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Synthesis of Highly Substituted Cyclobutane Fused-Ring Systems from *N*-Vinyl β-Lactams through a One-Pot Domino Process

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Abstract: In this contribution, aminocyclobutanes, as well as eight-membered enamide rings, have been made from *N*-vinyl β-lactams. The eight-membered products have been formed by a [3,3]-sigmatropic rearrangement, whereas the aminocyclobutanes have been derived from a domino [3,3]-rearrangement/6π-electrocyclisation process. The aminocyclobutanes have been obtained in a highly diastereoselective fashion. The cyclobutane ring system tolerates fusion even if adjacent quaternary centres are present. Systems containing up to four fused rings are readily accessible. The reaction profile has been investigated by using Gaussian 03. This study suggests that two reaction pathways for aminocyclobutane formation are possible. In one pathway the [3,3]-sigmatropic rearrangement is the rate-limiting step and in the second pathway the electrocyclisation is rate limiting. Taken together, these reactions should facilitate the construction of fused heterocycles.

Keywords: lactams · cyclobutanes · domino reactions · electrocyclic reactions · pericyclic reactions

Introduction

β-Lactams are important molecules because of their utility as therapeutic agents and as intermediates in chemical synthesis.[1] Numerous methods have been developed to prepare these molecules in both academic and industrial settings. The ester–enolate imine cycloaddition, olefin–isocyanate cycloaddition, Kinugasa reaction and the Staudinger reaction are just a few of the many methods used to make β-lactams.[2] The pharmaceutical industry has significant demands for β-lactams because of their biological activity.[3] Ever since the discovery of penicillin,[4] great strides were made towards synthesising various penicillin analogues to combat the growing resistance of bacteria against therapeutics.[5]

Compared with β-lactams, cyclobutanes are much less studied four-membered rings, but they are common motifs in many natural products.[6] Cyclobutanes can also serve as reactive handles for the synthesis of natural products.[7] The most common way to make cyclobutanes is by a photochemical [2+2] cycloaddition between two olefins. This photochemical pathway has inherent drawbacks, such as a lack of chemo- and stereoselectivity. Thermal [2+2] cycloadditions between olefins are known to take place, but they are much more rare because the olefins that participate in the reaction have to be electronically biased or must exhibit a great deal of strain.[8]

We have been interested in the synthesis and transformations of β-lactam and cyclobutane ring systems and recently reported a synthetic method to make aminocyclobutanes from *N*-vinyl β-lactams in a highly stereoselective manner through a pericyclic cascade sequence.[9] Herein, we present an account of the synthetic utility of *N*-vinyl β-lactams, which includes the synthesis of eight-membered enamide rings through a sigmatropic ring expansion, the synthesis of aminocyclobutanes through a ring-strain transposition domino sequence. While dwelling on mechanistic underpinnings of this reaction, we also performed a computational study of the mechanism, which provides evidence for the intermediates postulated along the reaction pathway.

Results and Discussion

N-Vinyl β-lactam starting materials can be prepared on a multigram scale in three steps that include a single purification (Scheme 1). The synthesis begins with a formal [2+2]

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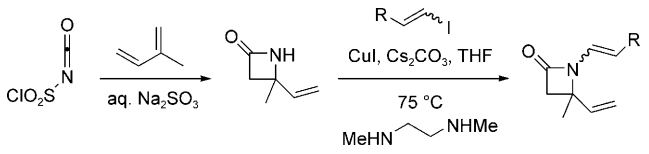
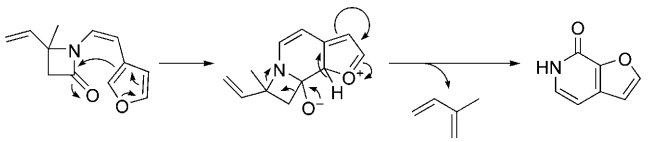


Scheme 1. Synthesis of *N*-vinyl β-lactams.

cycloaddition between a diene, such as isoprene, and chlorosulfonyl isocyanate[10] to afford the *N*-chlorosulfonyl β-lactam, which is cleanly reduced to the corresponding *N*-H β-lactam with aqueous sodium sulfite.[11] The *N*-H β-lactam is then cross coupled with a vinyl iodide[12] under copper-catalysed coupling conditions[13] to yield the corresponding *N*-vinyl β-lactam.

Upon thermal microwave heating of *N*-vinyl β-lactams, we observed the formation of eight-membered enamide rings[14] by a [3,3] sigmatropic rearrangement/tautomerisation sequence. As shown in Table 1, electron-rich, -poor and neutral enamide substituents **1a**–**4a** are tolerated, producing compounds **1b**–**4b**. Substrates containing various heterocyclic side chains, such as thiophene **7a**, pyrrole **8a** and furan **9a**, also participate in this chemistry. We note that fused aromatic heterocycles **8c** and **9c** are produced in addition to the eight-membered enamide rings when furan or *N*-methyl pyrrole side chains are used. The β-lactam component can be modified to contain an allene in place of an olefin. Allenes also partake in the [3,3] sigmatropic rearrangement leading to cross-conjugated triene ring systems, such as **10b**. When the R group is an alkyl substituent, the initial product is imine **6b**, which tautomerises into enamide **6c**.

