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Lewis acid mediated functionalization of β-lactams: mechanistic study and synthesis of C-3 unsymmetrically disubstituted azetidin-2-ones

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Abstract—A convenient and efficient route to novel unsymmetrically disubstituted azetidin-2-ones is described. β-Lactam carbocation equivalents of type **1** and active aromatic substrates in the presence of a Lewis acid promote a facile and stereoselective C-3 substitution to provide monosubstituted β-lactams (**3**,**4**) and symmetrically disubstituted β-lactams (**5**). *cis*-3-(4′-Methoxyphenyl)-3-phenylthioazetidin-2-ones (**4**) undergo further substitution with active aromatic substrates mediated by a Lewis acid to afford unsymmetrically disubstituted azetidin-2-ones (**7**).

The β-lactam skeleton is the key structural unit of the most widely employed class of antibacterial agents, the β-lactam antibiotics.[1–3] The discovery of new biologically active β-lactams such as cholesterol acyl transferase inhibitors,[4] thrombin inhibitors,[5] human cytomegalovirus protease inhibitors,[6] a human leukocyte elastase,[7] cysteine protease inhibitors[8] and antitumor active β-lactams[9] have motivated growing interest in the building of new β-lactam systems. Besides this, these heterocycles are used as intermediates in α- and β-amino acid synthesis, as well as building blocks for the synthesis of alkaloids, heterocycles and taxoids.[10] Further interest in the development of new methodologies capable of providing C-3 unsymmetrically disubstituted β-lactams with well defined stereochemistry was initiated by these new biologically active monocyclic β-lactams having a variety of alkyl/aryl substituents at C-3[4–9] and in view of the Structure-Activity Relationships (SAR) of the β-lactam heterocyclic nucleus reported by Clader et al.[11]

In our earlier studies towards C-3 functionalization of azetidin-2-ones,[12,13] the synthetic potential of cationic β-lactam equivalents was explored for the synthesis of symmetrically 3,3-disubstituted azetidin-2-ones. The prime objective of the present study was to develop a strategy to functionalize selectively C-3 of azetidin-2-ones for designing and synthesizing new unsymmetrically disubstituted azetidin-2-ones. We report here the stereoselective introduction of an active anisole group at C-3 of azetidin-2-ones by using the β-lactam carbocation equivalents **1** and their further substitution with different active aromatic substrates in the presence of a Lewis acid to afford unsymmetrically disubstituted azetidin-2-ones (Fig. 1).

β-Lactams **2a**–**d**, required for this study, were synthesized via annelation of phenylthioacetic acid and an appropriate imine using $POCl_3$ as the condensing reagent in the presence of triethylamine in CH_2Cl_2 at 0 °C. The starting substrates, *trans*-3-chloro-3-phenylthioazetidin-2-ones (**1a**–**d**), the most appropriate β-lactam carbocation equivalents, were prepared by

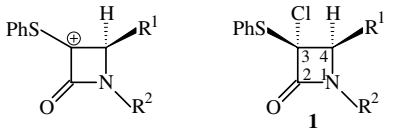

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Figure 1. Cationic β-lactam equivalents.

Keywords: Azetidin-2-ones; Lewis acid; Nucleophiles; Monosubstituted β-lactams; Unsymmetrically disubstituted azetidin-2-ones.
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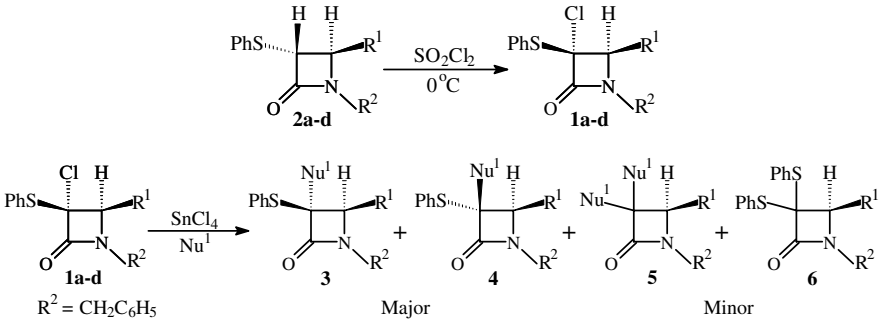


