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Forging structural complexity: diastereoselective synthesis of densely substituted β-lactams with dual functional handles for enhanced core modifications†

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The preparation of the β-lactam motif containing both C–Br and N–O bonds as functional handles remains an unmet synthetic challenge. Described herein is a novel and highly diastereoselective NBS-mediated cyclization of *N*-alkoxy α,β-unsaturated silyl imino ethers to furnish nearly three dozen α-bromo *N*-alkoxy β-lactams. The reaction gives rapid and convenient access to structurally diverse monocyclic, spirocyclic and fused β-lactams in moderate to good yields. The two functional handles were shown to be useful for the further elaboration of the β-lactam core.

Introduction

The development of efficient synthetic routes to β-lactams (2-azetidinones) has been vigorously pursued by both synthetic and medicinal chemists since Fleming's serendipitous discovery of penicillin in 1928.[1] These compounds are the most widely used class of antibiotics making up to 65% of the total antibiotics market in the US.[2] Monobactams or monocyclic β-lactams, a special subgroup distinguished by the lack of a fused ring to the 2-azetidinone core, have shown a broad spectrum of activity against Gram-negative bacteria. The mechanism of action of monobactams, which is similar to that of the mechanism of bicyclic β-lactam antibiotics, involves the inhibition of peptidoglycan biosynthesis in bacterial cell walls.[3] Aztreonam (Fig. 1) is currently the only monobactam approved by the FDA. Due to the high efficacy of these compounds against bacterial pathogens, and with aztreonam being the first of its class of antibiotics, there is an urgent demand for the creation of efficient synthetic methods to produce monocyclic β-lactams.[4]

A number of efficient synthetic methods have been developed for the preparation of the β-lactam scaffold.[5] The most common disconnections (Scheme 1A) include the thermal [2 + 2] cycloadditions of either ketenes with imines[6] or isocyanates with alkenes.[7] Despite the existence of these methods, the synthesis of densely functionalized β-lactams remain a very difficult task. Additionally, none of these synthetic protocols allow the convenient preparation of *N*-alkoxy β-lactams, which are useful synthons for the further functionalization of the azetidinone ring.[8] The Miller group pioneered the employment of the Mitsunobu reaction or intramolecular S_N2 to effect the cyclization of the hydroxamate esters for the synthesis of *N*-alkoxy β-lactams (Scheme 1B).[9] However, densely substituted β-lactams are difficult to prepare by these two methods due to severe steric crowding.

At the same time, α-bromo β-lactams have proven to be versatile synthons for the further functionalization of the β-lactam core *via* cross-coupling reactions,[10] metal-halogen

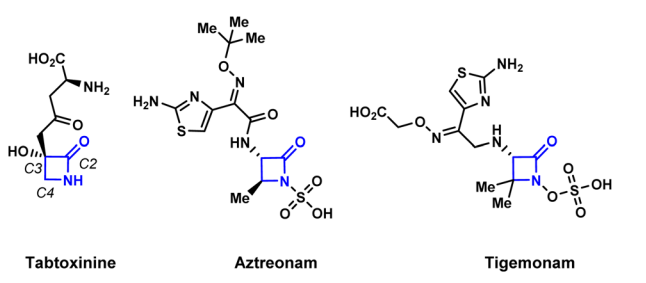

Fig. 1 Representative examples of biologically active monocyclic β-lactams.

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† Electronic supplementary information (ESI) available: Complete experimental and computational results, procedures and characterization including ^{1}H and ^{13}C NMR spectra and X-ray crystallographic data. CCDC 2301303, 2301304 and 2302628. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4sc01513d

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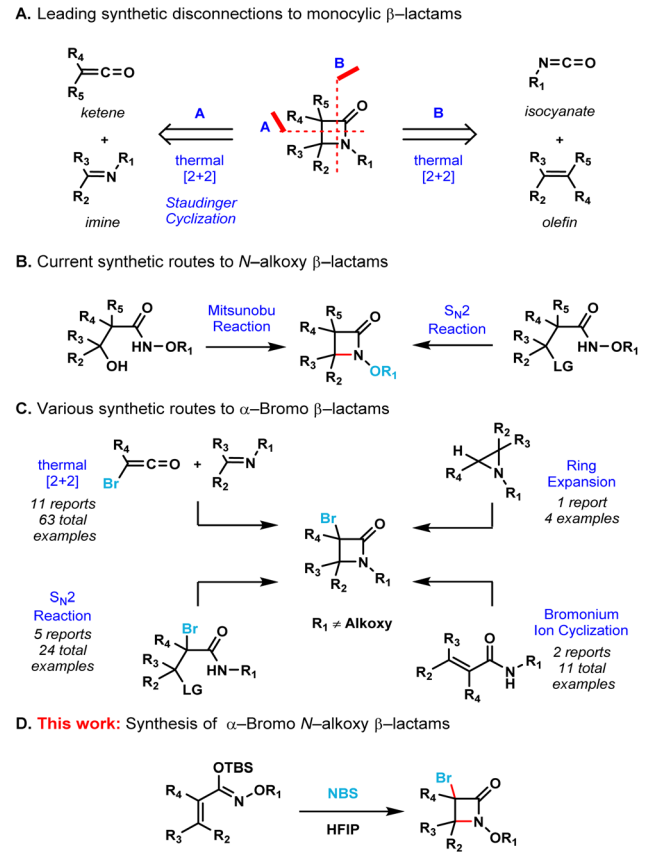


