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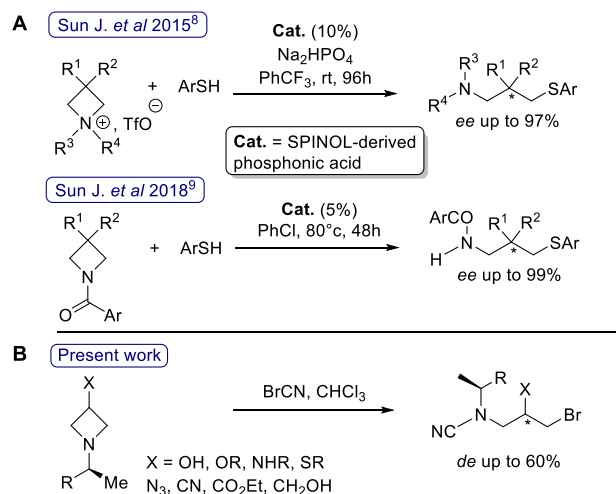
Diastereoselective ring cleavage of azetidines with cyanogen bromide

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Abstract: *N*-alkyl azetidines bearing a chiral substituent at the nitrogen atom, and a variable substituent at C-3 as a prochiral centre, react readily with cyanogen bromide even at low temperatures to produce the corresponding 3-bromo-*N*-cyanamides as diastereoisomeric mixtures *via* ring opening. This reaction was found to be diastereoselective (up to 80:20 *dr*). In one case, the major diastereomer could be isolated by recrystallization, and the configuration of the newly created stereocentre was determined by X-ray crystallography

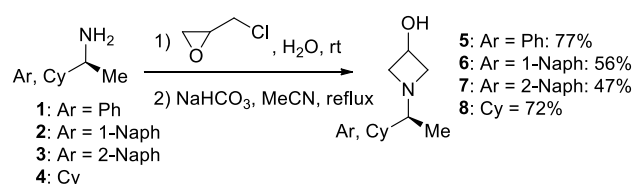
Strain in azetidines allows for many useful ring-opening and ring-expansion processes.¹ When the nitrogen atom within this heterocycle is not acylated or tosylated, the nucleophilic character, as well as the basicity, of the intracyclic amine is close to a linear amine, in contrast to aziridines where the basicity is considerably lower. Therefore, *N*-alkyl azetidines react with many electrophiles (eg chloroformates,² alkyl halides,³ alkyl sulfonates,⁴ triphosgene,⁵ cyanogen bromide⁶) to give a stable or transient azetidinium ion that can react further either by ring cleavage or by ring-expansion.⁷ In this area, it was recently reported⁸ (Scheme 1A) that C-3 substituted azetidiniums can be opened in an enantioselective manner in the presence of a catalytic amount of a SPINOL-derived phosphonate acting as a chiral counteranion for the azetidinium cation.



Scheme 1. Previous reports of enantioselective opening of achiral C-3 substituted azetidines (A), and overview of the present work (B).

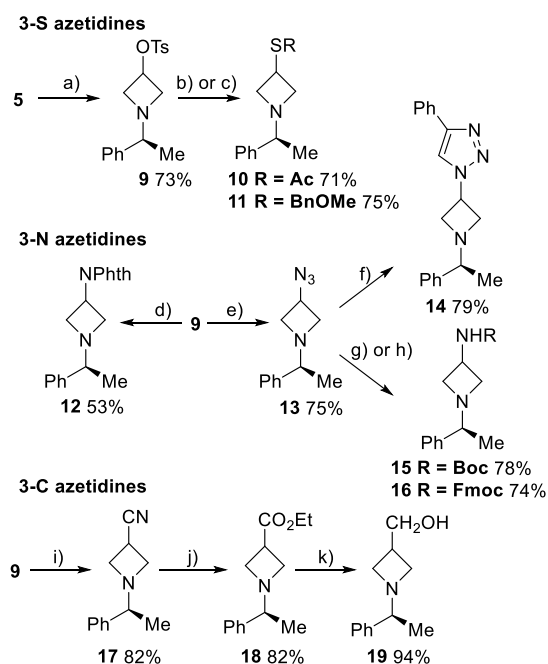
This study follows the pioneering work by the same group, involving enantioselective opening of *N*-acyl azetidines with chiral phosphonic acids acting as catalysts⁹ (Scheme 1). These recent reports led us to disclose our results in this field based on a different strategy. We studied the diastereoselective opening of azetidines of the type shown in Scheme 1B, fitted with a non-racemic substituent at the nitrogen atom (R = Ph, Cy, 1 or 2-naphthyl) and a functional group at C-3. These 3-substituted heterocycles constitute prochiral entities, which can be converted into a chiral synthon upon diastereoselective reaction at one of the symmetrical methylene groups at C-2 or C-4. We thus chose to react these azetidines with cyanogen bromide through the von Braun reaction, a process that we reported recently¹⁰ which produces 3-bromo-*N*-cyanamides through ring cleavage in a regioselective manner. The 3-bromo-*N*-cyanamides produced are versatile bis-electrophilic building blocks that were used for the preparation of cyclic guanidines.¹¹

