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Authors: Yongqiang Tu, Xue Han, Li-Xin Shan, Jin-Xin Zhu, Chang-Sheng Zhang, Xiao-Ming Zhang, Fu-Min Zhang, Hong Wang, Ming Yang, Wen-Shuo Zhang, and yong qiang Tu

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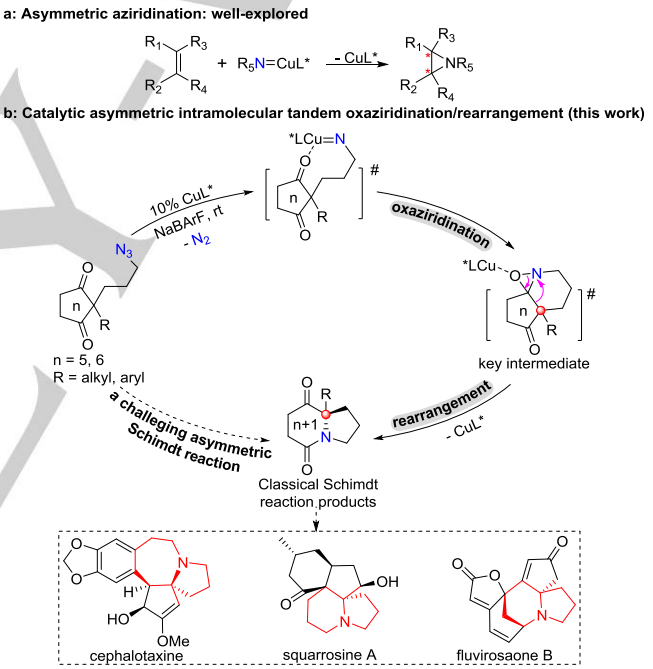
Copper-Nitrene-Catalyzed Desymmetric Oxaziridination/1,2-Alkyl Rearrangement of 1,3-Diketones toward Bicyclic Lactams

Xue Han, Li-Xin Shan, Jin-Xin Zhu, Chang-Sheng Zhang, Xiao-Ming Zhang, Fu-Min Zhang,* Hong Wang, Yong-Qiang Tu,* Ming Yang, Wen-Shuo Zhang

[*] X. Han, L.-X. Shan, C.-S. Zhang, Dr. X.-M. Zhang, Prof. Dr. F.-M. Zhang, Prof. Dr. Y.-Q. Tu, Prof. Dr. M. Yang, W.-S. Zhang
State Key Laboratory of Applied Organic Chemistry and College of Chemistry and Chemical Engineering
Lanzhou University
Lanzhou 730000 (China)
E-mail: zhangfm@lzu.edu.cn
tuyq@lzu.edu.cn
J.-X. Zhu, Prof. Dr. H. Wang
College of Pharmaceutical Science and Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals
Zhejiang University of Technology
Hangzhou 310014 (China)
Prof. Dr. Y.-Q. Tu
School of Chemistry and Chemical Engineering and Shanghai Key Laboratory of Chiral Medicine Chemistry
Shanghai Jiao Tong University
Shanghai 200240 (China)
E-mail: tuyq@sjtu.edu.cn

Abstract: Although copper-nitrene has been extensively studied as a versatile active species in various transformations, asymmetric reactions involving copper-nitrene have been limited to the aziridination of olefins. Herein, we report the novel copper-nitrene-catalyzed desymmetric oxaziridination reaction of cyclic diketones with alkyl azides and the subsequent rearrangement of the resulting highly active intermediate, which produces a synthetically challenging chiral bicyclic lactam containing a quaternary carbon center. This procedure not only enriches the copper-nitrene-catalyzed asymmetric reactions, but also provides an alternative strategy to address the inherent challenges of catalytic asymmetric Schmidt reactions. This unique reaction could inspire the investigation of novel copper-nitrene-catalyzed asymmetric transformations and their reaction mechanisms.