Scheme 1 Methods for the synthesis of monocyclic β-lactams.

exchange followed by trapping with activated electrophiles[11] and also *via* nucleophilic bimolecular substitutions (S_N2).[12] The known synthetic protocols for the preparation α-bromo β-lactams include thermal [2 + 2] cycloadditions of imines with bromoketenes or intramolecular S_N2 cyclization of amides (Scheme 1C).[13] These methods are limited to substrates that already contain the bromine atom in their scaffolds. The ring-expansion of aziridines in the presence of a halogenating agent[14] and the intramolecular cyclization of amides *via* a bromonium ion intermediate[15] are clever strategies that allow the incorporation of a bromine atom into the β-lactam core. However, none of these protocols allow the expedient synthesis of β-lactams containing both C–Br and N–O bonds as functional handles.

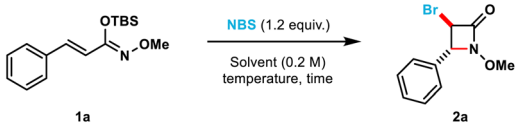
Therefore, we decided to develop an operationally simple strategy for the synthesis of monocyclic α-bromo *N*-alkoxy β-lactams. The presence of both the bromine at the C3 position and the alkoxy substituent on the nitrogen allow for the further diversification of the β-lactam core to access potentially bioactive compounds quickly and efficiently.

Results and discussion

We initially attempted the preparation of these target compounds with the already known strategies for β-lactam synthesis (Scheme 1A). Applying the classical conditions of the Staudinger ketene cycloaddition reaction (*i.e.*, [2 + 2]-cycloaddition between ketenes + imines) for the [2 + 2]-cycloaddition between ketenes and oximes failed to provide the corresponding *N*-alkoxy β-lactams. Another attempted [2 + 2] cycloaddition, between *N*-alkoxy isocyanates and olefins, similarly failed to provide the desired monocyclic *N*-alkoxy β-lactam core. We then shifted gears to a bromonium ion-mediated cyclization from α,β-unsaturated hydroxamate esters (Scheme 1C) as previously reported by Naskar and coworkers for the synthesis of N–H β-lactams.[15] However, all attempts led to the formation of only the corresponding α,β-unsaturated ester (*i.e.*, upon dimerization of the substrate and release of nitrogen gas as previously reported by Zhao *et al.* and Chattopadhyay *et al.*, see ESI page S4†).[16] With these results in hand, we proposed a bromonium ion-mediated cyclization approach starting from *N*-alkoxy α,β-unsaturated silyl imino ethers as substrates instead of α,β-unsaturated hydroxamate esters – this route circumvents the undesired dimerization pathway due to the absence of N–H bonds, while preserving *N*-nucleophilicity.

We began our preliminary studies using 1.2 equivalents of *N*-bromosuccinimide (NBS) as the electrophilic source of bromine and acetonitrile as the solvent at 0.2 M concentration under reflux conditions (Table 1, entry 1). Gratifyingly, our proof-of-concept experiment afforded the desired 3,4-*trans*

Table 1 Selected entries in the optimization of the cyclization reaction to afford monocyclic *N*-alkoxy β-lactams



1a 2a

Entry[a]	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	MeCN	Reflux	16	30
2	Toluene	Reflux	16	0[b]
3	DCM	Reflux	16	0[b]
4	IPA	r.t.	0.5	0[c]
5	THF	r.t.	16	0[c]
6	Methanol	r.t.	1	0[c]
7	TFE	r.t.	16	31
8	HFIP	r.t.	1	67
9[d]	HFIP : MeCN	40	16	15
10[d]	HFIP : toluene	r.t.	1	Trace
11[d]	HFIP : DCM	r.t.	1	70
12[e]	HFIP	r.t.	1	61
13[f]	**HFIP**	**r.t.**	**1**	**80**
14[g]	HFIP	r.t.	1	76
15[h]	HFIP	r.t.	1	80
16[i]	HFIP	r.t.	1	68
17[j]	HFIP	r.t.	1	47

[a] Reactions were conducted on a 0.5 mmol scale, 0.2 M concentration and using 1.2 equivalents of NBS. [b] No conversion was observed, only starting material was recovered. [c] Complete conversion was observed, starting material was fully consumed. [d] Solvent mixture is 1 : 1 in volume. [e] 1.0 equivalent of NBS was used. [f] 1.5 equivalents of NBS was used. [g] 2.0 equivalents of NBS were used. [h] 0.1 M in HFIP and 1.5 equivalents of NBS. [i] 0.5 M in HFIP and 1.5 equivalents of NBS. [j] 1.0 M in HFIP and 1.5 equivalents of NBS.

