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Diversity-Oriented Synthesis of β-Lactams and γ-Lactams by Post-Ugi Nucleophilic Cyclization: Lewis Acids as Regioselective Switch

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Heterocyclic fused α-methylene β-lactams were successfully synthesized by a post-Ugi In^{III}-catalyzed intramolecular addition reaction. Switching from $InCl_3$ to $AlCl_3$ led to the regioselective synthesis of α,β-unsaturated γ-lactams. Moreover, replacing terminal alkynes by substituted alkynes in the Ugi adducts resulted in the exclusive formation of γ-lactams with both catalytic systems.

Introduction

2-Azetidinones, commonly known as β-lactams, are well-established privileged scaffolds as proven by their widespread applications in medicinal chemistry.[1] The core structure of commonly used antibiotics such as penicillin, aztreonam, nocardicin A, and the cholesterol lowering drug ezetimibe is the β-lactam ring (Figure 1).[1,2] In addition, β-lactams also serve as versatile building blocks for the synthesis of various nitrogen-containing compounds such as vitamins, alkaloids, and β-amino acids.[3] The classical route for the construction of the β-lactam core is the Staudinger reaction through the [2+2] cycloaddition of imines to ketenes.[4] The generation of the latter requires treatment of activated carboxylic acid derivatives such as acyl chlorides, which sometimes lowers the synthetic utility. Considering the vast pharmacological significance of the β-lactam framework and the growing concern regarding bacterial resistance, the development of new methodologies towards the diversification of existing β-lactam antibiotics seems to be imperative.[5] As a result, several new synthetic approaches have been developed,[6] with particular emphasis on the generation of α-methylene β-lactams,[7] which are versatile compounds delivering building blocks for the construction of various β-lactam antibiotics[7c] (Scheme 1).

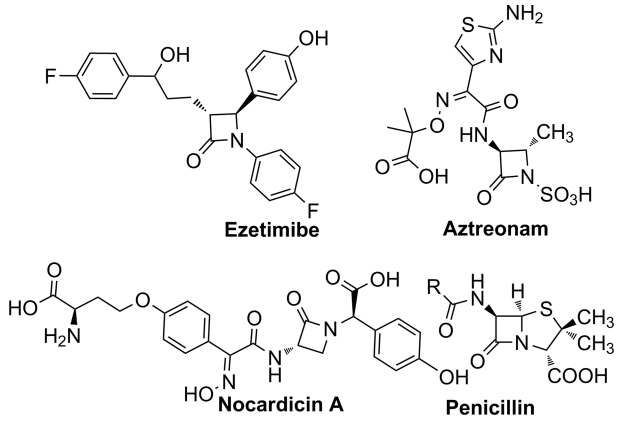

Figure 1. Examples of β-lactam-core-containing pharmaceuticals.

Over the last few decades, multicomponent reactions (MCR)[8] and transition-metal-catalyzed[9] post-MCR transformations have enabled easy access to complex heterocyclic scaffolds in a few steps.[10] Strategies for generating β-lactams by employing β-amino acids[11] or β-keto acids[12] as functionalized substrates in the Ugi reaction have also been developed. Recently, bromoacetic acid[13] and phenylpropiolic acid[14] have been used to synthesize functionalized β-lactams involving a sequential base-catalyzed tandem Ugi reaction and intramolecular cyclization. Nonetheless, newer methodologies in terms of increased substrate scope as well as starting material availability are always welcome. In continuation of our attempts towards the development of diversity-oriented syntheses of various heterocyclic scaffolds through post-Ugi transformations,[15] we envisioned the synthesis of heterocyclic fused α-methylene β-lactams by combination of a MCR with a metal-catalyzed cascade cyclization. Herein, we report post-Ugi In^{III}-catalyzed intramolecular nucleophilic cyclization for the synthe-

