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Synthetic Utility of *N*-Benzoyloxyamides as an Alternative Precursor of Acylnitrenoids for γ-Lactam Formation

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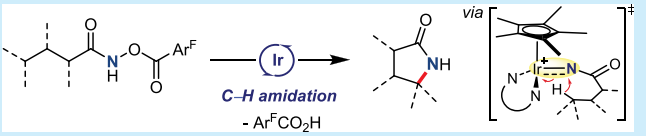
Supporting Information

ABSTRACT: Described herein is the development of a new entry of acylnitrenoid precursors for γ-lactam synthesis via an intramolecular C−H amidation reaction. Upon Ir catalysis, *N*-benzoyloxyamides serve as efficient substrates to afford 5-membered amides. Mechanistic studies revealed that the generation of a putative Ir−carbonylnitrenoid via N−O bond cleavage is facilitated by the chelation of countercations. This protocol offers a convenient and step-economic route to γ-lactams starting from the corresponding carboxylic acids.



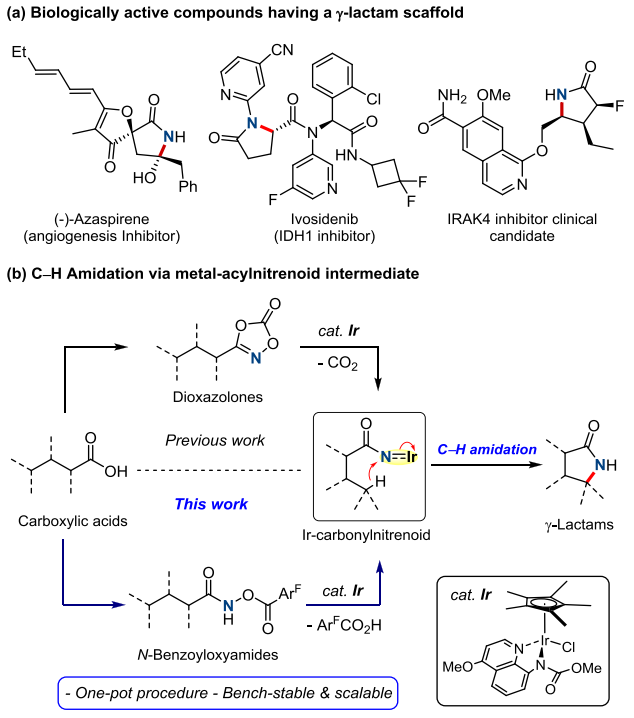
Cyclic amides are ubiquitous in alkaloid natural products and biologically active compounds.[1] In particular, γ-lactams are a privileged scaffold that is widely present in important pharmaceutical agents (Scheme 1a).[2] Therefore, the development of efficient and selective synthetic routes to this 5-membered amide starting from readily available compounds is of great interest. For example, Gaunt et al. developed a C−H carbonylative cyclization of secondary aliphatic amines using carbon monoxide to give functionalized lactams.[3] In addition, Schoenebeck and Rovis reported the transformation of primary amines to lactams via α-alkylation.[4]

On the other hand, a group-transfer approach based on the metal−acylnitrenoid intermediacy is also appealing in the construction of cyclic amides.[5] However, this method has been challenging mainly due to the difficulty in controlling the reactivity of the putative carbonylnitrene intermediates since they are prone to decompose to isocyanates via a Curtius-type rearrangement.[6] Recently, we showed that (pentamethyl)-cyclopentadienyl (Cp*)-based Ir complexes with engineered bidentate ligands display an unprecedented performance in catalytic C−H amidation of dioxazolones with effective suppression of such a side pathway (Scheme 1b, top).[7] The high reactivity was attributed to the modulated Lewis acidity of the Ir metal center in the tailored catalysts, thereby facilitating an oxidative coupling of dioxazolone substrates to generate the key Ir−nitrenoids. This approach allows a facile access to a broad range of γ-lactams starting from readily available carboxylic acids even in an asymmetric manner.[7c]

As part of our research program toward the development of selective and efficient C−H amidation reactions,[8] we wondered whether an alternative type of nitrene precursors in lieu of oxazolones could be applied in our Cp*Ir catalyst systems. Herein, we present a synthetic utility of *N*-benzoyloxyamides as an efficient substrate for the γ-lactam synthesis via a C−H insertion pathway (Scheme 1b, bottom).