disubstituted monocyclic *N*-methoxy β-lactam **2a** in 30% isolated yield. Only the *trans*-product was observed, which is in full agreement with the well-defined stereochemistry of the starting material (*E*)-silyl imino ether **1a**. Our initial optimization started with solvent screening (entries 2–8) which showed that the choice of solvent was key for this transformation. When nonpolar solvents (*i.e.* toluene and dichloromethane) were used, the starting material remained intact even when the reaction was kept at reflux temperatures overnight. When polar solvents (*i.e.* tetrahydrofuran, isopropanol and methanol) were used, the starting material was fully consumed and decomposition products were observed, however, no cyclized product was detected. When trifluoroethanol was employed (entry 7) product **2a** was obtained in 31% isolated yield. Finally, when hexafluoroisopropanol (HFIP) was employed, the reaction time was reduced to only 1 hour at room temperature affording product **2a** in 67% isolated yield (entry 8). A result of an extensive solvent screening can be found in the ESI (page S4†). Solvent mixtures (1 : 1) were also explored to decrease the amount of HFIP used in the reaction (entries 9–11). Notably, a 1 : 1 mixture of HFIP : DCM provided the desired product **2a** with no significant change in isolated yield (70%). Hence, small-scale reactions were performed using only pure HFIP as the solvent, while large-scale reactions were conducted using solvent mixtures (entry 10). Next, we explored the effect of varying the equivalents of NBS on the outcome of the reaction (entries 12–14). Increasing the amount of NBS (1.0 → 1.5 equivalents; entry 13) led to an improvement in the isolated yield of the desired product (70 → 80%). However, further increase in the amount of NBS used (1.5 → 2.0 equivalents; entry 14) the isolated yield was slightly reduced (80 → 76%), which led us to select 1.5 equivalents of the bromine source for the optimized reaction conditions. Subsequently, we decided to explore the effect of the concentration (entries 15–17) on the reaction outcome. When the reaction was diluted (*i.e.*, 0.2 → 0.1 M concentration), the isolated yield of the desired product remained at 80%. On the other hand, when the reaction was performed under more concentrated conditions (*i.e.*, 0.5 M and 1.0 M), the product was obtained in reduced isolated yields (*i.e.*, 68% and 47%, respectively). After screening eight different brominating, chlorinating and iodinating agents, we concluded that NBS was the best halogen source for the transformation (see ESI, Table 2†).

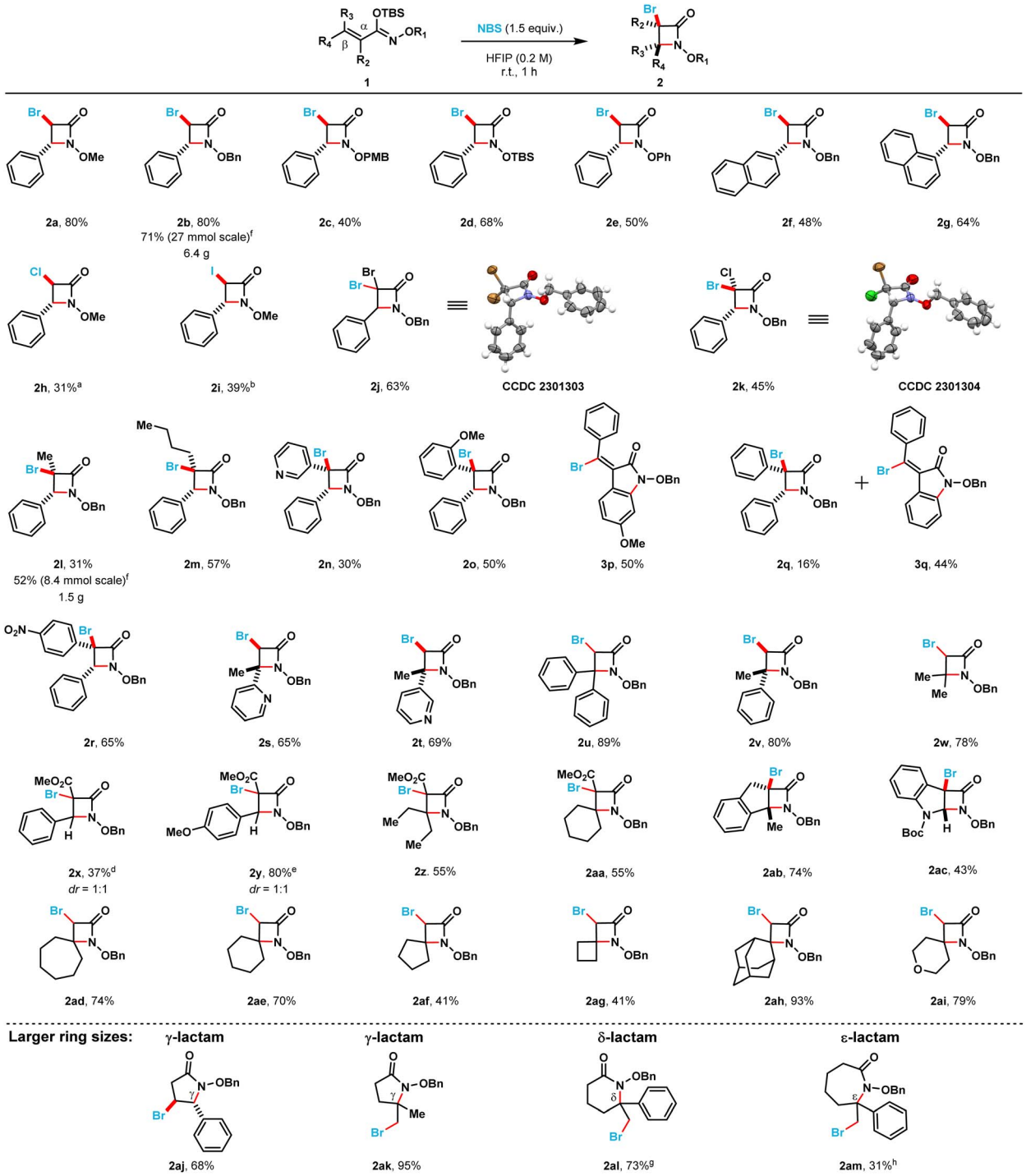
With the optimized reaction conditions in hand, we proceeded to explore the scope and limitations of this NBS-mediated cyclization to afford monocyclic β-lactams (Scheme 2). A diverse set of α,β-unsaturated silyl imino ethers were prepared from the corresponding hydroxamate esters (see ESI†).

