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# Synthesis of γ-Lactams by Formal Cycloadditions with Ketenes

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Cite This: *Org. Lett.* 2021, 23, 2449−2454 Read Online

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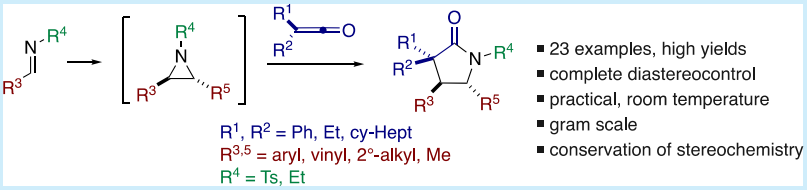


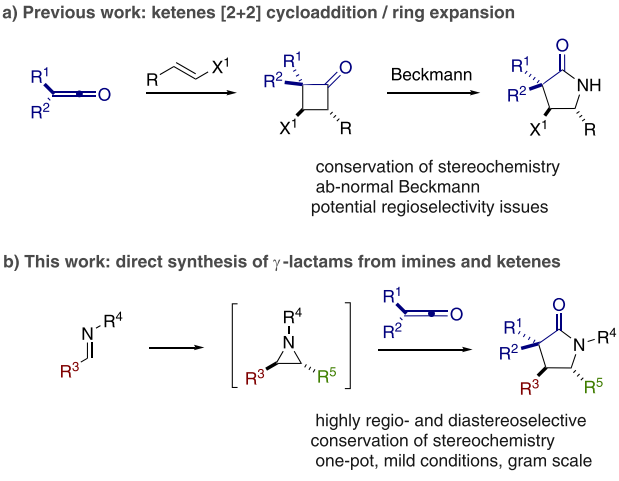

**ABSTRACT:** The synthesis of γ-lactams is reported by a formal (3+2) cycloaddition between readily available ketenes and aziridines or a one-pot formal (2+1+2) cycloaddition using imines as aziridine precursors. The method is practical, is scalable, and affords high yields. It also offers a high level of regio- and diastereoselectivity on a wide range of substrates as well as a high stereoselectivity in the case of enantiopure aziridines.



Ketenes have been extensively used in thermal [2+2] cycloadditions to afford a unique entry to four-membered ring scaffolds.[1] Their original heterocumulenic structure allows normally forbidden [2+2] thermal cycloadditions.[2] The reaction of ketenes with imines and aldehydes offers particularly straightforward access to β-lactams and β-lactones, respectively. The thermal [2+2] cycloaddition of ketenes with alkenes has also led to a wide diversity of functionalized cyclobutanones through a highly diastereoselective process with electron rich chiral enol ethers.[3] Due to their high ring strain, cyclobutanones can in turn undergo ring expansion to diversely substituted five-membered carbo- and heterocycles such as cyclopentanones (with diazoalkanes), γ-lactams (through a Beckmann transposition), and γ-lactones (via a Baeyer−Villiger oxidation).[4] In the past several decades, our group has been involved in the synthesis of a variety of γ-butyrolactams using the ketene [2+2] cycloaddition and ring expansion strategy in the context of the total synthesis of natural products (Scheme 1a).[5] During these syntheses, we often faced difficulties at the ring expansion step, particularly with the Beckmann transposition: yields and selectivities were highly sterically and electronically dependent. In fact, the normal Beckmann reaction is well-known to be often hampered by the formation of appreciable amounts of abnormal Beckmann nitrile derivatives.[6] We wondered whether a cycloaddition between a ketene and a suitable 1,3-dipole would be possible as it would allow direct access to the corresponding γ-lactams and thus offer an effective alternative preparation of these particularly useful pyrrolidine scaffolds.[7]

Compared to other reactions involving ketenes, only a few examples of (3+2) cycloadditions have been reported so far, most often involving nonclassical dipoles.[8] To the best of our knowledge, the only example in the literature that involves an aziridine is a genuine Huisgen type 1,3-dipolar cycloaddition giving a mixture of cycloadducts.[9] In this study, the 1,3-dipole is generated by the thermal C−C bond cleavage of an aziridine and reacted with a ketene to afford a mixture of two cycloaddition products, namely, the 2-oxopyrrolidine from cycloaddition on the C═C bond of the ketene and an oxazolidine from cycloaddition on the C═O bond. Even though aziridines are known to react as 1,3-heterodipoles through C−N bond cleavage, a (3+2) cycloaddition of aziridines with ketenes through this mode of cleavage has not yet been reported