Importantly, *N*-benzoyloxyamide derivatives display comparable reactivity with dioxazolones as a carbonylnitrenoid precursor under the employed Ir catalyst system. Moreover, *N*-benzoyloxyamides can be readily prepared from the corresponding carboxylic acids, and they are easy to handle and stable to storage. Experimental and theoretical studies revealed that the observed reactivity of *N*-benzoyloxyamides is

Scheme 1. γ-Lactams via C−H Amidation



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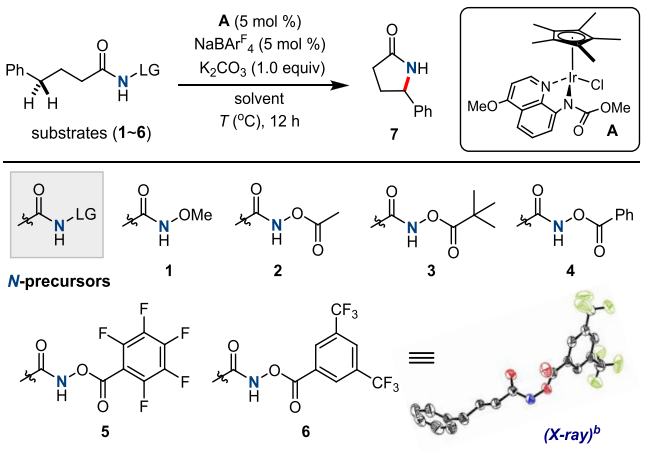
leveraged by the facile generation of key Ir−carbonylnitrenoid intermediate, where countercations of base additives were found to critically affect this process.

At the outset of the present study, we sought the optimal carbonylnitrene precursors for γ-lactam synthesis with iridium catalysis (Table 1). Iridium complex **A** was chosen as a model

Table 1. Optimization of Reaction Parameters[a]



entry	sub	T (°C)	solvent	7[c] (%)
1	**1**	60	$(CF_3)_2CHOH$ (HFIP)	NR
2	**2**	60	HFIP	18
3	**3**	60	HFIP	17
4	**4**	60	HFIP	30
5	**5**	60	HFIP	59
6	**6**	60	HFIP	85
7	**6**	60	CF_3CH_2OH (TFE)	>95
8	**6**	60	CH_3OH	87
9	**6**	60	CH_2Cl_2 (DCM)	70
10	**6**	60	$Cl_2CHCHCl_2$ (TCE)	48
11	**6**	60	CH_3CN	60
12	**6**	**40**	**TFE**	**>95**
13[d]	**6**	40	TFE	59
14[e]	**6**	40	TFE	31

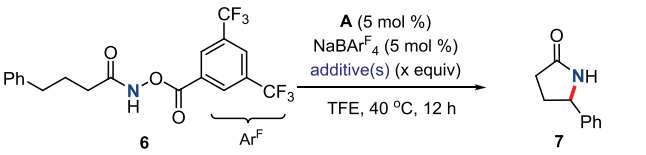
[a]Reaction conditions: substrate (0.05 mmol), **A** (5 mol %), $NaBAr^F_4$ (5 mol %), and K_2CO_3 (1.0 equiv) in the indicated solvent. [b]ORTEP diagrams of **6**. Disorder of fluorine atoms was omitted for clarity. [c]^1H NMR yield. [d]20 mol % of K_2CO_3. [e]Without K_2CO_3.

catalyst since it was proven to be highly effective when dioxazolones were employed in our recent report.[7a] As an acylnitrenoid precursor, hydroxamic acid derivatives were first envisaged to be examined since they can be readily prepared from the corresponding carboxylic acids.[9] In fact, a few research groups employed the related compounds as nitrogen sources in the intermolecular C−H amidation reactions under various conditions.[10] In addition, the Rovis group demonstrated that *N*-pivalyloxyamides were utilized as acylnitrene precursors in the catalytic diamidation reaction of terminal olefins.[11] When a substrate bearing *N*-methoxyamide (**1**) was subjected to iridium catalysis using **A** (5 mol %), no desired lactam product (**7**) was obtained (entry 1). In contrast, reactions of *N*-acyloxy variants (**2**, **3**, or **4**) showed promising reactivities (entries 2−4), suggesting that the nature of *N*-substituents is critical for the cyclization reactivity. Indeed, a notable product yield (59%) was obtained when *N*-(pentafluorobenzoyl)oxyamide (**5**) was subjected to the iridium catalytic conditions in hexafluoro-2-propanol (HFIP) solvent in the presence of a stoichiometric amount of K_2CO_3 additive (entry 5).