Scheme 1. Synthesis of C-3 substituted β-lactams.

stereospecific chlorination of **2a**–**d** using sulfuryl chloride (SO_2Cl_2) (Scheme 1).[12,13] Initial studies were carried out by reacting **1a** with anisole as the active aromatic substrate in the presence of 1 equiv of $SnCl_4$ at 0 °C,[14] which resulted in the formation of a mixture of four compounds.

These products, after column chromatographic purification, were identified as *trans*-1-benzyl-3-(2′-methoxyphenyl)-3-phenylthio-4-(4′-methylphenyl)azetidin-2-one **3a**, *cis*-1-benzyl-3-(4′-methoxyphenyl)-3-phenylthio-4-(4′-methylphenyl)azetidin-2-one **4a**, 1-benzyl-3,3-bis(4′-methoxyphenyl)-4-(4′-methylphenyl)azetidin-2-one **5a** and 1-benzyl-3,3-bis(phenylthio)-4-(4′-methylphenyl)-azetidin-2-one **6a** on the basis of their spectral analysis. To understand the nature of the nucleophile, suitable for the synthesis of monosubstituted β-lactams (**3**,**4**) other active aromatic substrates were studied under similar conditions. These activated substrates resulted in the formation of symmetrically disubstituted β-lactams (**5**,**6**) and the results are summarized in Table 1. However, when the nitrogen atom in the β-lactam ring was substituted with a *p*-methoxyphenyl group instead of benzyl, the formation of only symmetrically disubstituted β-lactams (**5**,**6**) was favoured.[12] The stereochemistry of monosubstituted β-lactams at C-3 was established through single crystal X-ray crystallographic analysis of **3a**[15] (Fig. 2) and **4a**[16] (Fig. 3).

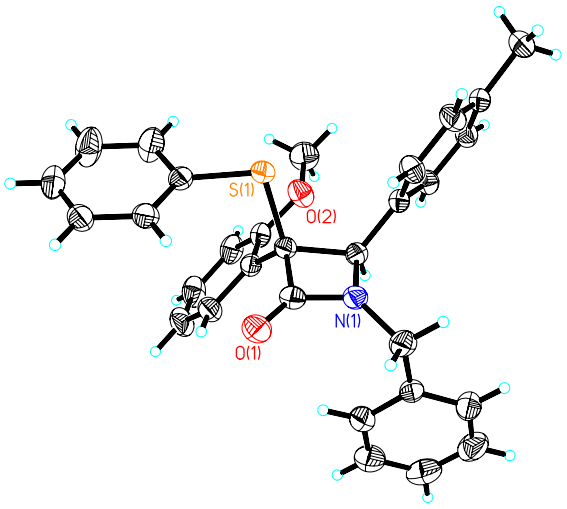


Figure 2. ORTEP diagram of compound **3a**.

Taking into consideration the formation of symmetrically disubstituted β-lactams (**5**) in this reaction, it was envisaged to study primarily the formation of C-3 unsymmetrically disubstituted β-lactams. It seems likely that these C-3 symmetrically disubstituted β-lactams are formed only from the C-3 monosubstituted β-lactams.[12] Thus, it was decided to probe the role of monosubsti-

Table 1. Reaction of **1a**–**d** with various active aromatic substrates using $SnCl_4$ as the Lewis acid