The azetidine substrates used herein were prepared in a straightforward manner by using Gaertner's seminal reported method for the preparation of 3-hydroxy azetidines¹² adapted to different (*S*)-ethylamines. Treatment of epichlorohydrin with ethylamines **1-4** in water, followed by basic treatment in acetonitrile gave average-to-good yields of azetidinsols **5-8** as crystalline compounds, without the need for chromatographic purification (Scheme 2).



Scheme 2. Preparation of 3-hydroxy azetidines.

The tosylate **9** derived from **5** was used to prepare *S*, *N* and *C* substituted azetidines by nucleophilic substitution (Scheme 3). The 3-thio azetidines **10** and **11** were obtained by reaction with potassium thioacetate or sodium methoxybenzyl thiolate in 71 and 75% yields respectively. Similarly, reaction with potassium phthalimide, sodium azide or potassium cyanide gave the 3-substituted azetidines **12** (53%), **13** (75%) and **17** (82%). The 3-azido azetidine **13** was further transformed either by a CuAAC reaction to give the triazole **14** (79%), or by Staudinger reduction with triphenylphosphine followed by Boc or Fmoc protection to give **15** (23%) and **16** (74%). The 3-cyano azetidine **17** gave ethyl ester **18** through acidic ethanolysis (82%), which was reduced to the primary alcohol **19** (94%) with LiAlH₄.



Scheme 3. Preparation of 3-substituted azetidines. a) TsCl, DMAP, TEA, CH₂Cl₂, 5°C; b) KSAc, acetone, 60°C; c) MeOBnSH, aq. NaOH, EtOH, 80°C; d) K phthalimide, EtOH, 80°C; e) NaN₃, EtOH, 40°C; f) phenylacetylene, CuSO₄, Na ascorbate, THF/H₂O, rt; g, h) PPh₃, THF/H₂O, 70°C, then g) Boc₂O, aq NaHCO₃, rt, or h) FmocCl, MeCN, rt; i) KCN, EtOH, 80°C; j) H₂SO₄, EtOH, 80°C; k) LiAlH₄, THF, rt.

The alcohols **5-8** were also alkylated in the presence of sodium hydride and an alkyl halide to give the ethers **20-29** (Figure 1).

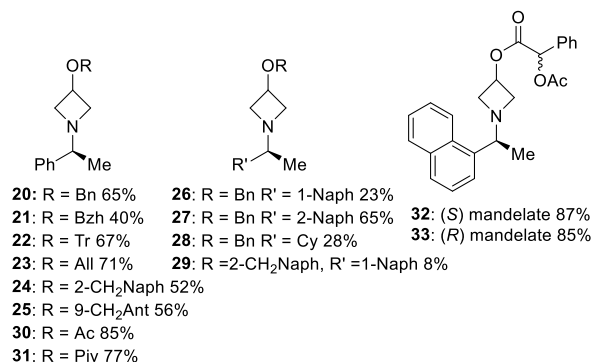
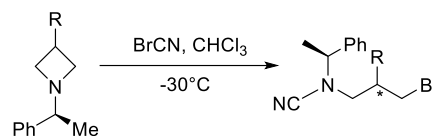


Figure 1. 3-*O*-alkyl and 3-*O*-acyl azetidines.

During these reactions some ring-opening of the azetidine by the alkyl halide occurred, leading to low yields of the ether product in some cases. This reactivity has already been observed by ourselves and others,¹³ and we intend to study further the diastereoselectivity of these ring openings. The alcohols **5** and **6** were also acylated to give the esters **30-33**, including both antipodes of a mandelate ester, introducing an additional stereogenic center around the azetidine ring (Figure 1).