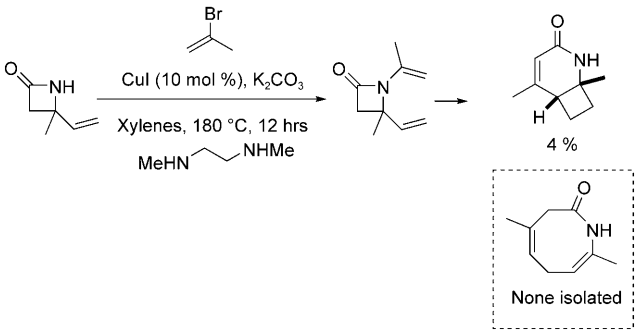
The structure of fused aromatic heterocycle **8c** (Table 1) was unambiguously proven through X-ray crystallography.[15] Formation of these fused aromatic heterocycles is likely to proceed by a Friedel–Crafts addition onto the β-lactam (Scheme 2), followed by extrusion of isoprene to yield the heterocycle. None of the other electron neutral or electron-rich substituted benzene rings followed this reaction pathway, which is consistent with a requirement for a fairly electron-rich ring to be present.



Scheme 2. Proposed mechanism of fused aromatic heterocycle synthesis.

The next task was to try and make the eight-membered enamide rings by generating the *N*-vinyl β-lactam in situ. The latter was projected to undergo a [3,3] sigmatropic rearrangement/tautomerisation sequence to yield the eight-membered enamide (Scheme 3).

In the event, there was substantial decomposition and none of the eight-membered enamide ring was obtained. Instead, a δ-lactam fused to the cyclobutane ring was isolated.



Scheme 3. Attempted one-pot-process synthesis of eight-membered enamides leading to aminocyclobutanes.

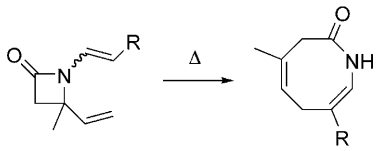
Despite the low yield of this reaction outcome, it captured our attention. A literature search of the fused cyclobutane δ-lactam fragment shows that the vast majority of procedures involve a photochemical reaction between two olefins to make the ring system.[16] Thus, our method appears to be a rare thermal process to make fused cyclobutane δ-lactams. The optimisation of the reaction conditions for the aminocyclobutane synthesis was focused on using *N*-vinyl β-lactams as starting materials rather than in situ synthesis of *N*-vinyl β-lactams from *N*-H β-lactams and vinyl halides.

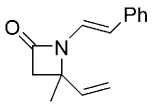
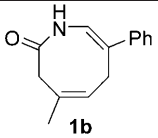
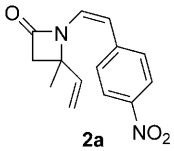
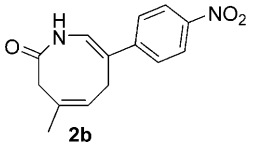
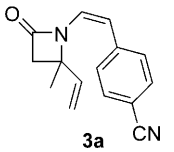
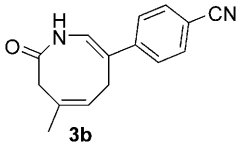
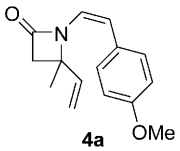
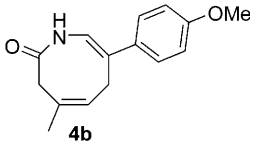
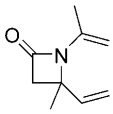
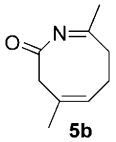
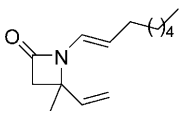
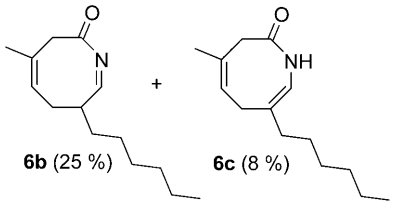
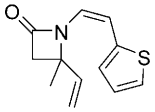
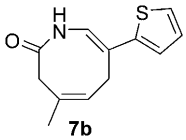
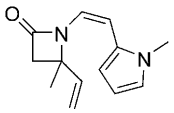
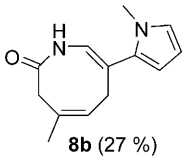
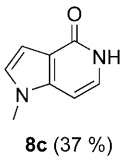
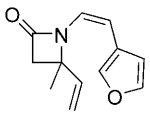
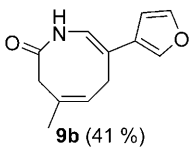
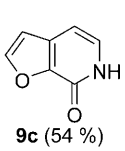
The one-pot reactions that lead to products through either tandem, domino or cascade reactions are of substantial value in organic synthesis. The syntheses of numerous complex natural products incorporate these reactions at various stages.[17] These reactions also have countless benefits, in that they can be atom, time and step economical.[18] In particular, domino reactions are one-pot processes in which all of the starting materials and reagents are present from the very beginning. The functional group(s) produced in the ensuing sequence of bond-forming and -breaking events feed into the following step, much like a game of dominos.[19]

Table 2 shows the results of optimising the reaction conditions for the synthesis of the aminocyclobutane from *N*-vinyl β-lactam **12a**. Microwave heating of **12a** in the temperature range between 140 and 200 °C without any additives afforded the eight-membered enamide product exclusively (Table 2, entry 1). As shown in entry 2, when caesium carbonate was added, we obtained a mixture of the 8-membered enamide and aminocyclobutane in a 4:6 ratio in favour of the latter with a combined yield of 75%. Finally, when both copper iodide and caesium carbonate were used, the aminocyclobutane was produced exclusively.