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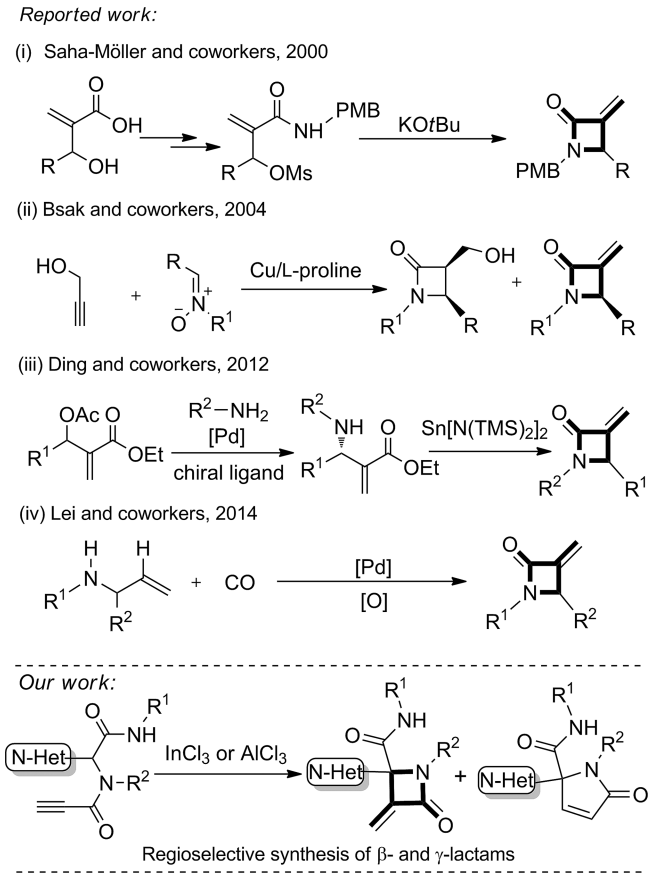


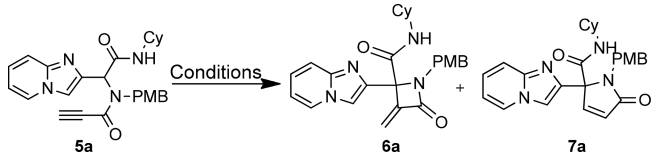
Scheme 1. Synthetic methods for α-methylene β-lactams; PMB = *p*-methoxybenzyl, Ms = methylsulfonyl.

sis of N-heterocyclic fused α-methylene β-lactams. Interestingly, switching from In^{III} to Al^{III} resulted in the generation of another important class of N-heterocycles, that is, unsaturated γ-lactams, starting from the same Ugi adduct (Scheme 1).

Results and Discussion

Initially, the Ugi four-component reaction (4-CR)[16] of imidazo[1,2-*a*]pyridine-2-carbaldehyde (**1a**), *p*-methoxybenzylamine (**2a**), propiolic acid (**3a**), and cyclohexyl isocyanide (**4a**) in methanol at room temperature generated adduct **5a** in 84% yield, which was selected to optimize the reaction conditions of the next step. In continuation of our previous success with gold and silver catalysis for the activation of alkynes,[14] we began our studies by screening these catalysts in 1,2-dichloroethane (DCE) at 120 °C for 12 h (Table 1, entries 1–3). However, none of the catalysts was able to complete the reaction. Moreover, the selectivity for desired α-methylene β-lactam **6a** was not good. Therefore, we turned our attention to In^{III} catalysts, as these have recently emerged as dual activators for carbonyl compounds as well as for terminal alkynes in various reactions.[17] Delightedly, the application of 10 mol-% of $InCl_3$ was able to complete the reaction, and desired *exo*-cyclized α-methylene β-lactam **6a** was isolated in 36% yield (Table 1, entry 4). Increasing the catalyst loading of $InCl_3$ to 20 mol-% led to isolation of **6a** in 73% yield (Table 1, entry 5). However, a further increase in the catalyst loading to 30 mol-% did not significantly enhance the outcome of the reaction (Table 1, entry 6). A drastic reduction in yield and selectivity was observed upon switching the catalyst to indium(III) trifluoromethanesulfonate [$In(OTf)_3$; Table 1, entry 7]. Changing the solvent to toluene gave a slightly improved yield of **6a** (Table 1, entry 8), whereas *o*-xylene and MeCN produced reduced yields (Table 1, entries 9 and 10). Increasing the catalyst loading to 30 mol-% in toluene delivered **6a** in 88% yield (Table 1, entry 11). No further improvement in yield or selectivity was observed upon further increasing the amount of catalyst (Table 1, entry 12) or reducing the reaction time or temperature (Table 1, entries 13 and 14). We next attempted to develop a catalytic system for the exclusive generation of *endo*-cyclized product, that is, γ-lactam **7a**, which was observed as a minor product in almost every case. Interestingly, replacing $InCl_3$ with the readily available Lewis acids $AlCl_3$ and $ZnCl_2$ resulted in the formation of γ-lactam **7a** in yields of 75 and 61%, respectively (Table 1, entries 15 and 16). However, with CuI and K_2CO_3 only decomposition of Ugi adduct **5a** was observed (Table 1, entries 17 and 18).