Different *N*-alkoxy and *N*-aryloxy substituents (**2a–2e**) were tolerated in moderate to good yields using the optimized reaction conditions. The *N*-benzyloxy substituted β-lactam (**2b**) was obtained in 80% yield while the *N*-*p*-methoxybenzyloxy substituted β-lactam (**2c**) was obtained in a diminished isolated yield (40%). The *N*-OTBS-substituted β-lactam (**2d**) was also prepared in 68% isolated yield. When the phenyl ring at the C4-position was switched with 1- and 2-substituted naphthyl rings (**2g** and **2f**) the isolated yields of the products decreased (80 → 64% and 80 → 48%, respectively). Different halogen electrophiles were evaluated (see ESI for complete screening, see page S6†). The α-chloro *N*-methoxy β-lactam **2h** was obtained in 31% isolated yield when TCCA was employed as the chlorine source. Additionally, the α-iodo *N*-methoxy β-lactam **2i** was obtained in 39% isolated yield when *N*-iodosuccinimide was used as the iodine source.

3,3,4-Trisubstituted monocyclic β-lactams (**2j–2r**) were obtained in moderate to poor yields (65% to 16%). 3,3-Dibromo (**2j**) and 3,3-bromochloro (**2k**) β-lactams were obtained in moderate yields 63% and 45%, respectively. Compound **2j** crystallized after purification, and we were able to confirm the structure of its β-lactam core by single crystal X-ray crystallography. Compound **2k** was also crystallized, and we were able to confirm the *trans* diastereoselectivity of this cyclization by single crystal X-ray crystallography. Alkyl substituents (compounds **2l** and **2m**) in the C3 position were tolerated, albeit these β-lactams were isolated in somewhat diminished yields (31% and 57%, respectively). A 3-pyridyl substituent (compound **2n**) was also possible to install, however, the corresponding β-lactam was only isolated in 30% yield. When electronically dissimilar aryl substituents in the C3 position of the target β-lactams were evaluated (compounds **2o–2q**), unexpected indoline-2-one side products were observed. The formation of these side products account for the decrease in the isolated yields of the corresponding β-lactams. When an *o*-methoxyphenyl substituent was present at the C3-position of the substrate silyl imino ether (**1o**), only β-lactam **2o** was obtained in 50% isolated yield. However, when a *p*-methoxyphenyl substituent was at the C3-position instead, only the indoline-2-one product (**3p**) was isolated in 50% yield. When an electronically neutral phenyl group was present at the C3-position, a mixture of β-lactam (**2q**) and indoline-2-one (**3q**) products were obtained in 16% and 44% isolated yields, respectively. Finally, when an electron-deficient *p*-nitrophenyl substituent was introduced at the C3-position of the substrate, only the corresponding β-lactam product (**2r**) was obtained in 65% isolated yield.

3,4,4-Trisubstituted monocyclic β-lactams (**2s–2w**) were isolated in moderate to good yields (65% to 89%). C4-Heterocycle-substituted 2-pyridyl (**2s**) and 3-pyridyl (**2t**) β-lactams could also be prepared and were obtained in 65% and 69% yield, respectively. When two phenyl substituents are at the C4 position in the substrate, β-lactam **2u** was obtained in an excellent isolated yield (89%). When one of the phenyl substituents is replaced by a methyl group (compound **2v**) the desired β-lactam product was obtained in an 80% isolated yield. 4,4-Dimethyl β-lactam **2w** was obtained in 78% yield. Fully substituted β-lactams (**2x–2aa**) were obtained in moderate to poor isolated yields (37% to 55%). 4,4-Diethyl β-lactam (**2z**) and spirocyclic β-lactam (**2aa**) were both obtained in 55% yield. Fused *N*-benzyloxy β-lactams could also be prepared in moderate to good yields. Indeno-lactam **2ab** was obtained in 74% isolated yield while the dihydroindole-fused lactam **2ac** was obtained in 43% isolated yield.