One of the notable features of the aminocyclobutanes is the combined effect of a cyclobutane and an α,β-unsaturated carbonyl system on the ^{13}C NMR chemical shift of the β carbon. The ^{13}C chemical shift of the β carbon ranges from $\delta = 150$ to 160 ppm in all of the aminocyclobutanes. The six-membered α, β- unsaturated lactams typically display the ^{13}C chemical shift of the β carbon around $\delta = 142.8$ ppm (CD_3OD, TMS).[20] In our case, the combination of a cyclobutane and an α, β-carbonyl system dramatically increases

Table 1. Synthesis of eight-membered enamide rings from *N*-vinyl β-lactams.[a]



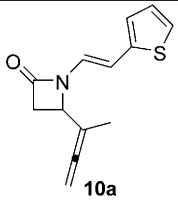
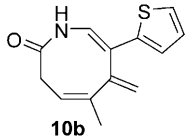
	β-Lactam	Product	Yield [%][b]
1	 **1a**	 **1b**	86
2	 **2a**	 **2b**	48
3	 **3a**	 **3b**	62
4	 **4a**	 **4b**	58
5	 **5a**	 **5b**	56
6	 **6a**	 **6b** (25 %) **6c** (8 %)	–
7	 **7a**	 **7b**	73
8	 **8a**	 **8b** (27 %)  **8c** (37 %)	–
9	 **9a**	 **9b** (41 %)  **9c** (54 %)	–

the chemical shift of the β carbon. This hints at the possibility that the β carbon can be a good electrophile for conjugate additions.

Table 3 shows the substrate scope of the aminocyclobutane formation. The substrates initially tested were compounds **6a**, **12a** and **13a**. The reaction works well in each case with moderate levels of diastereoselectivity and tolerates alkyl side chains as well as a tethered phenyl group. The geminally disubstituted enamides were then reacted to yield the aminocyclobutane products with a tertiary stereocentre adjacent to a quaternary stereocentre. The transformations of substrates equipped with alkyl substituents or tethered phenyl rings worked reasonably well to afford products **14b** through **17b**. In many cases the crude products did not require any purification. The reaction selectivity was not as high when starting materials **19a**–**21a**, containing aryl groups were used compared with starting materials containing alkyl groups. Both the aminocyclobutane and the eight-membered enamide ring product were isolated in these instances. Carbocyclic side chains, such as cyclopropyl, cyclobutyl and cyclohexyl, at the geminal position could also be used to make compounds **22b**, **23b** and **24b** in respectable yields. Lastly, the spirocyclic compound **25b** was made from a tetrasubstituted olefin. Single diastereoisomers were isolated in all cases in which *gem*-disubstituted olefins were used.

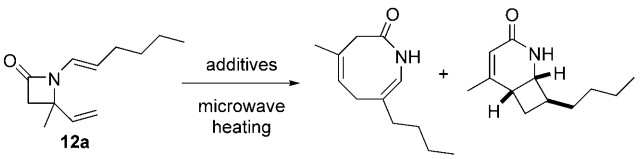
N-Vinyl β-lactams that contained carbocyclic trisubstituted olefins were also synthesised (Table 4). Subjecting these substrates to reaction conditions produced two fused rings with three contiguous stereocentres in a single step. With the five-membered carbocycle, the reac-

Table 1. (Continued)

	β-Lactam	Product	Yield [%][b]
10	 10a	 10b	48

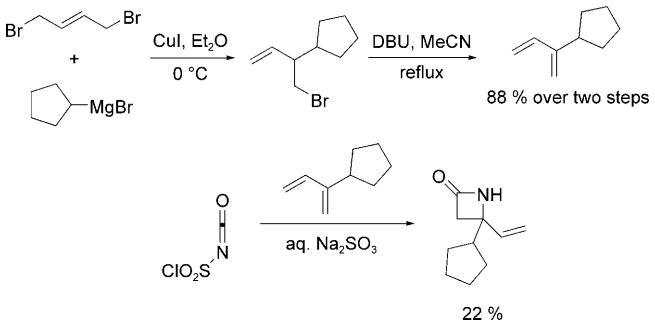
[a] Conditions: *N*-vinyl β-lactam (20.0 mg), DMF (500 μL), microwave heating 160–200 °C, see the Supporting Information.[9] [b] Isolated yield.

Table 2. Aminocyclobutane synthesis optimisation: additives screening.



	Additive	*T* [°C]	Result	Yield [%][a]
1	–	140–200	100:0	50
2	Cs_2CO_3	180	40:60	75
3	CuI (5 mol %), Cs_2CO_3 (1.5 equiv)	180	0:100	98

[a] Isolated yield.



Scheme 4. Synthesis of 2-cyclopentyl-1,3-butadiene and 4-cyclopentyl-4-vinylazetidin-2-one. DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene.

tion worked smoothly to produce **26b** in 75% yield. The six-membered ring produced both the aminocyclobutane and the 8-membered enamide ring with a combined yield of 95% in a 6:4 ratio favouring the former. The seven-membered carbocyclic substituent was also within the scope of the process, delivering compound **28b** in 83% yield. With the eight-membered carbocycle, the product produced was exclusively the aminocyclobutane, albeit as a mixture of diastereoisomers (2.60:1.00).