Table 1. Optimization of the intramolecular addition.[a]



Entry	Catalyst (mol-%)	Solvent	Time [h]	Temp. [°C]	Conversion [%][b] (**6a**/**7a**)
1	AgOTf (10)	DCE	12	120	90 (40:50)
2	$AgSbF_6$ (10)	DCE	12	120	78 (50:28)
3	AuCl (10)	DCE	12	120	80 (35:45)
4	$InCl_3$ (10)	DCE	12	120	100 (36:18)[c]
5	$InCl_3$ (20)	DCE	12	120	100 (73:8)[c]
6	$InCl_3$ (30)	DCE	12	120	100 (74:6)[c]
7	$In(OTf)_3$ (20)	DCE	12	120	100 (40:10)[c]
8	$InCl_3$ (20)	toluene	12	120	100 (78:8)[c]
9	$InCl_3$ (20)	*o*-xylene	12	120	100 (68:12)[c]
10	$InCl_3$ (20)	MeCN	12	120	100 (72:28)
11	$InCl_3$ (30)	toluene	12	120	100 (88:4)[c]
12	$InCl_3$ (40)	toluene	12	120	100 (86:5)[c]
13	$InCl_3$ (30)	toluene	6	120	100 (64:5)[c]
14	$InCl_3$ (30)	toluene	12	100	100 (56:5)[c]
15	$AlCl_3$ (10)	DCE	12	120	100 (0:75)[c]
16	$ZnCl_2$ (10)	DCE	12	120	100 (13:61)[c]
17	CuI (10)	DCE	12	120	n.d.[d]
18	K_2CO_3[e]	DCE	12	120	n.d.[d]

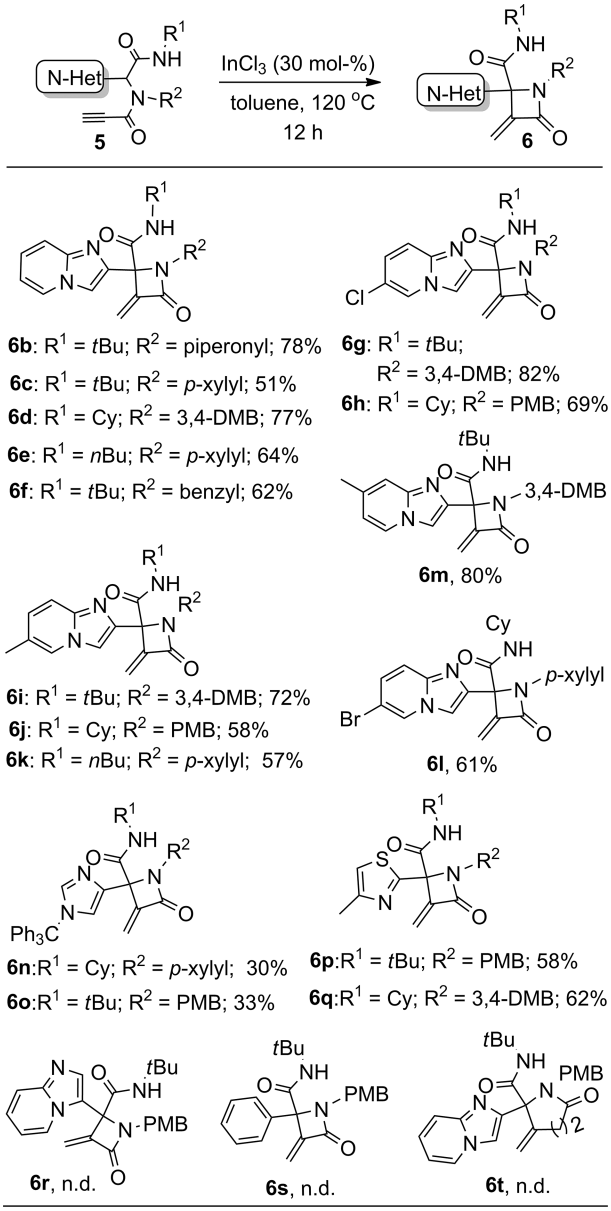
[a] All reactions were run on a 0.1 mmol scale of **5a** in the indicated solvent (2 mL). Cy = cyclohexyl. [b] Conversion and ratio based on analysis by ^1H NMR spectroscopy. [c] Yield of isolated product. [d] n.d.: not detected. [e] K_2CO_3: 1 equiv.