**Scheme 1. Ketene Cycloadditions in the Synthesis of γ-Lactams**




**Received:** January 28, 2021
**Published:** March 11, 2021

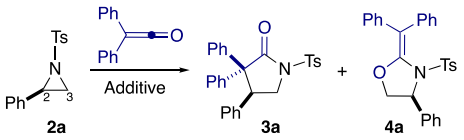



https://dx.doi.org/10.1021/acs.orglett.1c00335
*Org. Lett.* 2021, 23, 2449−2454

(Scheme 1b). The main challenges associated with this reaction are the selectivity between the two cleavable C−N bonds and the site selectivity of the addition to the ketene (C=C vs C=O).

The investigation started with *N*-tosyl-2-phenylaziridine **2a** and diphenyl ketene, both readily available.[10] The strong electrophilicity of ketenes prompted us to directly test its ability to act as the activating agent of the aziridine: mixing aziridine **2a** with diphenyl ketene, however, did not lead to lactam **3a**, the aziridine being quantitatively recovered (Table 1, entry 1). The

**Table 1. Influence of Additives on the Formal (3+2) Cycloaddition**[a]




| entry | additive | equiv | conversion (%)[b] | **3a**:**4a** ratio[c] |
|---|---|---|---|---|
| 1 | none | – | 0 | – |
| 2 | LiCl | 1 | 0 | – |
| 3 | LiBr | 1 | 60 | 75:25 |
| 4 | LiI | 1 | 98 | >95:5 |
| 5 | $nBu_4NI$ | 1 | 80 | 75:25 |
| 6[d] | LiI | 0.2 | 76 | >95:5 |
| 7[d] | LiI | 0.1 | 45 | >95:5 |
| 8 | LiI | 0.8 | 100 | >95:5 (88%) |

[a]Reaction conditions: diphenyl ketene (2.0 equiv, slow addition of ketene over 1 h), aziridine **2a** (1.0 equiv, 0.2 M), additive, THF, rt, 2 h. [b]NMR measurement, on the crude mixture, based on the transformation of aziridine **2a**. [c]Isolated yield in parentheses. [d]In this cases, the second equivalent of ketene was added after reaction for 8 h; the total reaction time was 18 h.

Lewis acid activation of aziridines into 1,3-heterodipoles by selective cleavage of the C−N bond is well documented.[11] We thus tested a wide variety of Lewis acids such as boron trifluoride,[11a] scandium triflate,[11b] copper triflate,[11c] zinc bromide,[11d] and nickel iodide,[11e] but in combination with ketene, all failed to produce any detectable amounts of lactam, affording only ketene dimers and aziridine ring-opened and unidentified side products.[10] The ring opening of the aziridine in the presence of carbon dioxide has also been reported to be triggered by first-row metal-halide.[12] We thus decided to test lithium halides as the co-activator, which turned out to be much more rewarding. While the addition of lithium chloride left the starting aziridine untouched (Table 1, entry 2), the use of lithium bromide led, for the first time, to the formation of two cycloaddition products: desired lactam **3a**, resulting from the ring opening at C-2, and oxazolidine **4a**, resulting from the opening of the aziridine at the less hindered C-3 (Table 1, entry 3).[16] Eventually, lithium iodide rewardingly afforded γ-lactam **3a** with complete conversion of the aziridine and only traces of oxazolidine **4a** (Table 1, entry 4).[14] Changing lithium to tetrabutylammonium led to incomplete conversion, and less repeatable reactions, producing the lactam and the oxazolidine in a 75/25 ratio (Table 1, entry 5). A substoichiometric amount of lithium iodide was also sufficient to effectively promote the reaction (Table 1, entries 6 and 7). However, at 20 mol %, the reaction became much slower, most probably favoring ketene dimerization, thus decreasing the level of formation of the lactam; introducing the ketene in two portions allowed to enhance the yield of lactam, 76% with 20 mol % lithium iodide and 45% with 10 mol % [reaction lasting 18 h instead of 2 h (Table 1, entries 6 and 7)]. Different solvents such as diethyl ether, dichloromethane, and toluene were also evaluated: minor variations were observed, tetrahydrofuran and diethyl ether being the best solvents, for both the yield and the selectivity.[10] Ultimately, the best conditions were obtained when the reaction was performed in tetrahydrofuran at room temperature using 0.8 equiv of lithium iodide, with slow addition of the ketene over 1 h [83% isolated yield (Table 1, entry 8)].