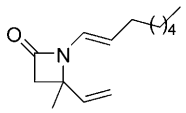
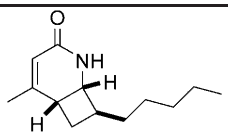
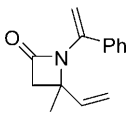
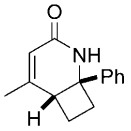
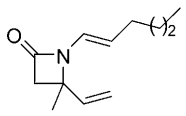
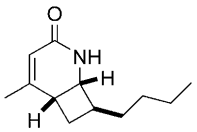
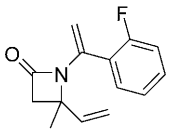
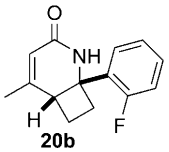
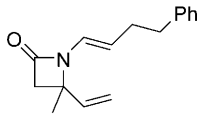
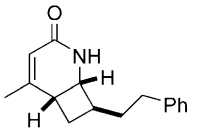
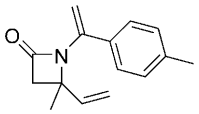
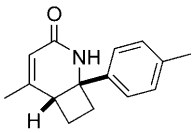
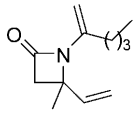
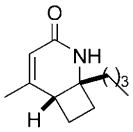
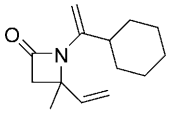
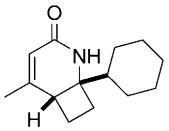
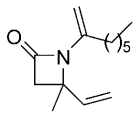
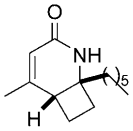
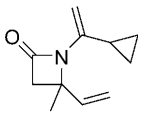
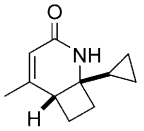
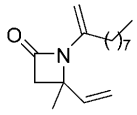
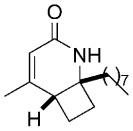
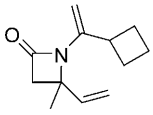
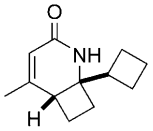
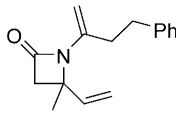
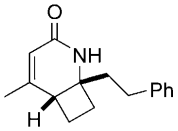
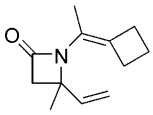
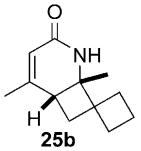
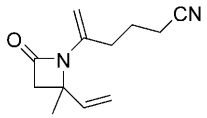
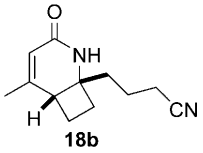
A common thread among all substrates shown in Tables 3 and 4 is that the *N*-vinyl β-lactam starting materials were derived from chlorosulfonyl isocyanate and isoprene (Scheme 1). We were interested in extending the reaction to *N*-vinyl β-lactams that were made from dienes other than isoprene. 2-Substituted 1,3-butadienes can be readily accessed from Grignard reagents and (*E*)-1,4-dibromobut-2-ene by using a two-step procedure reported recently by Sieburth et al.[21] The reaction delivered 2-cyclopentyl-1,3-butadiene from cyclopentyl magnesium bromide and (*E*)-1,4-dibromobut-2-ene in 88% yield over two steps. A [2+2] cycloaddition between 2-cyclopentyl-1,3-butadiene and chlorosulfonyl isocyanate occurred in modest yields,[15] but was scaleable such that gram scale quantities of the *N*-H β-lactam were accessible (Scheme 4). Table 5 shows the amino cyclobutanes accessible from the corresponding *N*-vinyl β-lactams derived from 2-cyclopentyl-1,3-butadiene. Long and short alkyl side chains can be used to make amino cyclobutanes **30b** and **31b** in reasonable yields. Tethered phenyl and cyano groups can both be tolerated to produce compounds **32b** and **33b** in respectable yields. Cyclopropyl and cyclobutyl carbocyclic side chains gave compounds **34b** and **35b**. The spirocyclic compound **36b** can be made from the tetrasubstituted olefin **36a**.

To push the scope further, β-lactams derived from 2,3-disubstituted 1,3-butadienes and chlorosulfonyl isocyanate were employed. These *N*-vinyl β-lactam systems can be transformed into an aminocyclobutane that would contain adjacent quaternary stereocentres. Table 6 shows the scope of the reaction when 2,3-dimethylbuta-1,3-diene was used as the diene partner to prepare the corresponding *N*-H β-lactam. Alkyl side chains are well tolerated yielding aminocyclobutanes **37b**–**39b** and the reaction worked fairly well when five- and seven-membered carbocycles, **40a** and **42a**, containing endocyclic trisubstituted olefins were used. Three ring systems with three contiguous stereocentres were produced in these instances. For reasons that are not yet clear, when the six-membered carbocycle **41a** was used, the reaction delivered eight-membered enamide ring **41b** as the major product.[15] Tethered phenyl and cyano groups are tolerated, as are vinyl carbocycles to provide aminocyclobutanes **43b**–**46b**. Finally, spirocycle **47b** with three contiguous quaternary carbons was made in 80% yield.

To further extend the reaction, spirocyclic β-lactams were used as the starting materials. The *N*-H β-lactam was projected to emanate from a formal [2+2] addition between chlorosulfonyl isocyanate and 1,2-dimethylenecyclohexane as the diene partner (Scheme 5). The latter diene is readily prepared in one step[22] and the corresponding spirocyclic *N*-H β-lactam can be made by using standard procedures described in Scheme 5.