The von Braun reaction of 3-*S*, 3-*N* and 3-*C* substituted *N*-((*S*)-1-phenylethyl) azetidines was investigated first under standard conditions (0.2 M of the azetidine in chloroform at -30°C, 3 equiv. of 3M BrCN in dichloromethane). Reactions were

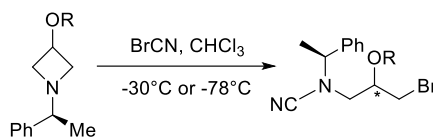
rapid and led to a diastereomeric mixture of ring-opened products with a diastereomeric ratio ranging from 55:45 to 70:30 (Table 1). No specific correlation could be deduced from the size or the nature of the functional groups at the 3-position on the selectivity of the reaction.



Substrate	R =	Product	dia. ratio ^a
10	SAc	34	55:45
11	SBnOMe	35	60:40
12	NPhth	36	60:40
13	N ₃	37	65:35
14	Ph-triazole	38	65:35
15	NHBoc	39	55:45
16	NHFmoc	40	55:45
17	CN	41	65:35
18	COOEt	42	65:35
19	CH ₂ OH	43	70:30

Table 1. Reaction of 3-*S*, 3-*N* and 3-*C* substituted *N*-((*S*)-1-phenylethyl) azetidines in the von Braun reaction. ^a From ¹H NMR spectra, rounded down to nearest 5%.

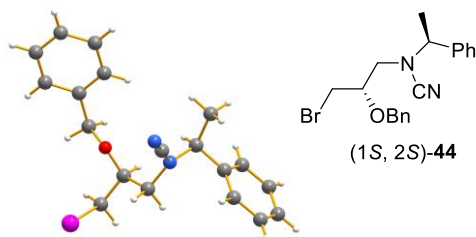
The reaction of 3-*O* substituted *N*-((*S*)-1-phenylethyl) azetidines with cyanogen bromide under the same conditions was studied next (Table 2). The reaction proceeded well with all the azetidines, but again diastereoselectivity was not correlated with the nature or the steric crowding of the *O*-substituents. Nevertheless, diastereoselectivity could be improved by carrying out the reaction at lower temperatures (eg. R = Bzh 50% *de* and



R = Bn 60% *de* at -78°C) (Table 2).

Substrate	R =	Product	dia. ratio (%) ^a
20	Bn	44	70:30 (-30°C)
			80:20 (-78°C)
21	Bzh	45	70:30 (-30°C)
			75:25 (-78°C)
22	Tr	46	65:35
23	All	47	70:30
24	2-CH ₂ Naph	48	70:30
25	9-CH ₂ Ant	49	60:40
9	Ts	50	70:30
30	Ac	51	55:45
31	Piv	52	60:40

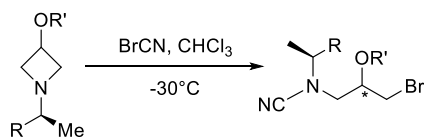
Table 2. Reaction of 3-*O* substituted *N*-((*S*)-1-phenylethyl) azetidines in the von Braun reaction. ^a From ¹H NMR spectra, rounded down to nearest 5%.



The major diastereoisomer of **44** could be purified by crystallization from a chromatographically inseparable mixture, allowing the determination of its (1*S*, 2*S*) configuration by X-ray crystallography (Figure 2).¹⁴

Figure 2. X-ray structure of (1*S*, 2*S*)-**44**

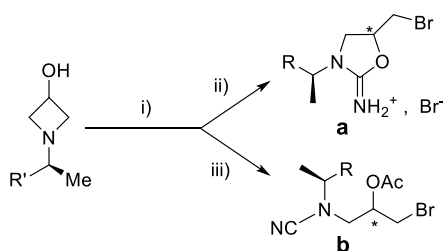
The influence of the *N*-substituent on the azetidine ring in the reaction of 3-*O* substituted azetidines was explored. Substrate **28** with an *N*-(*S*)-1-cyclohexylethyl group gave a lower *de* than the corresponding *N*-(*S*)-1-phenylethyl substrate **20**, while increasing the bulk of the *N*-substituent with a 1- or 2- naphthyl group gave better diastereomeric ratios at -30°C than for **20**. No further advantage was found in using a 3-*O*-2-CH₂-naphthyl at C-3 instead of the 3-*O*-Bn group. An interesting match/mismatch effect was found with the substrates **32** and **33**, bearing acetoxy-mandelate esters at C-3, with the (*R*)-mandelate ester giving a *de* of 50%, while for the (*S*)-mandelate no diastereoselectivity was observed (Table 3).