Entry	1	R^1	Substrate (Nu^1)	Temperature (°C)/time (h)	Products[a] (% yield)[b]			
					3	4	5	6
1	**1a**	$C_6H_4CH_3$-*p*	$C_6H_5OCH_3$	0/2	**3a**[c] (31)	**4a**[d] (38)	**5a** (9)	**6a** (7)
2	**1b**	C_6H_5	$C_6H_5OCH_3$	0/2	**3b** (29)	**4b** (47)	**5b** (8)	**6b** (6)
3	**1c**	$C_6H_4OCH_3$-*p*	$C_6H_5OCH_3$	0/2	**3c** (25)	**4c** (43)	**5c** (10)	**6c** (9)
4	**1d**	C_6H_4Cl-*p*	$C_6H_5OCH_3$	0/2	**3d** (30)	**4d** (39)	**5d** (9)	**6d** (7)
5	**1a**	$C_6H_4CH_3$-*p*	$C_6H_5OCH_3$	–78/4	**3a** (52)	—	—	—
6	**1a**	$C_6H_4CH_3$-*p*	$C_6H_5OCH_3$	25/3	**3a** (15)	**4a** (48)	**5a** (7)	**6a** (5)
7	**1a**	$C_6H_4CH_3$-*p*	$C_6H_5OCH_3$	41/2	**3a** (10)	**4a** (61)	**5a** (5)	**6a** (3)
8	**1a**	$C_6H_4CH_3$-*p*	1,3-$C_6H_4(OCH_3)_2$	0/2	—	—	**5e** (41)	**6a** (38)
9	**1c**	$C_6H_4OCH_3$-*p*	1,3-$C_6H_4(OCH_3)_2$	0/2	—	—	**5f** (39)	**6c** (43)
10	**1a**	$C_6H_4CH_3$-*p*	1,4-$C_6H_4(OCH_3)_2$	0/2	—	—	**5g** (36)	**6a** (32)
11	**1c**	$C_6H_4OCH_3$-*p*	1,4-$C_6H_4(OCH_3)_2$	0/2	—	—	**5h** (29)	**6c** (36)

[a] All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR, MS and CHN analysis.
[b] Isolated yields after purification by column chromatography.
[c,d] The structures of these molecules were also established from single crystal X-ray data (Figs. 2 and 3).

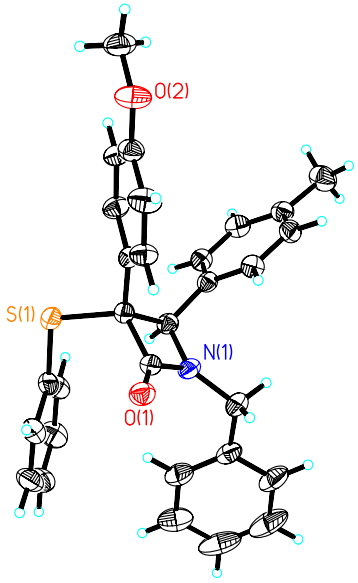


Figure 3. ORTEP diagram of compound **4a**.

tuted β-lactams **3** or **4**. Initial studies were undertaken with monosubstituted β-lactams **3b** and **4b** (Scheme 2).

Exposure of β-lactam **4b** to 1 equiv of a Lewis acid such as $TiCl_4$ in the presence of phenol as the active aromatic substrate (Nu^2) at low temperature (0 °C) under nitrogen in CH_2Cl_2, resulted in the formation of the desired product which, after column chromatographic purification, was identified as *cis*-1-benzyl-3-(4′-methoxyphenyl)-3-(4′-hydroxyphenyl)-4-phenylazetidin-2-one **7b**[17] on the basis of its spectroscopic data. Surprisingly, **3b** did not give any unsymmetrically disubstituted product under similar conditions. The reaction was found to be general with several substrates and the results are summarized in Table 2.

The C-3 stereochemical assignment for β-lactams **7** was finally deduced through single crystal X-ray crystallographic analysis of **7b**[18] as depicted in its ORTEP diagram (Fig. 4).