Additionally, the optimized reaction conditions allowed the synthesis of six spirocyclic *N*-benzyloxy β-lactams (**2ad–2ai**) in



Scheme 2 Scope of substrates for the NBS-mediated synthesis of β-lactams and a few examples of larger ring lactams. Reactions were conducted on a 0.5 mmol scale, using 1.5 equivalents of NBS at 0.2 M concentration in HFIP at room temperature for 1 h. [a]TCCA (1.5 equivalents) was used instead of NBS. [b]NIS (1.5 equivalents) was used instead of NBS. [c]The reaction was heated to 40 °C for 3 h. [d]The reaction was heated to reflux for 6 h. [e]The reaction was stirred for 6 h. [f]A 1 : 1 mixture of DCM : HFIP was used instead of only HFIP as the solvent. [g]Reaction was conducted on a 0.1 mmol scale. [h]Reaction was conducted on a 0.3 mmol scale.

moderate to excellent yields (41% to 93%). More strained spirocyclic systems were obtained in lower isolated yields [*i.e.*, 41% yield for both the four-membered (compound **2ag**) and five-membered (compound **2af**) β-lactams]. The less strained spirocyclic β-lactams were obtained in higher isolated yields [*i.e.*, 74% for the seven-membered compound **2ad** and 70% for the six-membered compound **2ae**]. The 2,2-adamantyl spirocyclic β-lactam **2ah** was obtained in 93%, while the heterocyclic tetrahydrofuranyl spirocyclic β-lactam **2ai** was obtained in 79% isolated yield, respectively. β-Lactams **2x** and **2y** were prepared

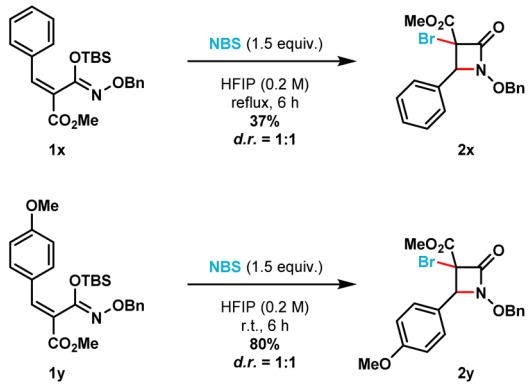
from the corresponding (*E*)-silyl imino ethers (*i.e.*, **1x** and **1y**, respectively) where the phenyl ring substituent is *cis* to the *N*-alkoxy silyl imino ether substituent (Scheme 3). β-Lactams **2x** and **2y** were each obtained as inseparable 1 : 1 mixture of diastereomers in 35% and 80% isolated yields, respectively.

The optimized reaction conditions also permitted the synthesis of 5-, 6-, and 7-membered *N*-benzyloxy lactams (**2aj–2am**) in moderate to excellent yields (31% to 95%). γ-Lactams **2aj** and **2ak** were both obtained in good to excellent isolated yields (68% and 95%, respectively). δ-Lactam **2al** was prepared in 73% isolated yield. In contrast, the somewhat larger ε-lactam **2am** was obtained in 31% isolated yield. Overall, we found that this NBS-mediated cyclization is readily scalable; the larger scale (8 to 27 mmol) afforded gram quantities of the β-lactam products **2b** and **2l** (6.4 g and 1.5 g, respectively) in excellent to moderate isolated yields (71% and 52%, respectively). Additionally, we found the isolation of the silyl imino ethers, *via* column chromatography, is not required for the cyclization to occur. The hydroxamates can be silylated under typical conditions (see ESI†), after a simple aqueous work-up with DI water and subsequent concentration, the crude silyl imino ethers can be used in the next step. NMR analysis of the crude samples indicated only the presence of silyl imino ethers and, in rare occasion, Si-based impurities that did not influence the next step. The crude silyl imino ethers can then be treated with the optimized conditions to yield the corresponding β-lactams in moderate to good yields over the 2 steps. Using this approach, β-lactam products **2b**, **2l** and **2v** were obtained in moderate to good yields in large-scale (12 to 60 mmol) over 2 steps using a 1 : 1 mixture of DCM : HFIP as the reaction solvent [*i.e.*, 49% isolated yield for compound **2b** in a 60 mmol scale (9.8 g of product); 60% isolated yield for compound **2l** in a 20 mmol scale (4.2 g of product); and 40% isolated yield for compound **2v** in a 12 mmol scale (1.6 g of product)].