As *N*-tosylaziridines are concomitantly generated with lithium iodide by reacting an *N*-tosylimine with iodomethyllithium,[15] a one-pot (2+1+2) reaction was an interesting alternative that would allow the formation of a lactam directly from the corresponding imines. This would not only provide a more straightforward route to γ-lactams but also eliminate the requirement to isolate the sometimes sensitive and potentially toxic aziridines. To our delight, the addition of methyllithium to a solution of diiodomethane and *N*-tosylimine **1a** at −78 °C, followed by a subsequent slow addition of 2 equiv of diphenyl ketene at room temperature, afforded γ-lactam **3a** in 88% yield, which compared favorably with the 66% combined yield obtained through the stepwise procedure (Scheme 2).

With these optimal conditions in hand for both the one-pot (2+1+2) and the stepwise (3+2) formal cycloadditions, the scope of the reaction was next explored. Interestingly, the two methods appeared to be very complementary, the one-pot (2+1+2) cycloaddition conditions being very effective from *N*-tosylimines and the (3+2) conditions being essential when alternative strategies are used to obtain the aziridines (Scheme 2).

The *p*-fluorophenyl- and *p*-bromophenyl-substituted aziridines **2b** and **2c** afforded lactams **3b** and **3c**, respectively, in very good yields, with equal efficiency for the one-pot and stepwise processes (Scheme 2). The next example was particularly striking as it also highlighted the advantage of the one-pot procedure over the stepwise protocol. Indeed, whereas *p*-methoxyphenyl lactam **3d** could be isolated in 75% in the one-pot process, the two-step sequence was unfruitful due to the inherent instability of aziridine **2d**, which could not be isolated in >25% yield. Another feature of the formal cycloaddition is the rather limited electronic influence of the substituents at the aromatic *para* position on the efficiency of the cycloaddition: both electron-donating and electron-withdrawing groups leading to high yields. The *p*-nitrophenyl group, however, led to a significant decrease in the yield of lactam **3e** (47%). This low yield of the one-pot process is essentially due to the rather inefficient formation of aziridine **2e**, isolated in only 57% yield from *p*-nitro imine **1e**, the subsequent (3+2) cycloaddition being very effective affording lactam **3e** in 94% yield. The *m*-fluoro-, *m*-bromo-, and *m*-methoxy-substituted phenyl derivatives (**1f**−**h**) afforded γ-lactams **3f**−**h**, respectively, in yields ranging from 71% to 87%, with again slightly better yields for the one-pot procedure. The *o*-tolyl lactam **3i** and 1-naphthyl lactam **3j** were obtained with equal efficiency, showing the compatibility of the cycloaddition with slightly more sterically demanding mono *ortho*-substituted aryl derivatives. Furyl-derived lactam **3k**, however, was isolated in only 15% yield in the one-pot sequence. This poor yield is again due to the inefficient formation and instability of aziridine **2k**, which in this case could not be isolated from imine **1k**.

To further test the scope of the reaction, non-aryl-substituted aziridines were next engaged. Hence, cinnamyl lactam **3l** was