The investigation of asymmetric transformations involving reactive intermediate species[1] has received considerable interest from the chemical community. In recent years, chiral metal-nitrene complexes[2], an important class of reaction intermediates, have received continued research attention. The transformations involving metal-nitrene intermediates are reliable and practical approaches to produce chiral compounds containing nitrogen atoms, which are widely found in clinical drugs,[3] bioactive natural products,[2c,2d,4] and functional materials.[5] Among transition metals, copper is preferred by synthetic chemists[6] because of its low cost, multivalence in catalytic cycles, and abundance in nature. However, the development of chemical transformations based on chiral copper-nitrene has mainly focused on the aziridination of C=C bonds to generate synthetically important aziridines[7] (Scheme 1a). To further explore other novel transformations involving chiral copper-nitrene species, we speculated that a polarized C=O bond could react with *in-situ* generated copper-nitrene and the resulting highly active intermediate oxaziridine[8] could subsequently rearrange to produce a synthetically challenging chiral lactam[4,9] (Scheme 1b). Such an asymmetric transformation could efficiently address the intrinsic challenges of the classic intramolecular Schmidt reaction,[10] including the use of azides with low nucleophilicity as a substrate, the general requirement for stoichiometric amounts of a strong Lewis or Brønsted acid to activate the carbonyl group of the other reactant, the relatively strong Lewis basic nature of the

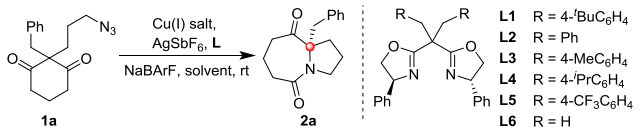


Scheme 1. The outline of Cu-catalyzed asymmetric reactions involving nitrenoid intermediates.

resulting lactam, and the lack of the corresponding catalytic asymmetric fashion. Notably, the resulting chiral bicyclic lactams could be used as the key precursors for the total synthesis of various bioactive alkaloids, such as cephalotaxine,[4b] squarrosine A,[4c] and fluvirosaone B.[4d] Herein, we report a novel copper-nitrene-catalyzed asymmetric intramolecular tandem oxaziridination/rearrangement reaction to produce a chiral fused bicyclic lactam.

Initially, we performed our designed catalytic asymmetric reaction with a combination of $Cu(CH_3CN)_4PF_6$ (10 mol%) and a bisoxazoline (BOX)-type ligand (**L1**) without any additive and used 2-benzyl-2- azidopropyl-1,3-cyclohexadione (**1a**) as the

Table 1. Optimization of ligand and reaction conditions[a]

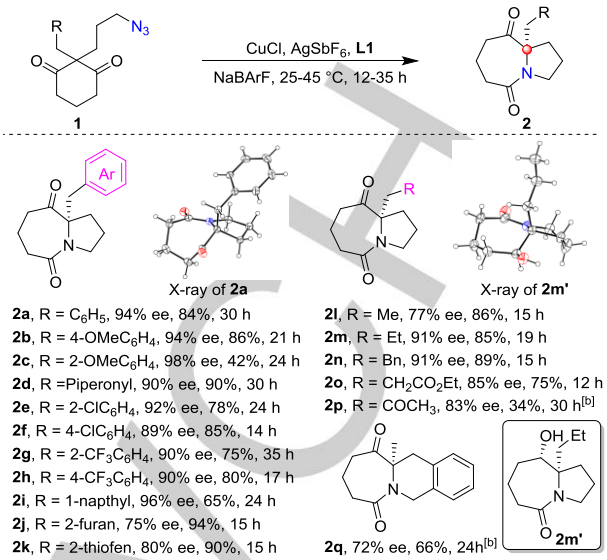


Entry	CuX/AgSbF$_6$	Additive	L	Solvent	Y[%][b]	ee[%][c]
1	Cu(CH$_3$CN)$_4$PF$_6$	-	**L1**	DCM	9	93
2[d]	CuCl	-	**L1**	DCM	NR	-
3	CuCl/AgSbF$_6$	-	**L1**	DCM	46	93
4	CuCl/AgSbF$_6$	-	**L1**	PhCF$_3$	19	92
5	CuCl/AgSbF$_6$	-	**L1**	CHCl$_3$	8	88
6[e]	CuCl/AgSbF$_6$	NaBArF	**L1**	DCM	55	94
7[f]	CuCl/AgSbF$_6$	NaBArF	**L1**	DCM	78	94
8[g]	CuCl/AgSbF$_6$	NaBArF	**L1**	DCM	84	94
9	CuCl/AgSbF$_6$	NaBArF	**L2**	DCM	52	94
10	CuCl/AgSbF$_6$	NaBArF	**L3**	DCM	65	94
11	CuCl/AgSbF$_6$	NaBArF	**L4**	DCM	67	94
12	CuCl/AgSbF$_6$	NaBArF	**L5**	DCM	67	82
13	CuCl/AgSbF$_6$	NaBArF	**L6**	DCM	30	94
14[h]	CuCl/AgSbF$_6$	NaBArF	**L1**	DCM	41	94