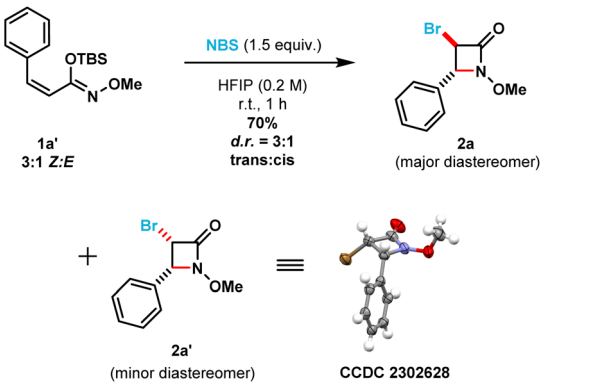
To shed light on the observed lack of diastereoselectivity in β-lactams **2x** and **2y** [*i.e.*, prepared from (*E*)-silyl imino ethers **1x** and **1y**], we decided to evaluate the β-lactam cyclization step using a structurally different (*Z*)-silyl imino ether (**1a′**) under the optimized reaction conditions (in which the phenyl ring substituent is *cis* to the *N*-alkoxy silyl imino ether substituent). Thus, using a 3 : 1 mixture of (*Z*) : (*E*) silyl imino ethers (**1a′**), we obtained a mixture of β-lactam diastereomers also in a 3 : 1 diastereomeric ratio (Scheme 4). However, to our surprise the *trans*-3,4-disubstituted β-lactam product (**2a**) was obtained as the major diastereomer, while the *cis*-3,4-disubstituted β-lactam product (**2a′**) as the minor diastereomer. The *cis*-relationship of the bromine and phenyl substituents in β-lactam **2a′** was confirmed using single crystal X-ray crystallography. Control experiments (see ESI, page S79†) indicated that: (1) no isomerization occurred between silyl imino ethers **1a′** and **1a** upon stirring **1a′** [3 : 1 (*Z*)/(*E*) ratio] in HFIP in the absence of NBS at room temperature for 12 h; (2) no desilylation occurred upon stirring **1a′** in HFIP in the absence of NBS at room temperature in 1 h; and (3) no desilylation of **1a′** occurred upon stirring in HFIP using 1.5 equivalents of NH-succinimide instead of NBS at room temperature for 1 h. Therefore, we can be confident that the removal of the silyl group only occurs after the electrophilic bromination of C=C double bond in the imino ether.

To computationally model the mechanism and selectivity of this cyclization/β-lactam forming reaction we considered *N*-bromosuccinimide as a source of a cationic bromine and examined the reaction with substrates **1a**, **1a′**, and **1y**. Based on the above control reactions, we assumed that the TBS group is not removed until after the cyclization. M06-2X[17a]/6-31G** (and LANL2DZ for Br)[17b,c] in Gaussian 16 (ref. 17d) was used to optimize all structures and frequency calculations were used to verify minima and transition states.

For bromination, a bridged bromonium type structure is generally assumed to be a possible ground state intermediate. However, for **1a** (and **1a′**/**1y**), all attempts to locate a bridged bromonium ion failed. Instead, optimized structures resulted in a benzylic carbocation intermediate, and example structure **Int-*Syn*** is shown in Fig. 2. We tried several alternative density functionals (*e.g.* B3LYP[17e]) and basis sets (*e.g.* def2-TZVP[17f]) and all gave only the benzylic carbocation structure. However, a constrained optimization suggests that the bromonium is only about 5 kcal mol^{-1} higher in energy. Because the barriers for cyclization are relatively small (*see* later discussion), it is likely that the rate limiting reaction step is formation of the benzylic carbocation. This provides a straightforward



Scheme 3 (*E*)-Silyl imino ethers **1x** and **1y** furnish a mixture of diastereomers for β-lactams **2x** and **2y**, respectively.



Scheme 4 Control experiments on the diastereoselectivity of the cyclization reaction.

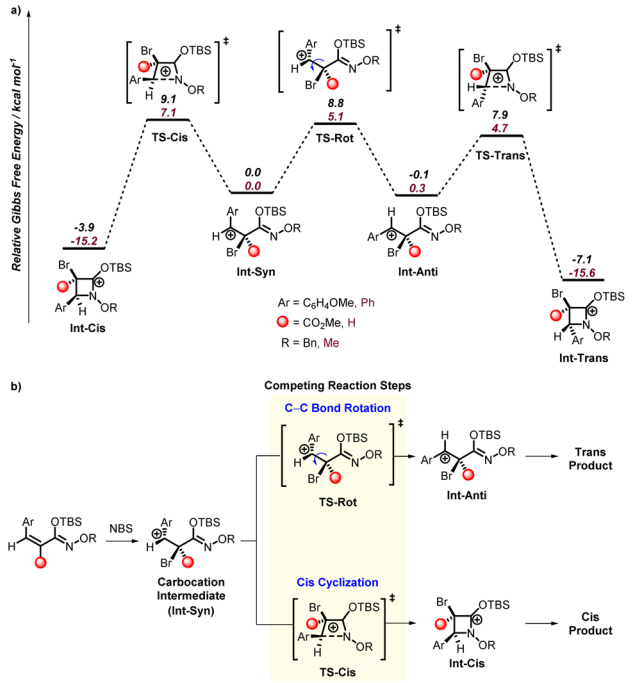


Fig. 2 (a) Gibbs energy surface showing the comparison of the *cis* cyclization process with C–C bond rotation that leads to the *trans* cyclization intermediate. (b) Outline of cyclization selectivity model.

explanation for the moderate reaction yield with acetonitrile and boosted reaction yield with HFIP. This was confirmed with calculations where we examined the thermodynamics for formation of the benzylic carbocation using two explicit HFIP solvent molecules. With no explicit HFIP molecules formation of the benzylic carbocation requires 20.0 kcal mol^{-1}. Inclusion of two HFIP molecules, one to stabilize the carbocation and one to stabilize the bromide, lowers benzylic carbocation energy to ~4 kcal mol^{-1} (see ESI† for details).