The reaction of the spirocyclic *N*-vinyl β-lactam under the developed rearrangement conditions fused cyclohexyl and cyclobutyl groups to a common δ-lactam in one step, giving a tricyclic system with two adjacent quaternary stereocentres. In most cases, the reaction was sluggish but still delivered the desired product in modest to good yields. Table 7

Table 3. Substrate scope of aminocyclobutane formation.[a]

	β-Lactam	Product	Yield [%][b]		β-Lactam	Product	Yield [%][b]
1	 **6a**	 **11b** (dr = 86:14)	95	9	 **19a**	 **19b**	42
2	 **12a**	 **12b** (dr = 83:17)	98	10	 **20a**	 **20b**	27
3	 **13a**	 **13b** (dr = 83:17)	93	11	 **21a**	 **21b**	34
4	 **14a**	 **14b**	83	12	 **22a**	 **22b**	84
5	 **15a**	 **15b**	89	13	 **23a**	 **23b**	89
6	 **16a**	 **16b**	81	14	 **24a**	 **24b**	95
7	 **17a**	 **17b**	82	15	 **25a**	 **25b**	93
8	 **18a**	 **18b**	74				

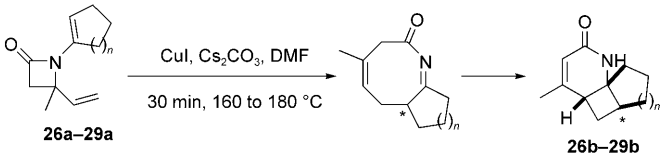
[a] Conditions: *N*-vinyl β-lactam (20.0 mg), CuI (10 mol%), Cs_2CO_3 (1.5 equiv), DMF (500 μL), microwave heating 30 min, 160 to 200 °C, see the Supporting Information.[9] [b] Isolated yield.

displays the scope of the process. The reaction works well with simple alkyl substituents, a tethered nitrile, a cyclopropyl and a cyclobutyl substituent to yield aminocyclobutanes **48b**–**51b**. Four ring systems can be made in a single step with three contiguous stereocentres as a single diastereoisomer, as shown in the case of products **53b** and **54b**.

Several facets of the aminocyclobutane reaction deserve further discussion. The proposed mechanism of the aminocyclobutane formation (Scheme 6) includes a pericyclic reaction sequence beginning with a [3,3] sigmatropic rearrangement followed by removal of the proton alpha to the ketone in the eight-membered-ring intermediate. Subsequently, a 6π-electron intermediate undergoes a disrotatory electrocyclisation.

It should be noted that deprotonation of the eight-membered ring is faster than tautomerisation of the imine to the unreactive eight-membered enamide ring. In a separate experiment we subjected eight-membered enamide ring **1b** (Table 1) to the aminocyclobutane reaction conditions to see if the process was reversible once the eight-membered enamide was made. In the event, only the starting material was recovered, which suggests that the eight-membered en-

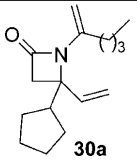
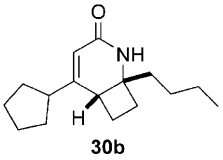
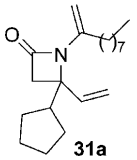
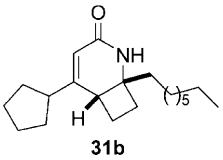
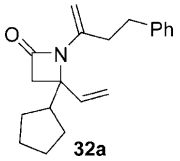
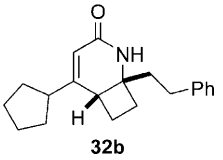
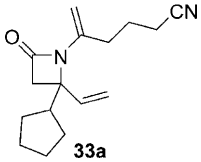
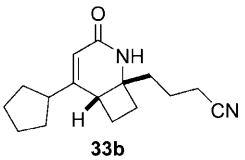
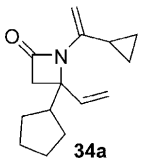
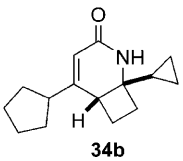
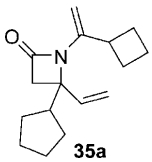
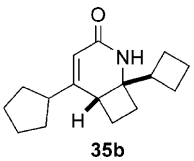
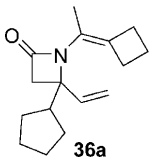
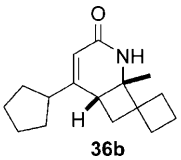
Table 4. Substrate scope using carbocyclic trisubstituted olefins.[a]



	β-Lactam (*n*)	Product (Yield[%])[b]
1	**26a** (1)	**26b** (75)
2	**27a** (2)	**27b** (52)[c]
3	**28a** (3)	**28b** (83)
4	**29a** (4)	**29b** (92)[c]

[a] Conditions: *N*-vinyl β-lactam (20.0 mg), CuI (10 mol%), Cs_2CO_3 (1.5 equiv), DMF (500 μL), microwave heating 30 min, 160 to 200 °C, see the Supporting Information. [b] Isolated yield. [c] See the Supporting Information.

Table 5. Aminocyclobutane substrate scope with a cyclopentyl substituent.[a]

	β-Lactam	Product	Yield [%][b]
1	 **30a**	 **30b**	40
2	 **31a**	 **31b**	77
3	 **32a**	 **32b**	66
4	 **33a**	 **33b**	70
5	 **34a**	 **34b**	58
6	 **35a**	 **35b**	77
7	 **36a**	 **36b**	77

[a] Conditions: *N*-vinyl β-lactam (20.0 mg), CuI (10 mol%), Cs_2CO_3 (1.5 equiv), DMF (500 μL), microwave heating 30 min, 160 to 180 °C, see the Supporting Information. [b] Isolated yield.