[a] Unless otherwise stated, the reactions were conducted with **1a** (0.2 mmol, 1 equiv), CuX/AgSbF$_6$ (0.1 equiv/0.12 equiv), **L** (0.12 equiv), NaBArF in solvent (4 mL). [b] Isolated yield. [c] Determined by chiral HPLC. [d] No reaction. [e] NaBArF (0.12 equiv). [f] NaBArF (0.3 equiv). [g] NaBArF (0.5 equiv). [h] CuCl/AgSbF$_6$ (0.05 equiv/0.06 equiv), **L1** (0.06 equiv), NaBArF (0.3 equiv).

substrate. The expected lactam (**2a**) was obtained with a 9% yield and 93% enantiomeric excess (ee) (Table 1, entry 1), which indicated a higher enantioselectivity compared to our previously developed asymmetric Schmidt reaction[10e] and Marsden's results.[10d] When Cu(CH$_3$CN)$_4$PF$_6$ was replaced with CuCl, no reaction was observed, and the unreacted azide **1a** was recovered (entry 2). Then, CuSbF$_6$ prepared *in situ* from CuCl and AgSbF$_6$ was examined in CH$_2$Cl$_2$, PhCF$_3$, and CHCl$_3$, which resulted in moderate to excellent ee values but low yields despite a prolonged reaction time (entries 3-5). From these experimental results, we speculated that a suitable chiral copper(I)-complex could induce high enantioselectivity while the above-tested Cu(I)-species did not convert substrate **1a** completely. Considering that sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF)[11] could generate an active LCuX complex,[12] NaBArF (12 mol%) was used as an additive to improve the reaction outcome. This resulted in an improved yield (55%) and higher ee (94%) (entry 6). Increasing the quantity of NaBArF to 50 mol% produced significantly improved results (entries 7 and 8). However, other structurally related BOX ligands (**L2**-**L4** with smaller H-, Me-, or *i*Pr-substituted phenyl groups, **L5** with a strong electron-withdrawing CF$_3$ substituent, and **L6** bearing merely a Me substituent) were investigated under the same reaction conditions used for entry 8, but the results did not improve (entries 9-13). Finally, a lower loading (6 mol%) of CuSbF$_6$/**L1** with 30 mol% NaBArF was tested, which produced unsatisfactory results. Therefore, the reaction parameters listed in entry 8 (Table 1) were selected as the optimal reaction conditions for further investigation.

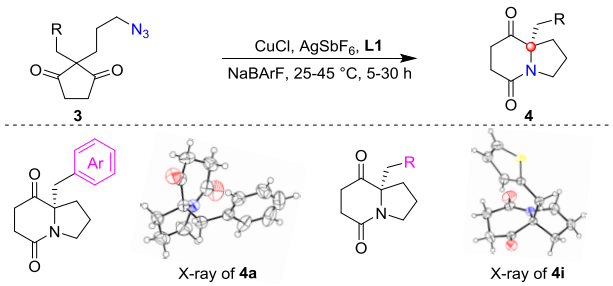
Table 2. Scope of 1,3-cyclohexanedione substrate[a]



[a] Unless otherwise specified, reactions were conducted at room temperature with **1a** (0.2 mmol, 1.0 equiv), CuCl (0.02 mmol, 0.1 equiv), AgSbF$_6$ (0.024 mmol, 0.12 equiv), **L1** (0.024 mmol, 0.12 equiv), NaBArF (0.5 equiv) in 4 mL DCM. Isolated yields. ee value was determined by chiral HPLC. [b] The reaction was carried out at 45 °C, and no product was observed at room temperature.