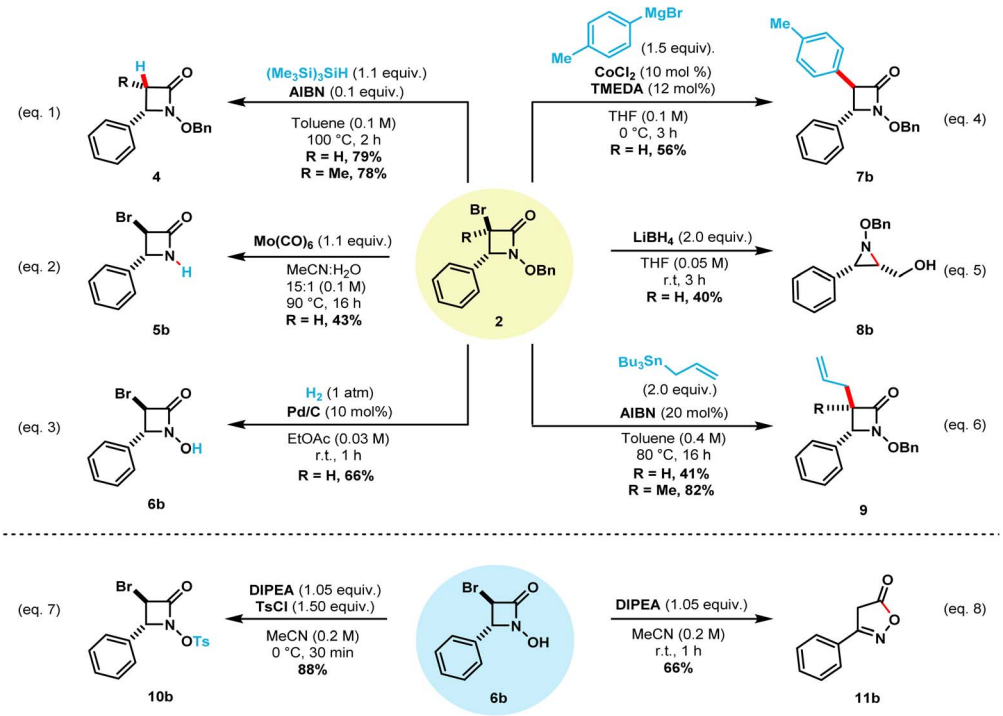
Notwithstanding the large atomic size of bromine, the optimization of a carbocation intermediate rather than a bridged bromonium intermediate was surprising because of the exclusive *trans* stereoselectivity found for the cyclization of **1a**. This prompted us to examine the transition states for cyclization from the benzylic carbocation intermediate. Fig. 2 shows the potential energy surface structures and the general selectivity model developed based on the intermediates and transition states. This energy surface was modelled with the SMD[17g] model of acetonitrile. This solvent was selected because this solvent does give conversion to products (see Table 1, entry 1) and is a parameterized solvent model available in Gaussian 16. HFIP is not available in Gaussian 16. However, test calculations with both explicit HFIP and trifluoroethanol showed very small changes to the energy surface presented in Fig. 2.

The transition state for C–N bond formation (**Int-*Cis*** and **Int-*Trans***) is exothermic and likely not reversible once formed, and after cyclization carbonyl formation would occur. The transition state leading to cyclization with the aryl and bromide groups in a *trans*-relationship (**TS-*Trans***) is only 4.7 kcal mol^{-1} and cyclization with these groups in a *cis*-relationship (**TS-*Cis***) is 7.1 kcal mol^{-1}. This 3.0 kcal mol^{-1} energy difference is consistent with nearly complete kinetic selectivity for the *trans*-product. DLPNO-CCSD(T) calculations (performed in ORCA)[17h] provide a nearly identical energy difference between these transition states and support the M06-2X energy difference.

It is useful to note that if the cyclization step is reversible, there is a 3.2 kcal mol^{-1} preference for the *trans*-cyclized intermediate (**Int-*Trans***) for **1y**. As expected, the selectivity for *trans* over *cis* cyclization is driven by the four-membered ring enforcing partial eclipsing of the bromide and aryl groups, although the aryl group can twist to relieve some of this repulsion. Consistent with our proposed benzylic carbocation mechanism, a few of the starting *N*-alkoxy α,β-unsaturated silyl imino ethers result in formation of a mixture of *trans*- and *cis*-products. However, it was surprising to us that these reactions generally produced a nearly equal mixture of *trans*- and *cis*-products since for **1a** there is a significant kinetic and thermodynamic preference for the *trans*-product.