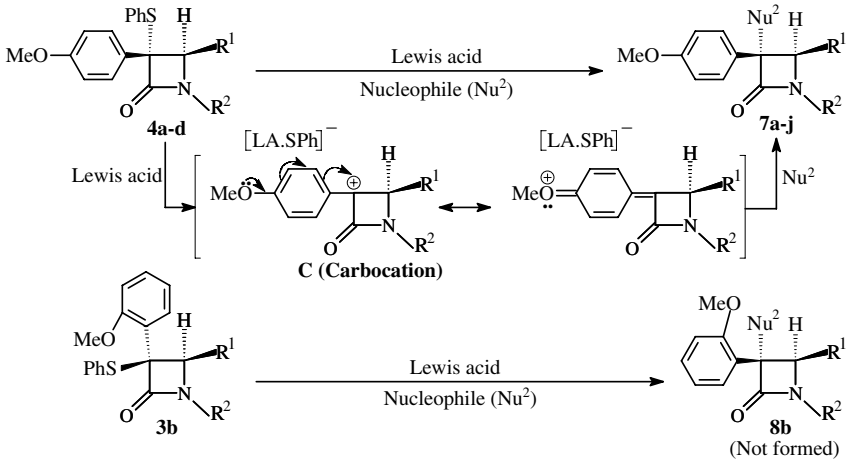
Table 2. Unsymmetrically disubstituted azetidin-2-ones of type **7**

Entry	**4**	Substrate (Nu^2)	Lewis acid	Temperature (°C)	Product[a] (**7**)	Yield[b] (%)
1	**4a**	C_6H_5OH	$TiCl_4$	0	**7a**	71
2	**4b**	C_6H_5OH	$TiCl_4$	0	**7b**[c]	81
3	**4c**	C_6H_5OH	$TiCl_4$	0	**7c**	63
4	**4d**	C_6H_5OH	$TiCl_4$	0	**7d**	75
5	**4a**	1,4-C_6H_4-$(OCH_3)_2$	$SnCl_4$	−10	**7e**	79
6	**4b**	1,4-C_6H_4-$(OCH_3)_2$	$SnCl_4$	−10	**7f**	57
7	**4c**	1,4-C_6H_4-$(OCH_3)_2$	$SnCl_4$	−10	**7g**	68
8	**4d**	1,4-C_6H_4-$(OCH_3)_2$	$SnCl_4$	−10	**7h**	70
9	**4a**	1,3-C_6H_4-$(OCH_3)_2$	$SnCl_4$	−10	**7i**	61
10	**4d**	$C_{10}H_7$-OCH_3-*o*	$SnCl_4$	−10	**7j**	63

[a] All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR and CHN analysis.
[b] Isolated yields after purification by column chromatography.
[c] The structure of this molecule was also established from single crystal X-ray data (Fig. 4).

We probed this nucleophilic substitution further by undertaking the reaction of **1a** with anisole at different temperatures (Table 1, entries 5–7). Surprisingly, only one product **3a**, was obtained at −78 °C. However, at room temperature (25 °C) and reflux (41 °C, CH_2Cl_2) the formation of product **4a** was favoured.

A plausible mechanism for the formation of monosubstituted β-lactams (**3**,**4**) is presented in Scheme 3. The reaction is believed to proceed through the formation of complex **A**. Increased reaction temperature favours the formation of **4** via *Path A*, in which complex **A** undergoes substitution at C-3 by rear attack of the nucleophile having a *p*-methoxy substituted phenyl group at C-3. However, *Path B* involves the formation of intermediate carbocation **B**, thus, as the reaction temperature is lowered to −78 °C, the stability of the intermediate carbocation **B** is increased and favours the



Scheme 2. Synthesis of unsymmetrically disubstituted azetidin-2-ones of type **7**.