Using the optimal conditions, the generality of this novel tandem reaction was investigated. Various substituents on the aryl ring were studied, and the results showed that the substrates bearing electron-donating or electron-withdrawing groups generated the expected lactams **2b**-**2i** with high enantioselectivities in moderate to high yields. The *o*-substituted phenyl and 1-naphthyl substrates produced the desired products with diminished yields and slightly higher enantioselectivities, which may be a result of the steric hindrance caused by the substituents (**2c**, **2e**, **2g**, **2i**). Heteroaromatic substrates also produced the corresponding lactams **2j** and **2k** in high yields with slightly reduced enantioselectivities (75% and 80% ee, respectively.). In addition to the different benzyl groups listed above, simple alkyl substituents such as ethyl, *n*-propyl, and 2-phenylethyl, were also examined. It was found that these substrates yielded the desired lactams in moderate to high yields. Esters and methyl ketones, which are functional handles for further derivation, were compatible with the current reaction conditions, and the corresponding lactams **2o** and **2p** were obtained with 85% and 83% ee in 75% and 34% yields, respectively. For the methyl ketone substrate **1o**, the competing reactions on the carbonyl group at the side chain may be accountable for the poor yield. The benzyl azide **1q** was also suitable under the optimal reaction conditions, and the desired tricyclic product **2q** was obtained with a 66% yield and 72% ee. The absolute configurations of products **2a**, **2c**, **2e**, and **2f** were further verified by X-ray crystallography, and the stereochemistry of the other lactams was assigned by their analogs. The ketone groups of the products could be utilized as versatile sites for structural functionalization. For example, the reduction of **2m** with NaBH$_4$ produced the cyclic alcohol **2m'** in a 71% yield as a major diastereoisomer.[13] The absolute configuration of **2m'** was confirmed by X-ray diffraction.

Table 3. Scope of 1,3-cyclopentanedione substrate[a]

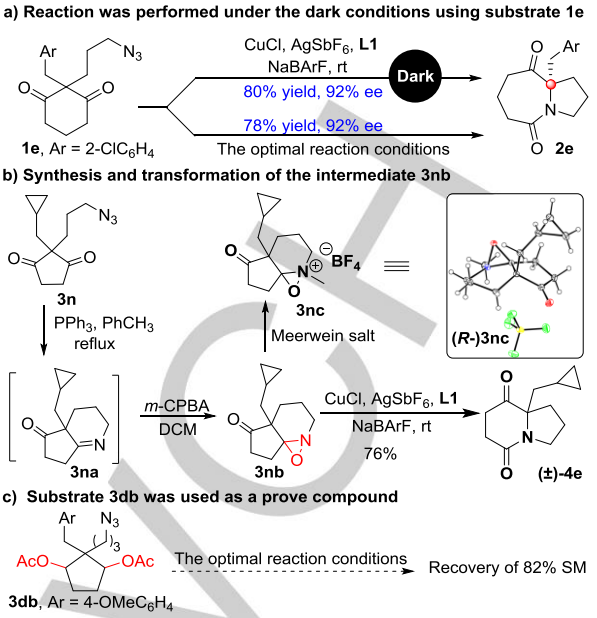


4a, R = C_6H_5, 99% ee, 88%, 12 h
4b, R = 4-MeC_6H_4, 99% ee, 84%, 24 h
4c, R = 2-MeC_6H_4, 99% ee, 63%, 19 h
4d, R = 4-OMeC_6H_4, 99% ee, 85%, 19 h
4e, R = 4-$CF_3C_6H_4$, 99% ee, 76%, 19 h
4f, R = 2-$NO_2C_6H_4$, 99% ee, 44%, 30 h
4g, R = 4-CO_2MeC_6H_4, 99% ee, 70%, 12 h
4h, R = 2-furyl, 99% ee, 78%, 14 h
4i, R = 2-thienyl, 99% ee, 75%, 24 h
4j, R = H, 99% ee, 86%, 5 h
4k, R = Me, 99% ee, 84%, 5 h
4l, R = Et, 99% ee, 78%, 12 h
4m, R = ^{i}Pr, 96% ee, 90%, 8 h[b]
4n, R = cyclopropyl, 99% ee, 76%, 12 h
4o, R = cyclopentyl, 97% ee, 80%, 8 h[b]
4p, R = 2-propenyl, 98% ee, 65%, 24 h[b]
4q, R = 2-(2-methylpropenyl), 99% ee, 82%, 10 h
4r, R = 2-propynl, 99% ee, 36%, 30 h[c]