With the optimized conditions for the synthesis of β-lactams in hand (Table 1, entry 11), we evaluated the scope and limitations of this intramolecular addition by using a vari-

ety of different Ugi adducts **5a**–**t** (Table 2). The intramolecular cyclization proceeded smoothly in most cases to give α-methylene β-lactams **6a**–**t** in moderate to good yields. A variety of substituents in the Ugi adducts were well tolerated. Employing the standard conditions to Ugi adducts **5n**/**5o** and **5p**/**5q** prepared from 1-trityl-1*H*-imidazole-4-carbaldehyde and 4-methylthiazole-2-carbaldehyde, respectively, produced corresponding alkylidene-β-lactams **6n**/**6o** and **6p**/**6q** in yields of 30/33 and 58/62%, respectively. However, in the case of Ugi adduct **5r** derived from imidazo[1,2-*a*]pyridine-3-carbaldehyde, no conversion was observed. Similarly, the failure of Ugi adduct **5s** derived from benzaldehyde to form **6s** manifests the necessity of employing a nitrogen-containing aromatic aldehyde in the Ugi reaction. Moreover, it was necessary to ensure that the use of propiolic acid resulted in intramolecular *anti*-Michael addition, as Ugi adduct **5r** from 4-pentynoic acid failed to produce the desired alkylidene-β-lactam.

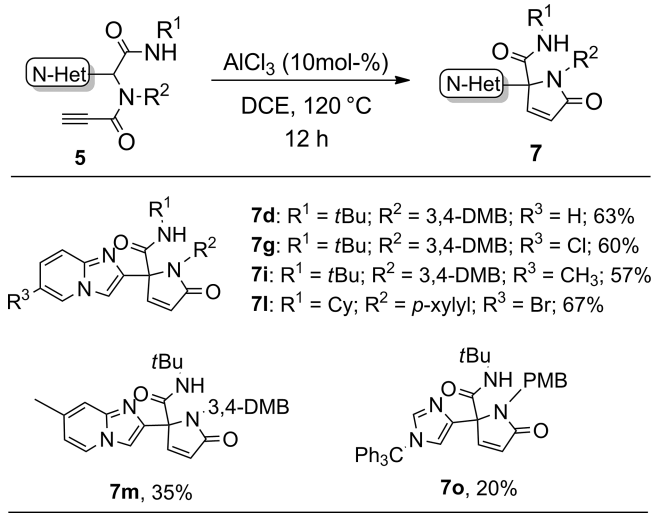
Further, the applicability of this protocol for the preparation of γ-lactams from Ugi adducts (e.g., **5d**, **5g**, **5i**, **5l**, **5m**, and **5o**) is shown in Table 3. Good to moderate yields were obtained for Ugi adducts obtained from various substituted imidazo[1,2-*a*]pyridine-2-carbaldehydes (e.g., **7d**, **7g**, **7i**, **7l**, and **7m**). However, a low yield was noticed for the Ugi adduct derived from 1-trityl-1*H*-imidazole-4-carbaldehyde (i.e., **7o**, Table 3). In addition, to scrutinize the necessity of propiolic acid, Ugi adduct **8a** was prepared from imidazo[1,2-*a*]pyridine-2-carbaldehyde by replacing propiolic acid with 2-butynoic acid (**3c**), and it was subjected to the