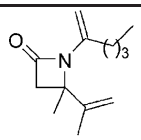
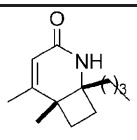
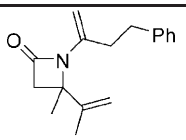
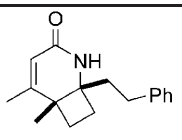
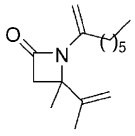
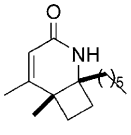
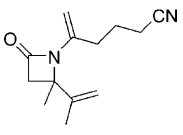
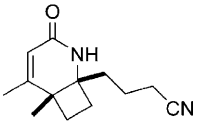
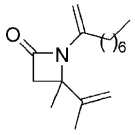
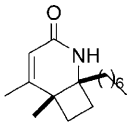
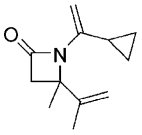
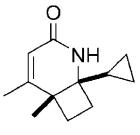
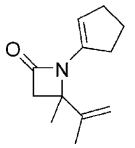
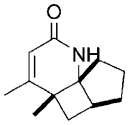
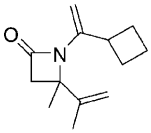
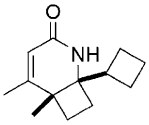
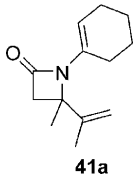
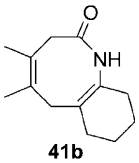
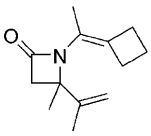
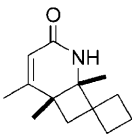
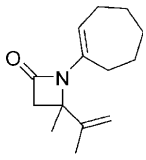
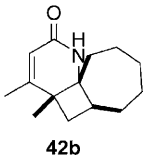
amide ring is stable and/or tautomerisation to the imine form is energetically unfavourable.

Realising that there is a 6π-electron intermediate that exists as an enol or enolate, we thought that the addition of base would affect the equilibrium. The addition of caesium carbonate (Table 2, entry 2) resulted in a 4:6 product distribution in favour of the aminocyclobutane over the 8-membered enamide. The reaction conditions that prompted the initial discovery of the aminocyclobutane (Scheme 3) contained copper iodide. When we evaluated copper iodide together with caesium carbonate, the aminocyclobutane was delivered as the exclusive product (Table 2, entry 3). It is plausible that copper iodide acts as a Lewis acid, coordinating to the carbonyl oxygen of the eight-membered ring intermediate or forms a chelate between the oxygen and the nitrogen (see Scheme 7). These events are expected to further assist in deprotonation of the α proton, leading to a 6π system.

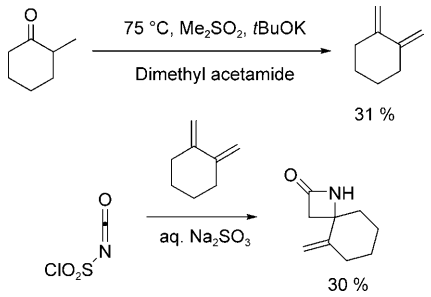
The aminocyclobutane formation can present issues of diastereoselectivity, depending on the substitution pattern of the *N*-vinyl olefin. When the olefin is *E* substituted, a mixture of diastereoisomers results, as exemplified with *N*-vinyl β-lactams **6a**, **12a** and **13a** and their respective aminocyclobutane products **11b**–**13b** shown in Table 3. The other case is when an *N*-vinyl β-lactam has a large carbocycle with an endocyclic olefin. This is exactly the case with substrate **29a** of Table 4. When the carbocycle contains eight or more carbons, the ring size is large enough such that electrocyclisation is not controlled by the α stereocentre of the imine.

A computational study was performed on the possible reaction intermediates and transition states by using Gaussian 03[23] (Scheme 8). The *N*-vinyl β-lactam **5a** was chosen as the starting material with a relative energy of 0 kcal mol^{-1}. The pathway to aminocyclobutane starts off with a [3,3] sigmatropic rearrangement, which was found to occur through two possible pathways. The first transition state (**A**) is an *endo*-boat transition, which is 63.5 kcal mol^{-1} greater in energy than the starting material **5a**. The second transition state (**A′**), is an *exo*-boat transition state, which is only 34.0 kcal mol^{-1} greater in energy than the starting material **5a**. A vibrational frequency analysis of **A** revealed that there was very little bond breaking or bond forming, which is consistent with a non-concerted mechanism that proceeds through a diradical intermediate. A similar analysis of **A′** revealed that there is a significant degree of bond breaking and making, which is in agreement with a concerted aromatic transition state and hence a lower activation barrier. Both **A** and **A′** have activation barriers that are in excellent agreement with previously reported calculations performed on the Cope reaction of 1,5-hexadiene.[24] For the purposes of simplifying calculations, we choose to examine the energy required for an electrocyclisation to occur from a 6π-enol species rather than a 6π-enolate species. After transition

Table 6. Synthesis of aminocyclobutane with adjacent quaternary stereocentres.[a]