[a] Unless otherwise specified, reactions were conducted at room temperature with **1a** (0.2 mmol, 1 equiv), CuCl (0.02 mmol, 0.1 equiv), $AgSbF_6$ (0.024 mmol, 0.12 equiv), **L1** (0.024 mmol, 0.12 equiv), NaBArF (0.5 equiv) in 4 mL DCM. Isolated yields. ee determined by chiral HPLC. [b] The reaction was carried out at 45 °C, and low isolated yield was obtained at room temperature. [c] The reaction was carried out at 45 °C, and no product was observed at room temperature.

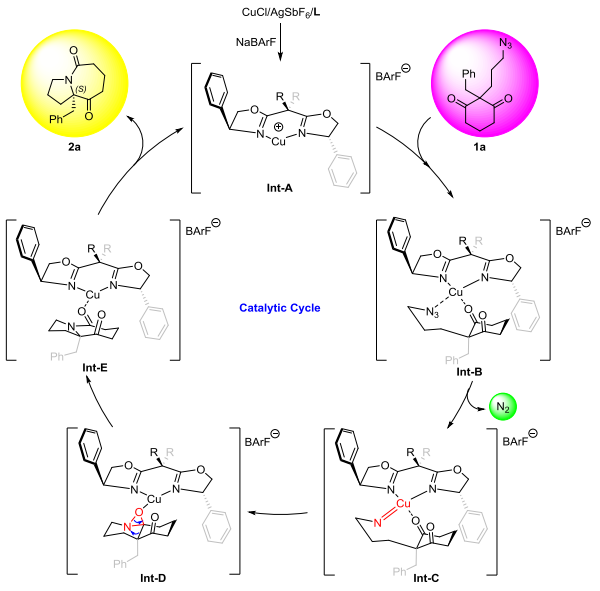
Considering the importance of lactams,[14] we then turned our attention to the scope of other ketones. Specifically, [6,5]-fused bicyclic lactams are important subunits found in various bioactive alkaloids (Figure 1); thus, a series of 1,3-cyclopentanedione derivatives were subjected to the optimized reaction conditions. The R group represented different aryl rings, such as phenyl (**4a**), 4-methyl phenyl (**4b**), 2-methyl phenyl (**4c**), 4-methoxyl phenyl (**4d**), 4-trifluoromethyl phenyl (**4e**), 2-nitro phenyl (**4f**) and 4-methoxyl carbonyl phenyl (**4g**), all of which all produced the desired [6,5]-fused bicyclic lactams with a high ee of 99%. Except for the *o*-substituted products **4c** (63% yield) and **4f** (44% yield), the yields produced were >70%. Notably, both 2-furyl and 2-thienyl substrates produced significantly improved results (99% ee) than their 1,3-cyclohexanedione analogs. Different alkyl groups were also tested under the optimized reaction conditions. In addition to the linear methyl, ethyl and *n*-propyl groups and the sterically hindered *i*-propyl groups, the cyclopropyl and cyclopentyl groups produced the desired lactams with high enantioselectivities. A simple alkenyl group was also suitable under the optimized conditions; it produced lactams containing C=C bonds with 98% ee (**4p**) and 99% ee (**4q**), respectively. The substrate **3r**, bearing an alkynyl group, yielded the lactam **4r** with a 99% ee but low yield of 36%. Additionally, the activity of the key catalyst possibly reduced because of the coordination of the alkyne to the copper center. The acyclic 1,3-dicarbonyl substrates did not produce the desired lactams.

A few designed control experiments were conducted to gain further information regarding the reaction mechanism. When the substrate **1e** was reacted under dark reaction conditions, the desired product **2e** was isolated in a 80% yield with a 92% ee. This implied that the photoinduced transformation was not the dominant mechanism in the current reaction (Scheme 2a).



Scheme 2. The designed control experiments.