A greater improvement was achieved when *N*-{3,5-bis(trifluoromethyl)benzoyl}oxyamide (**6**) was applied (entry 6). Finally, a quantitative product yield was attained in 2,2,2-trifluorethanol (TFE) solvent at 60 °C (entry 7). However, the choice of solvent was found to be influential on the reaction efficiency as demonstrated in entries 6−11. A similar level of cyclization was observed even at slightly lower temperature in TFE (40 °C, entry 12). However, the amount of K_2CO_3 additive affected the reaction progress significantly (compare entries 12 and 13), and only low product yield was obtained in the absence of K_2CO_3 (entry 14).

Having observed the promising reactivity on the lactamization, we attempted to preliminarily rationalize the working mode of *N*-benzoyloxyamides as an efficient carbonylnitrenoid precursor under the employed Ir catalyst system (Scheme 2).[7a]

Scheme 2. Effects of Countercations of Carbonates



Additive(s)	Li_2CO_3 (1.0)	Cs_2CO_3 (1.0)	Na_2CO_3 (1.0)	K_2CO_3 (1.0)	K_2CO_3 (1.0)/ 18-crown-6 (2.0)
Yield (%)	32	75	>95	>95	50

As seen in Table 1 (entries 12−14), the effect of K_2CO_3 additive was especially noteworthy in the lactam formation. In fact, Lebel and co-workers described that countercations of carbonates are involved in the generation of putative Rh−nitrene species in the C−H amination of *N*-sulfonyloxycarbamates.[12] We first performed a series of catalytic reactions in the presence of analogous base additives (Scheme 2). While lithium carbonate and cesium carbonate were less effective, Na_2CO_3 was almost as effective as K_2CO_3 in the cyclization of **6**. On the other hand, the additive effect of K_2CO_3 was significantly decreased when the reaction was carried out in the presence of 2 equiv of 18-crown-6. This result led us to assume that the countercations of carbonate additives would be involved presumably in the nitrenoid-generating stage.

For a better understanding of the role of countercations in the reaction progress, their working mode was evaluated with density functional theory (DFT) calculations on the basis of plausible intermediates (Figure 1). We chose the potassium system as a representative model to rationalize the proposed cation assistance. Recently, the group of Lebel showed that a countercation is embedded in the presumed carbamate-coordinated Rh species via a κ^2-bidentate chelating mode.[12d] On the basis of this literature, complexes **I-1** (7-membered-κ^2-*O*,*O*′-chelate; marked with blue), **I-2** (5M-κ^2-*N*,*O*; black), and **I-3** (5M-κ^2-*O*′,*O*″; red) were considered (Figure 1a). In the subsequent formation of the putative Ir−carbonylnitrenoid intermediate **II**, the individual complex was calculated to traverse **I-TS-1**, **I-TS-2**, and **I-TS-3**, respectively, via a potassium-assisted N−O bond cleavage.[13] The activation barrier was estimated to be 15.6 kcal/mol for **I-1** (via **I-TS-1**), whereas higher energy was calculated for the other

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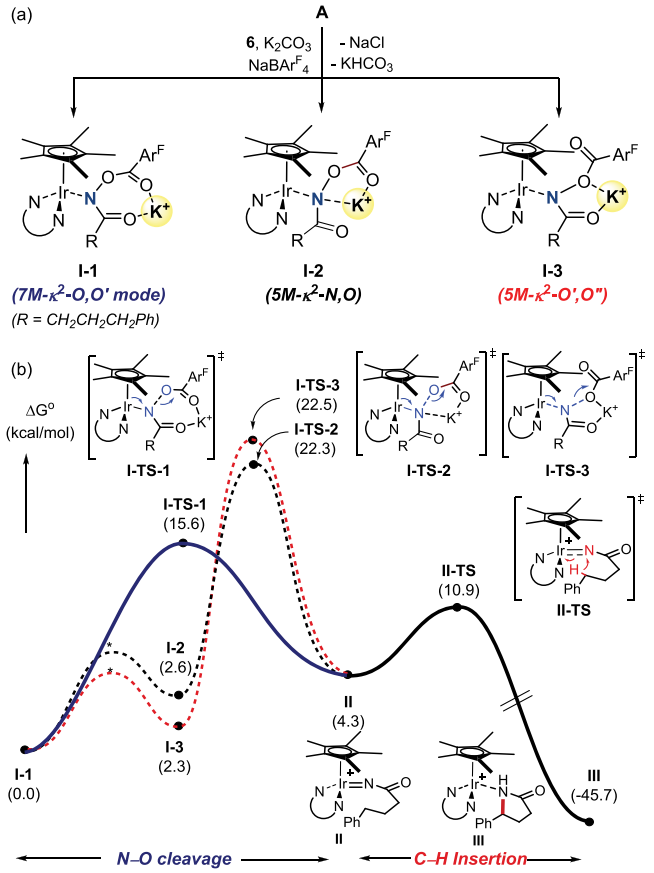