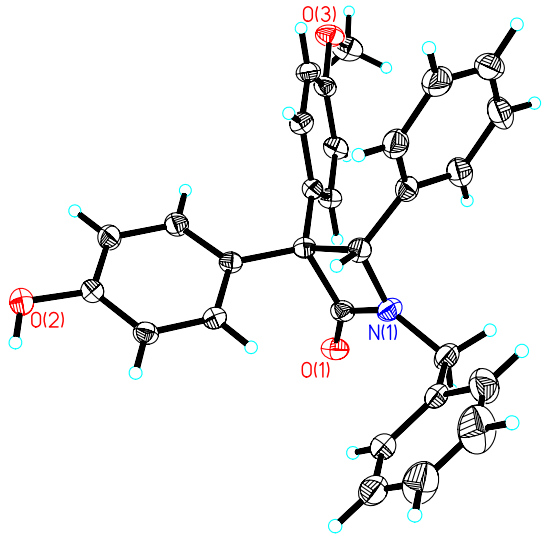


Figure 4. ORTEP diagram of compound **7b**.

formation of **3**, which is kinetically controlled. At low temperature the substitution *ortho* to methoxy in the anisole takes place preferentially as compared to the *para* position owing to the increased electron density and availability of the *ortho* position as compared to the *para* position. Thus, as the reaction temperature is increased through 0–41 °C, the stability of the carbocation **B** decreases, leading to a decrease in the yield of product **3**. Hence, at raised temperature formation of the thermodynamically stable product **4** is favoured. The formation of **3** having a *p*-methoxy substituted phenyl substituent at C-3 has not been observed at all in this reaction. This fact was also fully corroborated by the X-ray crystallographic studies confirming the formation of **3** possessing an *o*-methoxy substituted phenyl substituent at C-3 at low temperature and **4** having a *p*-methoxy substituted phenyl substituent at C-3 at high temperature. The possible role of the activated aromatic nucleophile, favouring monosubstituted products may be a combined effect of both, the activating groups attached to the benzene ring and the steric bulk of the incoming nucleophile.

Mechanistically, the synthesis of unsymmetrically disubstituted azetidin-2-ones (**7**) from monosubstituted β-lactams **4** seems to proceed via intermediate carbocation **C** (Scheme 2), which is resonance stabilized by the *p*-methoxyphenyl ring substituent at C-3. Subsequent approach of the nucleophile (Nu^2) to this carbocation (**C**) from the less hindered face would lead to the observed stereochemistry. The inability of monosubstituted β-lactam **3** to undergo further substitution by a second nucleophile (Nu^2) may be attributed to the non-availability of a resonance stabilized intermediate C-3 carbocation.

In conclusion, a novel entry to unsymmetrically disubstituted azetidin-2-ones **7** has been developed by using Lewis acid mediated functionalization of β-lactams **4** with various active aromatic substrates. The strategy employed is easily adaptable to the combinatorial approach for creating libraries of C-3 unsymmetrically disubstituted monocyclic β-lactams. Additionally, we have shown that reactions of *trans*-3-chloro-3-phenylthio-β-lactams (**1a–d**) with active aromatic substrates provide an easy access to novel C-3 monosubstituted β-lactams and symmetrically disubstituted β-lactams.

Acknowledgements

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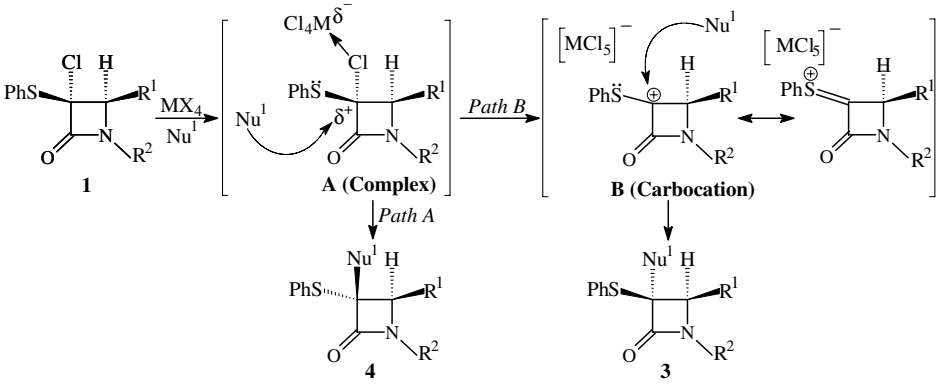

Scheme 3. Plausible reaction pathway for the formation of monosubstituted β-lactams (**3**,**4**).

