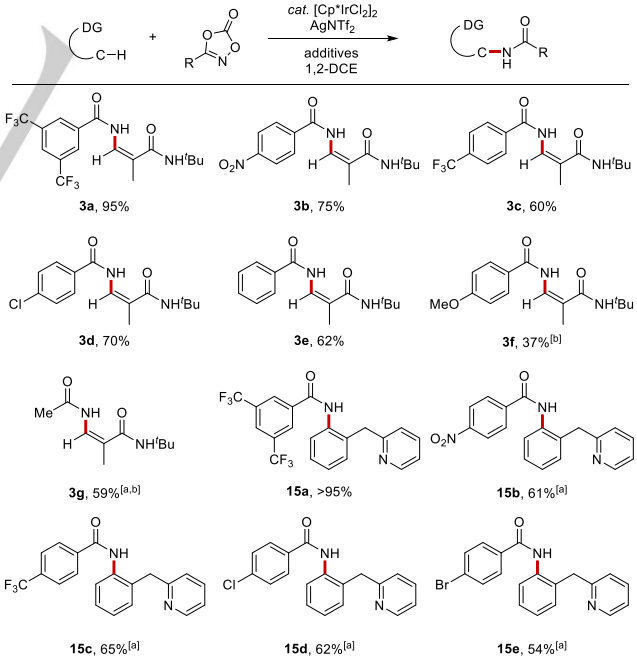


Scheme 3. Substrate scope with **B** as the amide source. Yields with **A** are in parenthesis. Reaction conditions: substrate (0.1 mmol), amino source (1.1 equiv), $[Cp^*IrCl_2]_2$ (4.0 mol %), and $AgNTf_2$ (16.0 mol %) at 50 °C for 12 h. R'= $C(O)Ar^F$. Additives: [a] AgOAc (30.0 mol %). [b] LiOAc (30.0 mol %). [c] AcOH (30.0 mol %). [d] AcOH (15.0 mol %) and Li_2CO_3 (15.0 mol %). Temperature: [e] Room temperature. [f] 30 °C. [g] 40 °C. Reaction time: [h] 5 h. [i] 6 h. [j] 24 h.

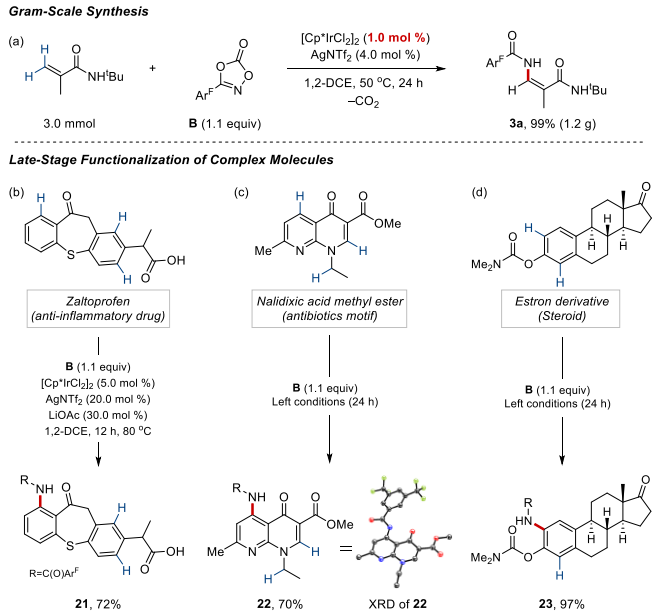
pivaloylindoline underwent the C–H amidation in excellent yields in each case (**19**–**20**). It is noteworthy that the amidation product yields were always greater or equal in reactions with dioxazolone when compared to those with acyl azide even after longer period (12 h), thereby implying that kinetic efficiency is maintained over the course of the C–H amidation progresses.

The scope of dioxazolone amidating reagents was reasonably broad to efficiently install benzoyl amido groups bearing electron-withdrawing and neutral substituents (Scheme 4). However, phenyldioxazolone having an electron-donating group was less effective (**3f**).

The current C–H amidation showed great reactivity also in large scale synthesis (Scheme 5a). Introduction of amino functionality into enamide could be conducted in a gram scale in excellent yield with low catalyst loading. Synthetic utility of the present C–H amidation protocol was next briefly examined. We were pleased to see that our current procedure was successfully adapted in the selective direct C–H amidation of highly functionalized drugs or their derivatives (Scheme 5b-d). For example, Zaltoprofen, known as anti-inflammatory drug,[19] was readily amidated in high yield (**21**). Significantly, the existing carboxylic acid and thio groups did not inhibit the reaction efficiency under the present conditions. In addition, methyl ester of Nalidixic acid[20] was selectively amidated at the C-5 position (**22**), and its structure was unambiguously characterized by an X-ray crystallographic analysis.[17] Carbamate derivative of Estron was also successfully amidated at the sterically more accessible site in excellent yield (**23**).



Scheme 4. Substrate scope with various dioxazolones. Reaction conditions: substrate (0.1 mmol), 1,4,2-dioxazol-5-one (1.1 equiv), $[Cp^*IrCl_2]_2$ (4.0 mol %), and $AgNTf_2$ (16.0 mol %) at 50 °C for 12 h. [a] At 80 °C. [b] For 24 h.



Scheme 5. Synthetic applicability.

Conclusions

In summary, we showcased that the understanding of kinetics on the stoichiometric C–N coupling path enabled the development of efficient catalytic C–H amidation. Theoretical investigations unrevealed that asynchronous nature of the decarboxylation process is the key feature of dioxazolones to serve as an efficient amidating agent. Synthetic utility and applicability of the new catalysts system in combination with dioxazolones were successfully validated with a broad range of challenging substrates, drugs and bioactive molecules. We anticipate that the strategy disclosed herein may serve as an inspiring example for the the rational appraoch towards the developemnt of efficient C–H functionalziations.

Acknowledgements

This research was supported by the Institute for Basic Science (IBS-R010- D1).

Keywords: C–H amination, C–N coupling, dioxazolones, iridium catalysis, late-stage C–H functionalization

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10.1002/chem.201702397

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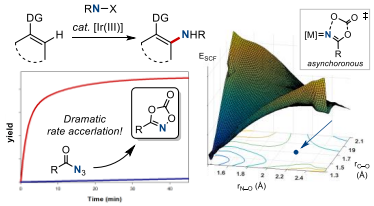

Having asynchronous transition state was identified as a secret for an efficient amidating agent in catalytic C–H amidation. Combined reaction kinetics and theoretical study guided the development of versatile Ir(III) catalysis with various challenging substrates, including late-stage functionalization of drug molecules.

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