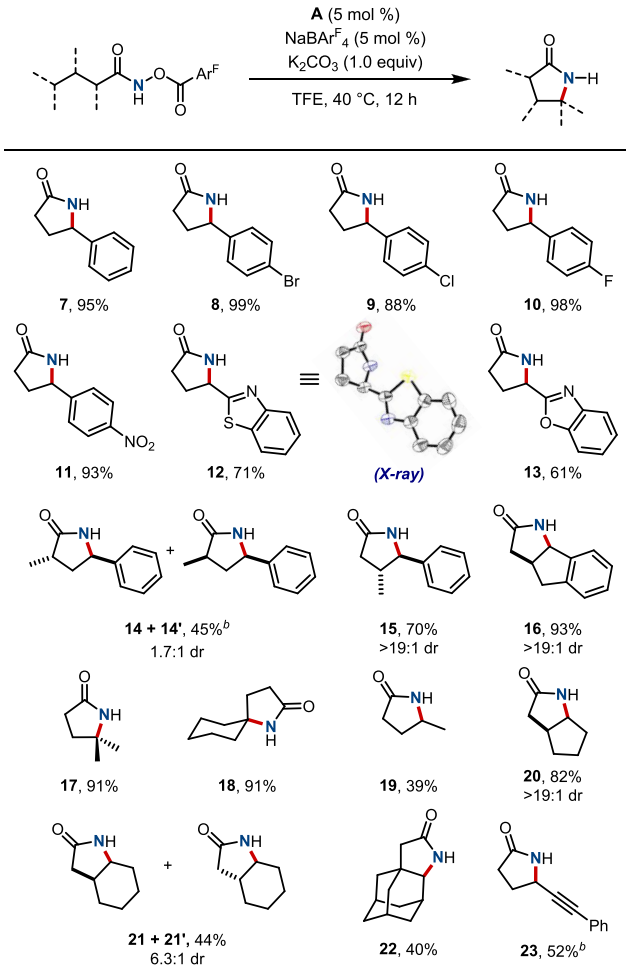
Figure 1. (a) Three plausible binding modes of a countercation. (b) Energy profiles for the proposed pathways at the PCM(TFE)-M06/SDD+6-311++G**//B3LYP/Lanl2dz+6-31G** level.

proposed complexes: 22.3 kcal/mol for **I-2** (via **I-TS-2**) and 22.5 kcal/mol for **I-3** (via **I-TS-3**).

Most importantly, this process of forming the Ir−carbonylnitrenoid intermediate **II** was calculated to become energetically more demanding without potassium assistance in which the barrier was calculated to be 21.3 kcal/mol in the absence of potassium ion (see the SI for details). This result demonstrates that the existence of countercations exerts a beneficial effect, in particular on the generation of Ir−nitrenoid. The reaction efficiency was dependent on each countercation of base additives, although the exact reason is not clear at the present stage. Finally, C−H insertion of the resultant intermediate **II** will occur in a concerted and asynchronous manner with a barrier of only 10.9 kcal/mol to furnish the desired product **III**.

The general applicability of the present amidation of *N*-{3,5-bis(trifluoromethyl)benzoyl}oxyamides was next explored (Scheme 3). Substrates bearing benzylic γ-C−H bonds smoothly underwent the desired amidation to afford 5-aryl-2-pyrrolidinones in excellent yields (**7**−**11**). Heterocycles such as benzothiozole and benzoxazole were well tolerated under the optimal reaction conditions (**12** and **13**, respectively). The position of a substituent in the alkyl linker was found to affect the diastereoselectivity in substituted γ-lactam products. For instance, when a methyl group is present at the α-position relative to the amide, a mixture of *anti*- and *syn*-isomers was obtained in a 1.7:1 ratio (**14**/**14′**) in moderate combined yields. In contrast, the C−N bond formation occurred almost exclusively in an *anti*-selective manner with higher yield when a methyl group is positioned at β- to the amide moiety (**15**). In

Scheme 3. Substrate Scope[a]



[a]Reaction conditions: substrate (0.2 mmol), **A** (5 mol %), $NaBAr^F_4$ (5 mol %), and K_2CO_3 (1.0 equiv) in TFE (2.4 mL) at 40 °C for 12 h. [b]**A** (10 mol %) and $NaBAr^F_4$ (10 mol %) were used.

addition, a tricyclic lactam **16** was readily synthesized with high selectivity and efficiency.