https://dx.doi.org/10.1021/acs.orglett.1c00335
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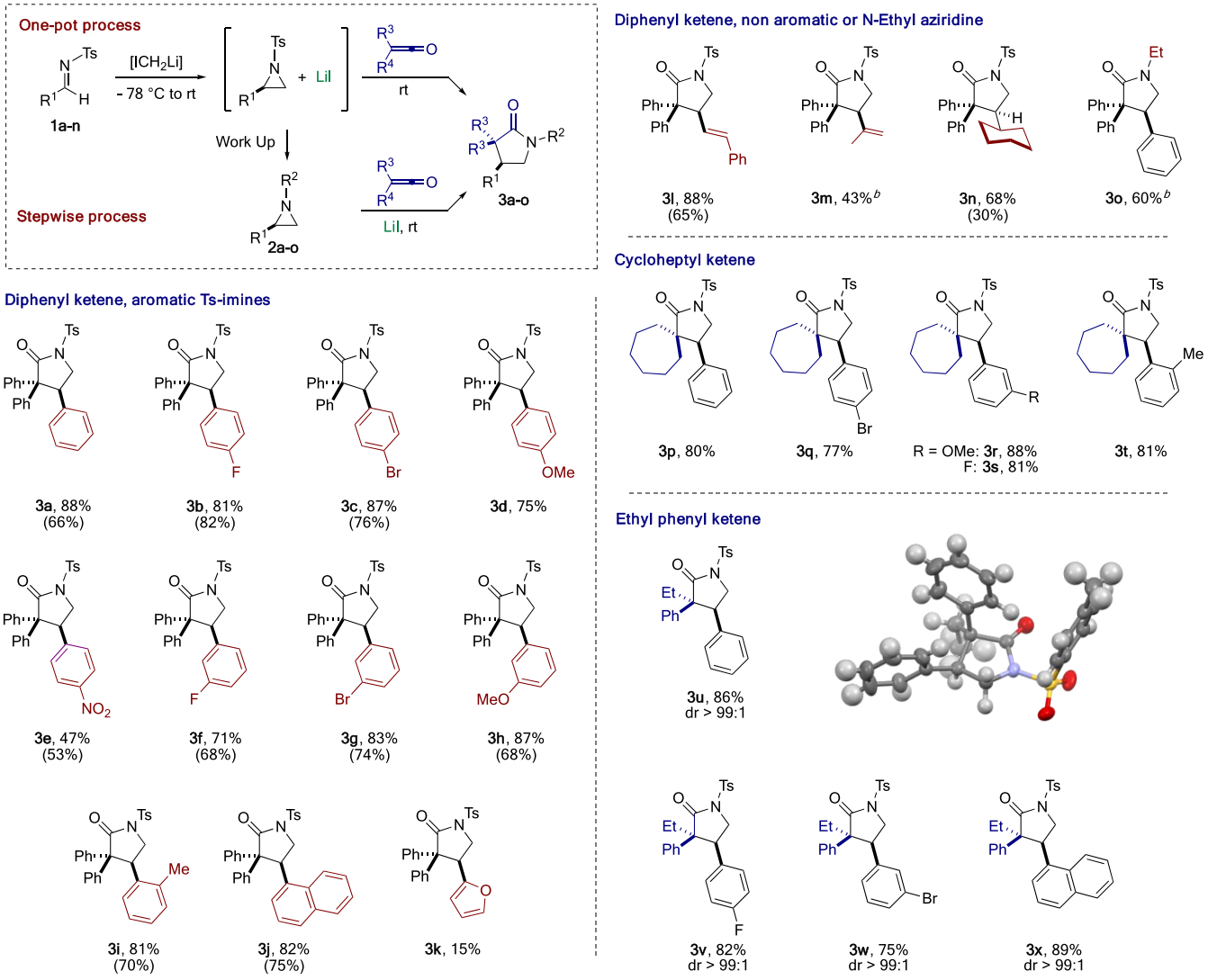
**Scheme 2. Scope of the (2+1+2) and (3+2) Cycloaddition**[a]




[a]Reaction conditions A for the (2+1+2) reaction: imine **1** (1 equiv, 0.2 M), $CH_2I_2$ (2 equiv), MeLi (2 equiv), THF, −78 °C for 1 h and then rt for 30 min, then ketene (2.0 equiv, added over 1 h), rt, 3 h. Reaction conditions B for the (3+2) reaction: ketene (2.0 equiv, added over 1 h), aziridine **2** (1.0 equiv, 0.2 M), LiI (0.8 equiv), THF, rt, 3 h. All reactions performed on a 0.2−0.3 mmol scale. See the experimental section in the Supporting Information for full details. Yields are those of isolated products of the one-pot process; yields in parentheses, when present, refer to the combined yields of the two-step procedure. [b]Yields for the (3+2) cycloaddition step.

obtained through both the one-pot and stepwise processes from cinnamyl imine **1l** in 88% and 65% yields, respectively. Lactam **3m** was obtained in 43% yield starting from isopropenyl aziridine **2m**.[16] To further evaluate the scope of the reaction, cyclohexyl-substituted imine **1n** was engaged in the formal cycloaddition and interestingly also proved to be compatible: the corresponding lactam **3n** was obtained in 68% yield. Finally, we also evaluated the necessity of having an electron-withdrawing group on the nitrogen atom by performing the reaction with *N*-ethyl aziridine **2o**. The latter, prepared from dimethylsulfurane ylide and ethylamine,[17] provided the corresponding *N*-ethyl lactam **3o** in a decent 60% yield, thus showcasing the wide scope of the method.