Therefore, we analyzed the cyclization from the benzylic carbocation intermediate (**Int-*Syn***) derived from **1a′** and **1y** as shown in Fig. 2. In both cases the *trans*-cyclization transition state (**TS-*Trans***) is lower than the *cis*-cyclization transition state (**TS-*Cis***). Also, there is a significant thermodynamic preference for the *trans*-cyclized intermediate (**Int-*Trans***) compared to the *cis*-cyclized intermediate (**Int-*Cis***). This prompted us to examine the possibility that *cis*-to-*trans* isomerization of the carbocation intermediates might determine the *trans*/*cis* ratio. Using a nudged elastic band method in ORCA to examine this C–C bond rotation transition states (**TS-Rot**) we found that they are indeed higher in energy than the *trans*-cyclization transition states (**TS-*Trans***). Therefore, the model that emerged to explain the diastereoselectivity is that from these carbocation intermediates the *trans*/*cis* selectivity is likely governed by the rate of *cis*-cyclization (**TS-*Cis***) *versus* the rate of C–C bond rotation (**TS-Rot**) that is followed by faster *trans*-cyclization (**TS-*Trans***). For the carbocation intermediate derived from **1y** the energy difference between the *cis*-cyclization transition state (**TS-*Cis***) and C–C bond transition state (**TS-Rot**) is only 0.3 kcal mol^{-1}, and this is qualitatively consistent with experiment. For the carbocation derived from **1a′** the difference in these transition states is 2 kcal mol^{-1}. In both cases these small energy differences are consistent with the mixture of *trans* and *cis* products found experimentally. But again, the calculated energy difference is only expected to be qualitative. This is because transition states for bond rotations are inherently anharmonic and difficult to have highly quantitative values. Therefore, the calculated values are qualitative, but do provide a rationale for the unexpected selectivity.

This NBS-mediated cyclization method allows the straightforward synthetic access to a wide variety of α-bromo *N*-alkoxy β-lactams. The obtained compounds contain valuable functional handles that can be utilized for further transformations and modifications.[8e,g,10c,d,11b,11c,16] To this end, we carried out a few representative transformations (Scheme 5). Debromination of compound **2b** can be achieved in 79% isolated yield by treatment with tris(trimethylsilyl)silane and catalytic AIBN when heated to 100 °C (eqn (1)).[13a] Under this reaction conditions,



Scheme 5 Synthetic applications of β-lactams.

compound **2l** also undergoes debromination in 78% isolated yield, to provide only the *cis* β-lactam **4l**. Treatment of the *N*-benzyloxy β-lactam **2a** with $Mo(CO)_6$ selectively cleaved the N–O bond while keeping bromine handle to afford N–H β-lactam **5b** in 43% isolated yield (eqn (2)).[18] Next, catalytic hydrogenation of **2b** afforded *N*-hydroxy β-lactam **6b** in 66% isolated yield after one hour (eqn (3)).[9b] The treatment of compound **2a** with 2.0 equivalents of $LiBH_4$ allowed the synthesis of N–OB*n* aziridine **8b** in 40% yield upon reduction of the carbonyl bond and ring-opening followed by intramolecular cyclization (eqn (5)).[19]

Keck radical allylation of compounds **2b** and **2l** employing allyltributylstannane afforded the corresponding allylated β-lactams **9b** and **9l** in 41% and 82%, respectively (eqn (6)).[20] Further transformations of compound **6b** are also showcased. Selective tosylation using Hunig's base in ice-cold MeCN afforded compound **10b** in 88% isolated yield (eqn (7)). Finally, treatment of compound **6b** with Hunig's base at room temperature afforded compound **11b** in 66% yield (eqn (8)).

Conclusions

In conclusion, we report a new synthetic protocol that allows the facile preparation of α-bromo *N*-alkoxy β-lactams from the corresponding *N*-alkoxy-α,β-unsaturated silyl imino ethers using NBS. This approach permits the convenient access to a wide variety of monocyclic, fused and spirocyclic α-bromo *N*-alkoxy β-lactams that have never been reported before. Our novel strategy allows the synthesis of densely substituted β-lactams in both the C3 and C4 positions. The presence of both C–Br and N–O bond functional handles provides a platform for the facile modification to access highly substituted and functionalized β-lactams. In addition, we have provided a mechanistic and computational rationale for the observed diastereoselectivity of this transformation. Further studies on the potential synthetic applications of these versatile building blocks are underway.

Data availability

Data supporting this manuscript are available in the associated ESI files† and *via* the CCDC (numbers 2301303, 2301304 and 2302628).

Author contributions

L. K. conceived the idea and designed the research. A. R. performed the experiments and analyzed the data. S. P. and P. L.-T. equally contributed with experiments setup and data analysis. J. K., M. D. and D. E. performed the calculations and theoretical work. U. A. and M. Y. analyzed the crystal data by X-ray crystallography.

Conflicts of interest

There are no conflicts to declare.

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