Substrate	R =	R' =	Product	<i>dia. ratio</i> (%) ^a
26	1-Naph	Bn	53	80:20
27	2-Naph	Bn	54	75:25
28	Cy	Bn	55	70:30
29	1-Naph	2-CH ₂ Naph	56	80:20
32	1-Naph	(<i>S</i>)-mandelate	57	50:50
33	1-Naph	(<i>R</i>)-mandelate	58	70:30

Table 3. Reaction of 3-*O* substituted azetidines in the von Braun reaction. ^a From ¹H NMR spectra, rounded down to nearest 5%.

The reaction of the azetidin-3-ols **5-8** bearing different chiral substituents at the nitrogen was finally investigated. In this case, the 2-hydroxy cyanamides formed cyclized on evaporation of the reaction solvent to give the corresponding 2-imino oxazolidines, isolated as their bromide salts. The corresponding *O*-acetyl cyanamides could be isolated if the reaction mixture was treated by addition of acetic anhydride before evaporation. The diastereomeric excess ranged from 20% to 40% at -30°C, and was again dependent upon the nature of the *N*-substituent of the azetidine (Table 4). Improved diastereoselectivity was found for reactions carried out at -78°C (60% *de* for **5**).



Substrate	R =	Product	<i>dia. ratio</i> (%) ^a
5	Ph	59a, 51	75:25 (-30°C) 80:20 (-78°C)
6	1-Naph	60a,b	70:30
7	2-Naph	61a,b	70:30

Table 4. Reaction of azetidin-3-ols. i) BrCN, CHCl₃ -30°C; ii) solvent concentration; iii) Ac₂O. ^a From ¹H NMR spectra, rounded down to nearest 5%.

We previously carried out a detailed *in silico* study of the von Braun reaction applied to azetidine substrates to better understand the reaction pathways involved.¹⁵

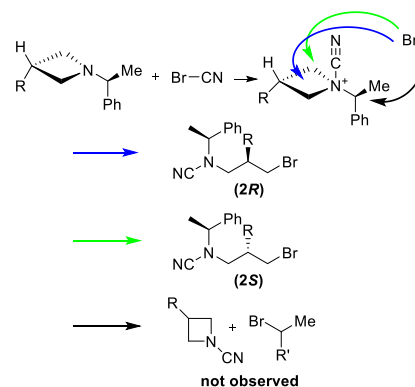


Figure 3. Reaction paths in the von Braun reaction of azetidines

This revealed that the azetidine reacts initially with cyanogen bromide yielding a quaternary ammonium salt, which can then undergo bromide substitution to give a mixture of two diastereomeric open chain products, and/or an *N*-cyanoazetidine and an alkyl bromide. Only the open chain products were obtained with the substrates used in this study. Using a simplified model, these theoretical studies showed little difference (0.2 kcal.mol⁻¹) in the total free energies of the transition states leading to each diastereomer, leaving us with no valid tools to predict diastereoselectivity. Experimentally, no systematic relationship between the size or the nature of the functional groups at the 3-position was found to explain the outcome of the von Braun reaction.

In conclusion, we have prepared a large set of new, diversely 3-substituted azetidines bearing a chiral centre at the ring nitrogen atom and studied their reactivity towards cyanogen bromide. The diastereoselectivity of the von Braun reaction was low to moderate with no evident correlation between the size and the nature of the C3-substituent. However, changes in the nature of the chiral group on the nitrogen atom of these strained heterocycles appeared to influence diastereoselectivity. Unsurprisingly, by performing the reaction at a lower temperature (-78°C), it was possible to increase diastereoselectivity. Desymmetrization of azetidines with other electrophiles is currently under investigation in our laboratory.

Acknowledgments

The University of Versailles St-Quentin-en-Yvelines, University Paris-Saclay and the CNRS are acknowledged for financial support. MR thanks the Ministère de l'Enseignement Supérieur de la Recherche et de l'Innovation for a PhD fellowship.

Supplementary data

Supplementary data to this article can be found online at

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