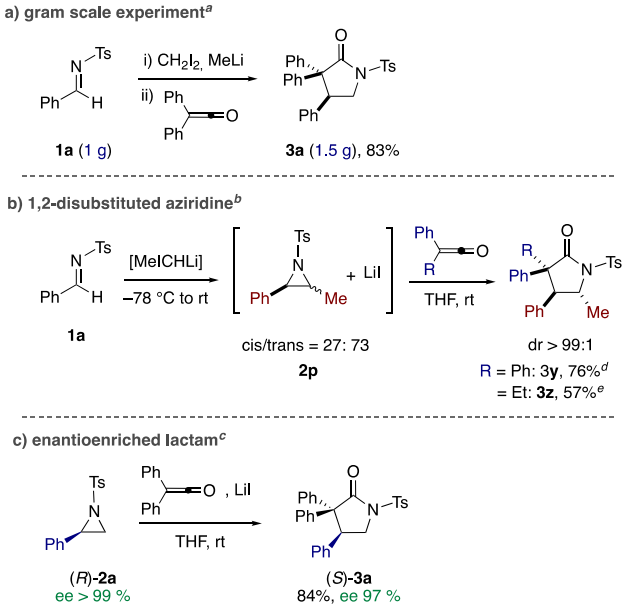
After exploring various structural variations on both the aziridine and the imine, we next focused on the ketene. Both the cycloheptyl ketene[18] and the ethyl phenyl ketene[19] were subjected to the optimized one-pot (2+1+2) formal cycloaddition conditions (Scheme 2). Interestingly, cycloheptyl ketene led to the corresponding lactams with the same efficiency as diphenyl ketene from imines **1a** and **1c** under the one-pot conditions. With *m*-substituted aromatic imines **1h** and **1f**, similar results were observed affording lactams **3r** and **3s** in 88% and 81% yields, respectively. Lactam **3t**, bearing an *o*-tolyl substituent, was also efficiently formed (81% yield). The next question to address was the potential control of the diastereoselectivity using unsymmetrical ketenes. Interestingly, ethyl phenyl ketene and imine **1a** led to the corresponding lactam **3u** in 83% yield as a single diastereoisomer, hence with full control of the quaternary stereogenic center. The same result was obtained starting from *p*-fluorophenyl imine **1b** and *m*-bromophenyl imine **1g**, which both afforded the corresponding lactams **3v** and **3w** as single diastereoisomers. Finally, 1-naphthyl-derived lactam **3x** was also obtained with complete


https://dx.doi.org/10.1021/acs.orglett.1c00335
Org. Lett. 2021, 23, 2449−2454

control of the diastereoselectivity. The *cis* orientation of the phenyl groups in lactam **3u** was determined by X-ray analysis.[13]

To further demonstrate the synthetic utility of the method, the reaction was run on a gram scale with diphenyl ketene and imine **2a**: 1.5 g of lactam **3a** was obtained in 83% yield, comparable to the result obtained on a smaller scale [88% (see Schemes 2 and 3a)].

**Scheme 3. Additional Scope of the Ketene (3+2) Cycloaddition**



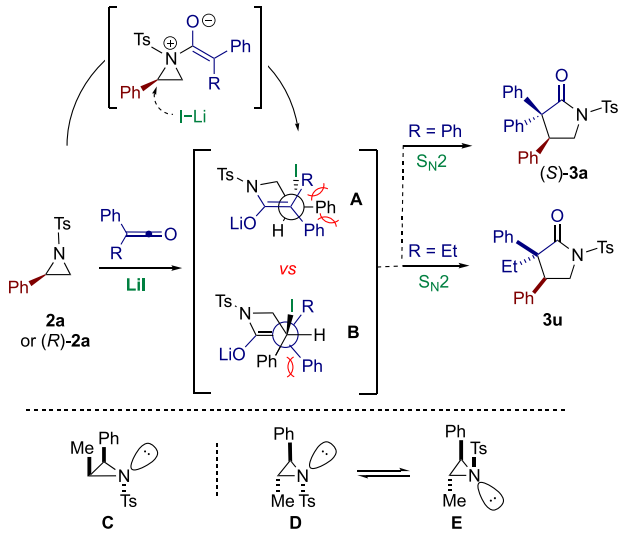

[a]Under reaction conditions B with imine **1a** (1.0 g, 3.9 mmol). [b]Using conditions B on a 0.2 mmol scale. [c]Using conditions A on a 0.2 mmol scale. [d]Yield of **3y** and *cis*-**2p** (76:24). [e]Yield of **3z** and *cis*-**2p** (65:32).