	β-Lactam	Product	Yield [%][b]		β-Lactam	Product	Yield [%][b]
1	 **37a**	 **37b**	94	7	 **43a**	 **43b**	56
2	 **38a**	 **38b**	69	8	 **44a**	 **44b**	68
3	 **39a**	 **39b**	50	9	 **45a**	 **45b**	94
4	 **40a**	 **40b**	81	10	 **46a**	 **46b**	77
5	 **41a**	 **41b**	65[c]	11	 **47a**	 **47b**	80
6	 **42a**	 **42b**	68				

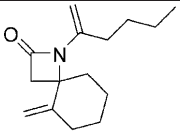
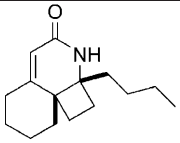
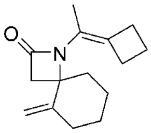
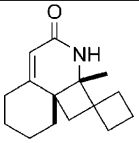
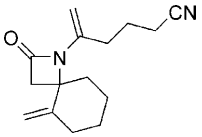
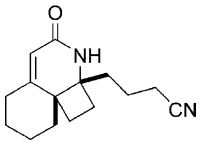
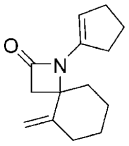
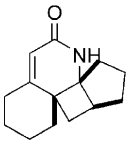
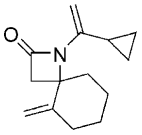
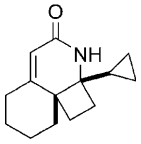
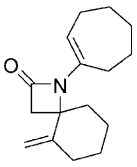
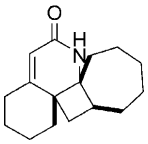
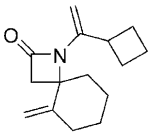
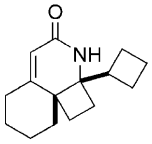
[a] Conditions: *N*-vinyl β-lactam (20.0 mg), CuI (10 mol%), Cs_2CO_3 (1.5 equiv), DMF (500 μL), microwave heating 30 min, 160 to 200 °C, see the Supporting Information. [b] Isolated yield. [c] See the Supporting Information.



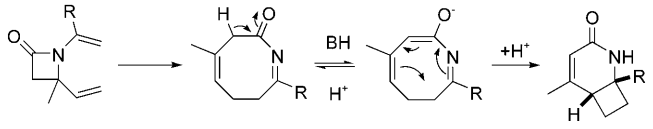
Scheme 5. Synthesis of 1,2-dimethylenecyclohexane and 5-methylidene-1-azaspiro[3.5]nonan-2-one.

state **A**, the eight-membered imine **B** is more stable than the starting material **5a** by 16.4 kcal mol^{-1}. The tautomerisation of **B** into enol **C** is followed by a 6π electrocyclisation. There have been reports discounting a [3,3] sigmatropic rearrangement occurring through a diradical transition state due to the high-energy requirement.[24] In our case, this reaction pathway appears to be quite possible. We have isolated species **B** (Table 1, entry 5), which can only arise via an *endo*-boat transition state. In addition, we have obtained no theoretical support for the transformation of **B′** into **B**, had the former been the kinetic product. For the pathway where the [3,3] sigmatropic rearrangement proceeds via an *exo*-boat-type transition, the reaction is endothermic because the eight-membered ring intermediate **B′** contains an *E* olefin. Tautomerisation of the 8-membered ring **B′** into enol **C′** followed by a rate-limiting 6π electrocyclisation would occur to give the aminocyclobutane. In principle, the reaction pathway that produces an eight-membered ring containing an *E* olefin is more energetically favourable, but the intermediate in less stable than the starting material and cannot be isolated. It is further reacted in situ to give the aminocyclobutane.

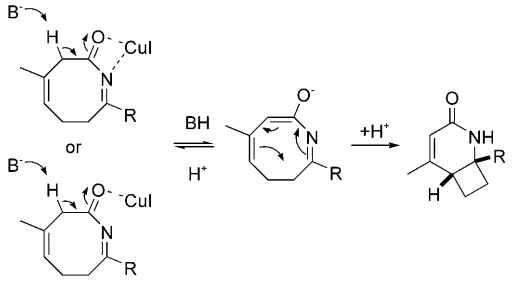
Table 7. Synthesis of aminocyclobutane with adjacent quaternary stereocentres.[a]

	β-Lactam	Product	Yield [%][b]		β-Lactam	Product	Yield [%][b]
1	 **48a**	 **48b**	43	5	 **52a**	 **52b**	78
2	 **49a**	 **49b**	42	6	 **53a**	 **53b**	28[c]
3	 **50a**	 **50b**	55	7	 **54a**	 **54b**	81[c]
4	 **51a**	 **51b**	68				

[a] Conditions: *N*-vinyl β-lactam (20.0 mg), CuI (10 mol%), Cs_2CO_3 (1.5 equiv), DMF (500 μL), microwave heating 30 min, 160 to 200 °C, see the Supporting Information. [b] Isolated yield. [c] See the Supporting Information.



Scheme 6. Proposed mechanism of aminocyclobutane synthesis.