Generation of a quaternary carbon center in a lactam scaffold was enabled efficiently via the amidation of tertiary C−H bonds (**17** and **18**). Significantly, aliphatic secondary C−H bonds of *N*-benzoyloxyamide substrates bearing *n*-butyl, cyclopentyl, cyclohexyl, and adamantyl groups were successfully amidated to give the corresponding lactams **19**, **20**, **21**, and **22**, respectively. In addition, a γ-lactam product bearing a propargylic substituent could be obtained albeit in moderate yield (**23**).[14]

A practical aspect of the present protocol was briefly examined (Scheme 4). Representatively, a substrate **6** was demonstrated to be prepared in a step-economical fashion from 4-phenylbutyric acid (**24**, 73% yield). It should be noted that most substrates examined in this study are bench-stable crystalline solid (for a few months), and they can be readily isolated by recrystallization. When the reaction was conducted on a larger scale, product **7** was isolated in 82% yield with recovery of 3,5-bis(trifluoromethyl)benzoic acid in 69% yield (Scheme 4a). Lastly, the current procedure of γ-lactam formation starting from *N*-benzoyloxyamides was briefly compared with our previous dioxazolone procedure (Scheme 4b). Starting from phthalimide-protected L-β-leucine **25**, the

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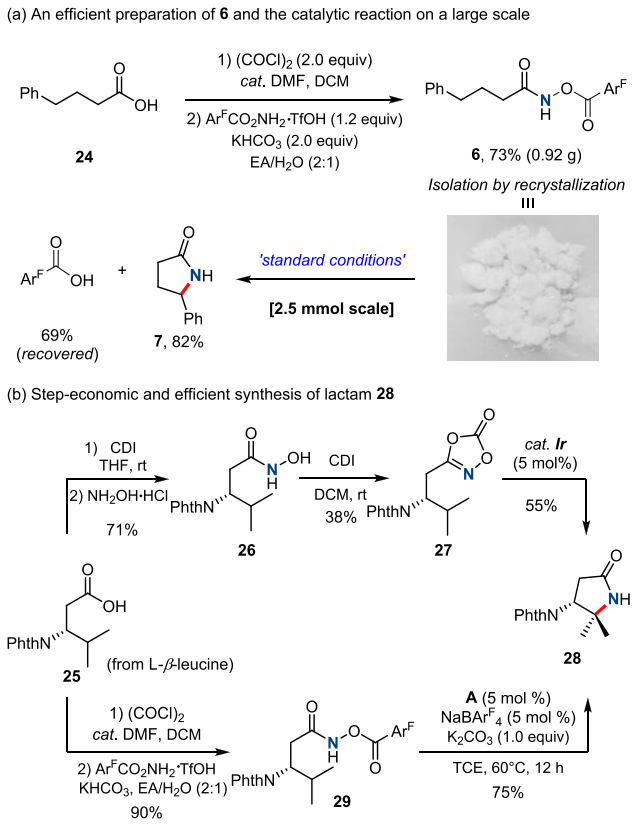
Scheme 4. Practical Aspect of Present Protocol



synthesis of a lactam **28** (99% ee) was achieved in three steps (15% overall yields) through the dioxazolone route.[7a] On the other hand, the present protocol was found to be more efficient to produce the same product **28** also with no erosion of enantiomeric excess.

In summary, we have successfully utilized a new type of nitrenoid precursor, *N*-benzoyloxyamide derivatives, toward the Ir-catalyzed intramolecular C−H amidation reaction. Mechanistic studies revealed that the putative Ir−carbonylnitrene intermediate forms more readily in the presence of carbonate additives presumably by the countercation-assisted N−O bond cleavage. The present protocol of using *N*-{3,5-bis(trifluoromethyl)benzoyloxy}amides was found to be a convenient alternative to the previous dioxazolone procedure toward the γ-lactam formation from carboxylic acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00791.

Cartesian coordinates and structures for the optimized structures and transition states; additional crystallographic and NMR data (PDF)

Accession Codes

CCDC 1900860−1900861 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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