Table 2. Scope and limitations for β-lactam formation.[a]



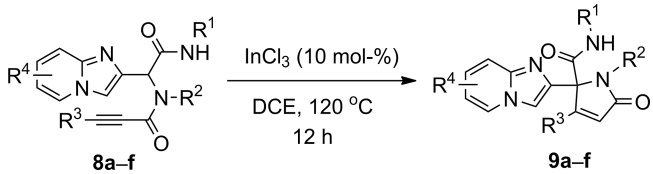
[a] All reactions were run on a 0.3 mmol scale of **5** with $InCl_3$ (30 mol-%) in toluene (2 mL) in a screw-capped vial at 120 °C for 12 h. 3,4-DMB = 3,4-dimethoxybenzyl.

Table 3. Scope and limitations for γ-lactam formation.[a]



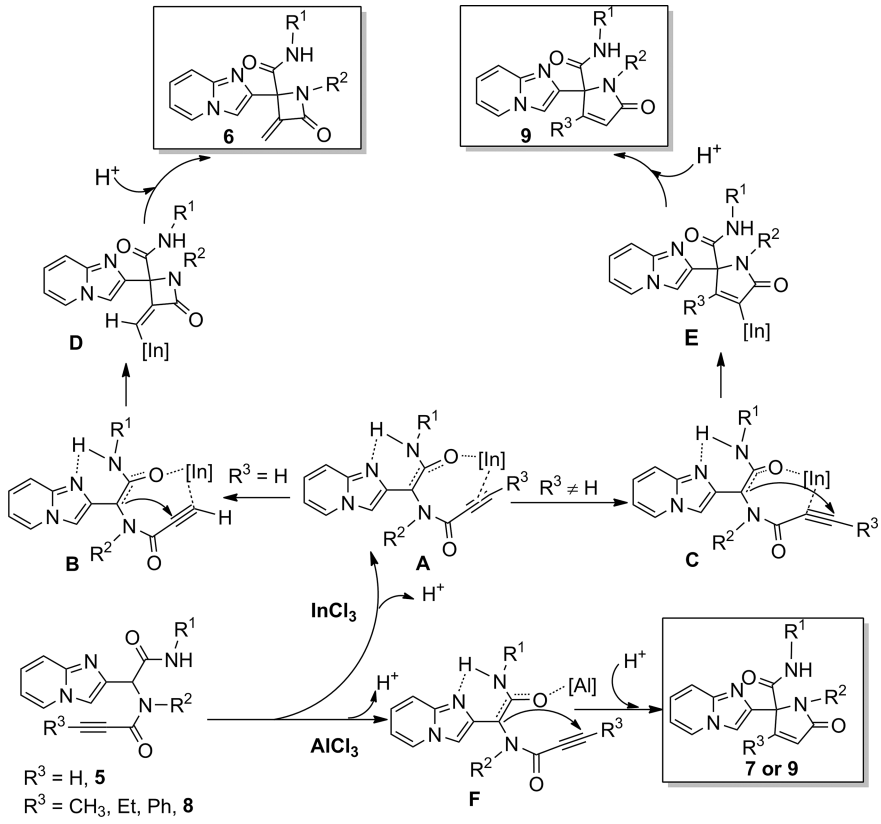
[a] All reactions were run on a 0.3 mmol scale of **5** with $AlCl_3$ (10 mol-%) in DCE (2 mL) in a screw-capped vial at 120 °C for 12 h.