Moreover, the liberation of gases was observed under these mild reaction conditions, preliminarily excluding the involving of a classical Schmidt rearrangement in the current transformations. Although a series of trapped experiments were performed, the capture of the active copper-nitrene intermediate failed (for details, see SI). Considering the high reactivity of the copper-nitrene species, the oxaziridine was the key intermediate, followed by a rapid 1,2-alkyl shift process with Cu(I) as the catalyst, which produced the corresponding lactam. As we could not isolate the oxaziridine under these copper-catalyzed reaction conditions, the oxaziridine **3nb** was prepared *via* a two-step synthesis, and its structure was confirmed by an X-ray analysis of its derivative **3nc**.[15] Then, the intermediate **3nb** was subjected to the optimized reaction conditions, and the racemic product **4e** was obtained in a 76% yield (Scheme 2b).



Scheme 3. The proposed reaction mechanism.

Additionally, when the probe compound **3db** was subjected to the optimal reaction conditions, the recovery of the starting material was observed (Scheme 2c), therefore, demonstrating that the carbonyl group of substrates is necessary in the current transformation. These results supported our speculation that the copper(I)-catalyzed oxaziridination is a vital step in the current reaction.

Based on the above results and previous literature, a possible reaction mechanism was proposed, as shown in Scheme 3. First, CuCl complexed with a BOX-type ligand and then reacted with $AgSbF_6$ to yield an intermediate, which was stabilized by the sterically bulky anion BArF to generate the intermediate **Int-A**. Subsequently, the substrate **1a** reacted with the intermediate **Int-A** to release N_2 and produce the key active species Cu-nitrene[1a,16] **Int-C** through the complex **Int-B**. The electronic interactions between the carbonyl group and the copper center perhaps had a crucial role in this process. Subsequently, **Int-D** was generated by asymmetric oxaziridination, resulting in the origin of the enantiocontrol in this procedure. Then, the three-membered ring was opened *via* a N-O bond cleavage accompanied by an alkyl C-N 1,2-shift[17] to generate **Int-E**, which produced the final product lactam **2a** and simultaneously released the catalyst **Int-A** for the next catalytic cycle (Scheme 3).

In conclusion, we have developed a novel copper(I)-catalyzed asymmetric intramolecular tandem oxaziridination/rearrangement reaction. This reaction facilitated the production of various chiral bicyclic lactams with moderate to high enantioselectivities under the mild reaction conditions. This novel reaction could be used to solve practical synthetic problems associated with the classic asymmetric Schmidt reaction. Furthermore, it could be useful as a synthetic method for the discovery of new therapeutics and agrochemicals composed of lactams. Notably, this study provides novel information on the asymmetric transformations involving Cu-nitrene species and their corresponding mechanisms. Further exploration of these unique Cu-nitrene-catalyzed asymmetric transformations and their detailed mechanistic investigation is currently underway.

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Crystallographic Data

Crystallographic data generated during this study has been deposited in the Cambridge Crystallographic Data Centre (CCDC) under accession numbers CCDC: 2058848 (**2a**), 2058852 (**2c**), 2058853 (**2e**), 2058850 (**2f**), 2058851 (**2i**), 2058855 (**2k**), 2058856 (**4a**), 2058860 (**4c**), 2058857 (**4g**), 2059059 (**4i**), 2058849 (**2m′**) and 2059060 (**3nc**).

Keywords: chiral copper-nitrene • oxaziridination • rearrangement reaction • Schmidt reaction • bicyclic lactams

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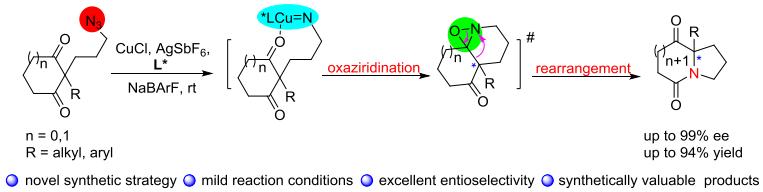

Cu-nitrene-catalyzed asymmetric transformation is merely limited in the aziridination of C=C double bonds in the past decades. Herein, we not only developed a novel Cu-nitrene catalyzed oxiazididdition of C=O double bonds, but also achieved a tandem asymmetric oxiazidation/rearrangement reaction of cyclic diketones, affording a series of bicyclic lactams bearing a quaternary carbon center.