Considering the diastereoselectivity obtained with unsymmetrical ketenes, it was appealing to test the reaction with unsymmetrical ketene and a 2,3-disubstituted aziridine. Upon addition of iodoethyllithium to imine **1a**, a *cis*/*trans* mixture of *N*-tosyl-2-phenyl-3-methyl aziridine **2p** was obtained (27:73, *cis*/*trans* mixture).[20] The latter was subsequently reacted with diphenylketene to afford trisubstituted lactam **3y** as a single *trans* diastereoisomer, isolated as a mixture with unreacted *cis*-**2p** [76%, 76:24 **3y**:*cis*-**2p** (Scheme 3b)]. Surprisingly, only the *trans* aziridine reacted to form the corresponding lactam **3y**. In fact, pure *cis*-**2p**, prepared by nitrene aziridination of *cis*-*β*-methylstyrene,[21] did not lead to any detectable amount of lactam. Even more striking was the result obtained with the unsymmetrical ethyl phenyl ketene, which afforded 3,4,5-substituted lactam **3z** as a single diastereoisomer along with unreacted aziridine *cis*-**2p** [57%, 65:35 **3z**/*cis*-**2p** (Scheme 3b)]. The relative stereochemistry of lactams **3y** and **3z** was assigned by NOE experiments.

The final aspect that needed to be evaluated was the stereospecificity of the (3+2) formal cycloaddition starting from an enantioenriched aziridine. Aziridine (*R*)-**2a** was thus synthesized from the corresponding enantiopure amino alcohol[11d] and engaged with diphenyl ketene under the (3+2) conditions. To our delight, the resulting lactam (*S*)-**3a** was obtained with an only slight erosion of enantiopurity (Scheme 3c).[22]

Considering the observed selectivities and reactivity, in combination with previous DFT studies of aziridine ring opening,[23] we can propose a mechanism for the formal aziridine/ketene cycloaddition in the presence of lithium iodide. No reaction occurs when the aziridine and lithium iodide are mixed at room temperature, which is in agreement with the fast formation of the aziridine from the imine and iodomethyl lithium.[15] An initial reversible complexation of the aziridine by the ketene is necessary to weaken the C–N bond,[24] followed by an $S_N2$-like ring opening of the aziridine at the most substituted side of the aziridine[25] by the iodide to produce an enolate type intermediate that subsequently cyclizes (Scheme 4). The

**Scheme 4. Proposed Mechanism Involving Two $S_N2$-like Pathways**




selective ring opening can be attributed to the stabilization of a developing positive charge by a neighboring aryl and even more strikingly alkyl substituent, even though in the latter case the yield is slightly lower. The observed retention of the configuration starting from the enantioenriched aziridine comes from a double inversion. The formation of a single diastereoisomer with unsymmetrical ketenes would come from a geometrically defined enolate,[19] followed by an intramolecular $S_N2$ cyclization minimizing *gauche* interactions (**B** being more favorable than **A**) (Scheme 4). Finally, the apparent absence of reactivity of *cis*-aziridine can be attributed to a more difficult initial complexation of this *cis* isomer with ketene, due to unfavorable steric interactions. Considering the different conformers of the $sp^3$-hybridized nitrogen on the aziridines,[26] in conformer **C**, the ketene should approach through the most hindered side (two steric interactions with methyl and phenyl), whereas for **D** and **E**, a single unfavorable steric interaction would be present.

In summary, we have developed an unprecedented direct synthesis of *γ*-lactams starting from imines, through a formal (2+1+2) cycloaddition process that involves iodoalkyllithium species and isolable ketenes, and a (3+2) formal cycloaddition starting from aziridines. These formal cycloadditions show a great diversity, remarkable selectivities, and, notably, conservation of the chiral information with an enantioenriched aziridine. Additional studies are ongoing to broaden the scope and add further insights into the mechanism and observed diastereoselectivities of this unusual reaction.



https://dx.doi.org/10.1021/acs.orglett.1c00335
Org. Lett. 2021, 23, 2449–2454

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00335.

Full experimental details, compound characterization, and $^{1}H$ and $^{13}C$ NMR spectra for all new compounds (PDF)

### Accession Codes

CCDC 1998270−1998271 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.

## ■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the ANR (project ketflo ANR-18-CE07-0035-01) and EUR-CBH (ANR-11-LABX-0003-01) for financial support. The authors are also thankful for support from ICMG FR 2607, Grenoble, through which NMR, MS, and X-ray analyses have been performed.

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https://dx.doi.org/10.1021/acs.orglett.1c00335
*Org. Lett.* 2021, 23, 2449−2454