Table 4. Scope and limitations for γ-lactam formation from substituted propargylamides.[a]



Product	R^1	R^2	R^3	R^4	Yield [%]
9a	*t*Bu	PMB	Me	H	72/69[b]
9b	*n*Bu	piperonyl	Me	6-Cl	99
9c	*t*Bu	PMB	Et	H	77
9d	*t*Bu	piperonyl	Et	6-Cl	81
9e	*t*Bu	3,4-DMB	Ph	H	76
9f	Cy	PMB	Ph	6-Me	82

[a] All reactions were run on a 0.3 mmol scale of **8** with $InCl_3$ (10 mol-%) in DCE (2 mL) in a screw capped vial at 120 °C for 12 h. [b] $AlCl_3$ (10 mol-%) was used.



Scheme 2. Plausible reaction mechanism.

optimized conditions. However, instead of expected α-methylene β-lactam, γ-lactam **9a** was observed as the only product resulting from Michael addition (Table 4, entry 1). After checking the influence of solvents, catalysts, and so on (see the Supporting Information), the optimal conditions for this Michael addition process were found to be 120 °C for 12 h in DCE as the solvent with $InCl_3$ (10 mol-%) as the catalyst. It is notable that employment of $AlCl_3$ (10 mol-%) gave γ-lactam **9a** in 69% yield. The optimal process was applied successfully to diversely substituted Ugi adducts **8b**–**f** (see the Supporting Information) to deliver γ-lactams **9b**–**f** in good to excellent yields. Remarkably, upon employing a bulky substituent such as a phenyl group on the alkyne, no steric hindrance was observed, and compounds **9e** and **9f** were formed in yields of 76 and 82%, respectively.

On the basis of these observations and previous reports on In^{III},[17] we postulate a plausible mechanism for the nucleophilic 4-*exo*-*dig* and 5-*endo*-*dig* additions (Scheme 2). Moreover, preliminary DFT calculations were also performed to understand the reaction mechanism and selectivity with the different substrates and Lewis acids (for details, see the Supporting Information). In an initial step, we assume that the Lewis acid coordinates to the substrate, which thereby generates the enolate by deprotonation. Loss of a chloride ion from the Lewis acid leads to neutral enolate **A**, in which the alkyne group is coordinated to the metal center. Transition states for 4-*exo*-*dig* and 5-*endo*-*dig* ring closure have been located for R^3 = H and Me, and for M = Al and In, all of which lie 8–21 kcal mol^{-1} above the enolate. Considering the likely computational errors, the relative energies of these transition states are in good agreement with experimentally observed ring-closure selectivities: the formation of the four-membered ring is predicted to be more favorable in the case of R^3 = H and M = In ($\Delta\Delta E^{\ddagger}$ = 3.4 kcal mol^{-1}), whereas the barriers for five-membered ring formation are lower in all other cases (e.g., $\Delta\Delta E^{\ddagger}$ = –7.5 kcal mol^{-1} in the case of R^3 = H, M = In). The products of these steps are vinyl–metal species that should undergo facile protonolysis of the C–M bonds. Partial atomic charge calculations (see the Supporting Information) suggest that the relative electrophilicity of the two acetylenic carbon atoms and thereby the selectivity is tuned by the R^3 substituent and coordination to the metal.

Conclusions

In summary, we elaborated a diversity-oriented post-Ugi intramolecular approach for the synthesis of α-methylene β-lactams and α,β-unsaturated γ-lactams by employing Ugi adducts with terminal and substituted alkynes. The diversity of the desired products is guaranteed by the first step, the Ugi 4-component reaction. The operational simplicity together with the synthetic efficiency of the protocol will facilitate the development of new antibiotics for countering bacterial resistance. The biological activity of the generated compounds is under current investigation.