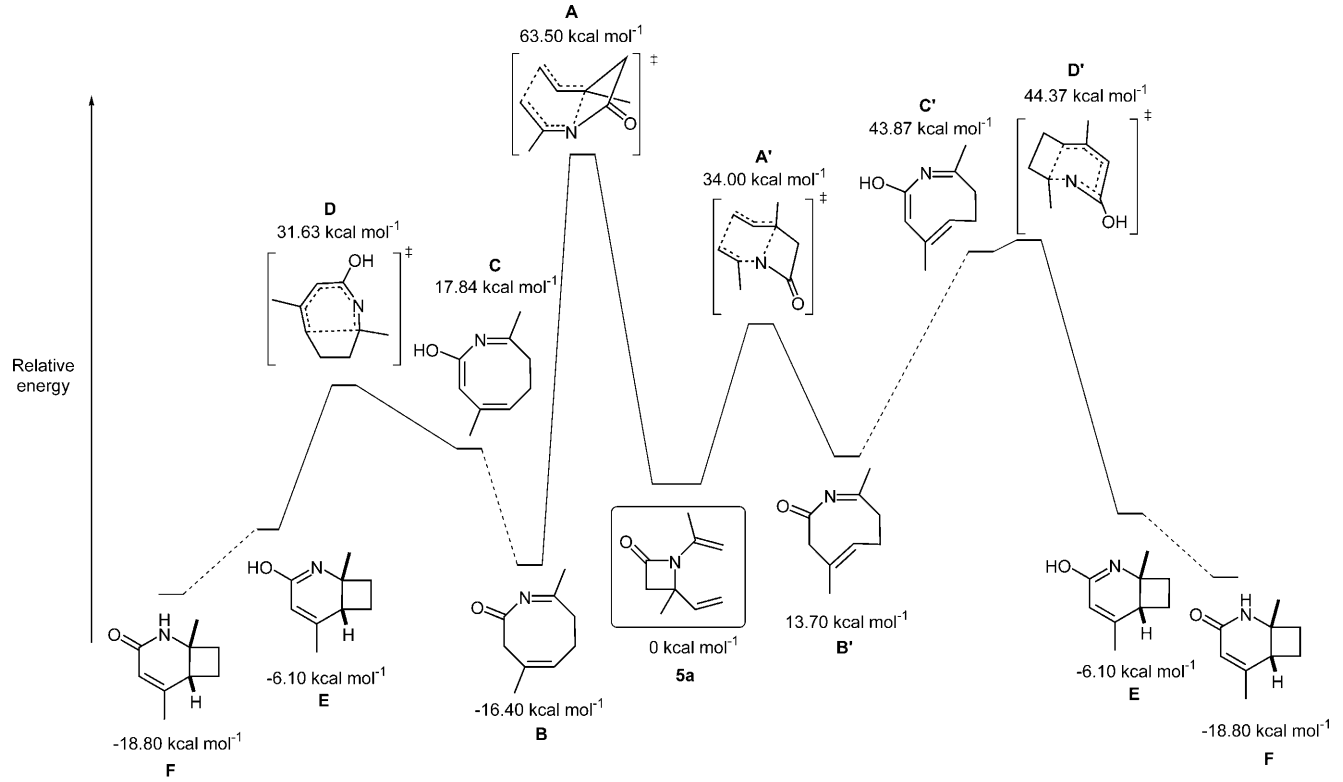


Scheme 7. The role of CuI as a Lewis acid.

After screening the reaction conditions, we uncovered that the reaction requires a temperature of roughly 160 °C for 30 min to achieve full conversion. The relatively high reaction temperature is believed to be needed on the basis that the ground-state conformation of the β-lactam is flat, based on computational optimisation, where the carbon, nitrogen and oxygen atoms of the β-lactam core lie in the same plane. Novak and Chua[25] have shown that there is roughly 24.5 kcal mol^{-1} of ring-strain energy in an unsubstituted β-lactam. Roughly 21.6 kcal mol^{-1} of "amide resonance energy" is allocated to the nitrogen lone-pair donation into the carbonyl carbon. In order for the [3,3] sigmatropic rearrangement to occur, the two reacting olefins must orientate into a boat-type conformation. The olefin bonded to the nitrogen is in the plane of the β-lactam and cannot align with the other olefin partner because it is out of the plane of the β-lactam. A high temperature is thus needed to overcome the 21.6 kcal mol^{-1} of amide resonance energy such that the nitrogen can convert into a tetrahedral state with both olefins aligned in a boat-type conformation.

Conclusion

We have developed a method of broad applicability to make various aminocyclobutanes from *N*-vinyl β-lactams. This approach relies on readily accessible starting materials and allows for rapid assembly of multiple rings fused to an aminocyclobutane. Several stereocentres can be created in a single-pot domino reaction with high stereoselectivity. A computational study suggests that the reaction proceeds through an eight-membered ring intermediate that contains an *E* olefin, not a common feature amongst small-ring-strain-release [3,3]-sigmatropic rearrangements.[26] Future



Scheme 8. Computational investigation of the reaction mechanism using Gaussian 03[23] with a calculation method of RB3LYP and a basis set of 6-31G(d).

work will encompass the synthetic utility of aminocyclobutanes and will be reported in due course.

Experimental Section

Representative procedure for aminocyclobutane synthesis: CuI (10 mol%) and Cs_2CO_3 (1.5 equiv) were charged into a Biotage Microwave vial with a capacity of 0.2–0.5 mL equipped with a stirrer bar. A solution of an *N*-vinyl β-lactam (20 mg) in DMF (450 μL) was added to the vial and the vial was capped and crimped. Microwave heating was performed for 30 min with the following settings: 1 min pre-stirring, absorption level of high and with fix hold time on. The temperature used is listed with the characterisation of the compound. After the microwave heating was complete, the contents of the vial were emptied into a test tube, the vial was then rinsed with water and CH_2Cl_2. The organic layer was separated and the aqueous layer was washed two more times with CH_2Cl_2. The combined organic layers were dried with magnesium sulfate, filtered, concentrated and purified by column chromatography.

Acknowledgements

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