Experimental Section

General Procedure for the Synthesis of Ugi Products 5 and 8: Na_2SO_4 (0.3 g), amine **2** (1.2 equiv.), acid **3** (1.2 equiv.), and isocyanide **4** (1.2 equiv.) were added successively to a solution of carbaldehyde **1** (200 mg, 1 equiv.) in methanol (3 mL) in a screw-capped vial equipped with a magnetic stir bar. The mixture was stirred at room temperature for 24–48 in the closed vial. Upon completion of the reaction, the mixture was diluted with EtOAc (100 mL) and was extracted with water (50 mL). The organic layer was washed with brine (50 mL), dried with magnesium sulfate, and evaporated under reduced pressure to obtain a residue, which was subjected to column chromatography (silica gel, 1–5% MeOH in CH_2Cl_2) to afford desired product **5** and **8** as a solid. Ugi products appear as a mixture of two rotamers, so the ^1H NMR and ^{13}C NMR spectra are not very characteristic.

General Procedure for the Synthesis of Alkylidene β-Lactams 6 thorough $InCl_3$-Catalyzed *anti*-Michael Addition: A glass vial was charged with $InCl_3$ (30 mol-%) and dry toluene (2 mL). Ugi product **5** (0.3 mmol) was added. The mixture was stirred at 120 °C until completion of the reaction. Upon completion, the mixture was purified by column chromatography (silica gel, 1–3% MeOH in CH_2Cl_2) to afford compound **6**.

General Procedure for the Synthesis of γ-Lactams 7 thorough $AlCl_3$-Catalyzed Michael Addition: A glass vial was charged with $AlCl_3$ (10 mol-%) and dry DCE (2 mL). Ugi product **5** (0.3 mmol) was added. The mixture was stirred at 120 °C until completion of the reaction. Upon completion, the mixture was purified by column chromatography (silica gel, 1–3% MeOH in CH_2Cl_2) to afford compound **7**.

General Procedure for the Synthesis of γ-Lactams 9 thorough $InCl_3$-Catalyzed Michael Addition: A glass vial was charged with $InCl_3$ (10 mol-%) and dry DCE (2 mL). Ugi product **8** (0.3 mmol) was added. The mixture was stirred at 120 °C until completion of the reaction. Upon completion, the mixture was purified by column chromatography (silica gel, 1–3% MeOH in CH_2Cl_2) to afford compound **9**.

The products were characterized by ^1H NMR and ^{13}C NMR spectroscopy and HRMS, and the data were all in good agreement with the assigned structures (for detailed experimental procedures and data, see the Supporting Information).

General Procedure for DFT Calculations: Briefly, DFT calculations were performed by using the B3LYP functional, the SVPP basis set for all atoms other than In, and the SDD core potential and associated basis set for In in the Gaussian 09 program package.[18] Reported energies include corrections for zero-point energy and dispersion [-D3(BJ) correction]. Full details of the computational protocol and additional results are in the Supporting Information.

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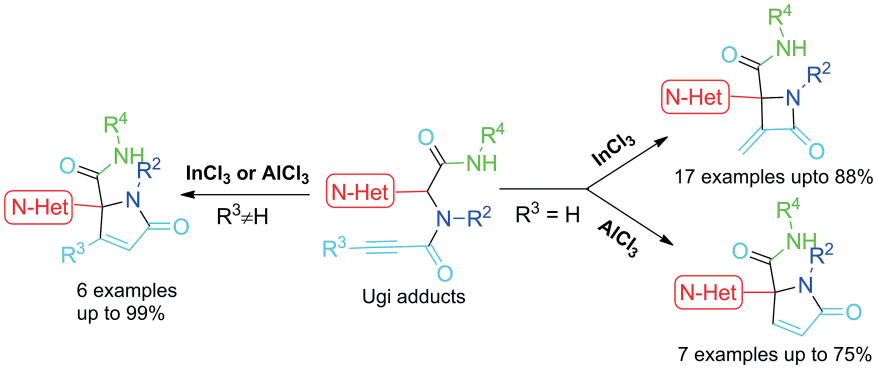
β-Lactam Synthesis



A regioselective approach for the synthesis of heterocyclic fused α-methylene β-lactams and α,β-unsaturated γ-lactams by employing a Ugi reaction followed by In^{III}- or Al^{III}-catalyzed intramolecular nucleophilic addition is reported.

Keywords: Multicomponent reactions / Nucleophilic cyclization / Regioselectivity / Lewis acids / Lactams