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14. Compounds **3**–**8**[12,13] were prepared by the procedures described in the cited references.
15. Crystal data for **3a**: Empirical formula, $C_{30}H_{27}NO_2S$; formula weight, 465.59; colourless, long prism crystals; triclinic; $P1^-$; $a = 9.165(1)$ Å, $b = 9.301(1)$ Å, $c = 15.513(1)$ Å; $\alpha = 80.48(1)°$, $\beta = 83.99(1)°$, $\gamma = 76.01(1)°$; $V = 1262.6(2)$ Å^3; $Z = 2$; $\rho_{Calcd} = 1.225$ Mg/m^3; μ(Mo-Kα) = 0.155 mm^{-1}; full matrix least-square on F^2; $R_1 = 0.0386$, $wR_2 = 0.0970$ for 3387 reflections $[I > 2\sigma(I)]$; $T = 293(2)$ K; GOF = 1.023. Crystallographic data (excluding structure factors) for the structure **3a** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 604665.
16. Crystal data for **4a**: Empirical formula, $C_{30}H_{27}NO_2S$; formula weight, 465.59; colourless, block crystals; monoclinic; $P2_1/n$; $a = 11.125(1)$ Å, $b = 13.674(2)$ Å, $c = 16.706(2)$ Å; $\alpha = 90°$, $\beta = 102.9(1)°$, $\gamma = 90°$; $V = 2477.2(5)$ Å^3; $Z = 4$; $\rho_{Calcd} = 1.248$ Mg/m^3; μ(Mo-Kα) = 0.158 mm^{-1}; full matrix least–square on F^2; $R_1 = 0.0399$, $wR_2 = 0.0994$ for 2924 reflections $[I > 2\sigma(I)]$; $T = 293(2)$ K; GOF = 1.012. Crystallographic data (excluding structure factors) for the structure **4a** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 604666.
17. Typical experimental procedure for the synthesis of **7**: To a stirred solution of *cis*-1-benzyl-3-(4′-methoxyphenyl)-3-phenylthio-4-phenylazetidin-2-one (**4b**) (0.11 mmol, 0.050 g) and phenol (0.12 mmol, 0.010 g) in dry methylene chloride (10 mL) at 0 °C was added $TiCl_4$ (0.13 mmol, 0.025 g, 0.016 mL) rapidly under a nitrogen atmosphere. The resulting solution was stirred for 1 h at the same temperature. The progress of the reaction was checked by TLC, which showed the appearance of a spot different from the starting compound. The reaction was quenched with water, extracted with methylene chloride (4 × 10 mL), washed with 5% $NaHCO_3$ solution (2 × 5 mL) and then dried over anhydrous Na_2SO_4. The residue, after solvent evaporation in vacuo, was purified by silica gel column chromatography (10% EtOAc/hexane). The product on recrystallization from EtOAc/hexanes furnished **7b** as colourless crystalline solid (0.036 g, 75%); mp: 166–168 °C; IR (KBr): 3343 (OH), 1728 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–6.54 (18H, m, Ph), 5.53 (1H, br s, –O*H*, D_2O exchangeable), 5.05 (1H, s, C4–*H*), 4.98 (1H, d, $J = 14.9$ Hz, CH_aH$_b$Ph), 3.90 (1H, d, $J = 14.8$ Hz, CH$_a$H$_b$Ph), 3.67 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 158.2, 154.9, 135.4, 135.1, 133.3, 129.7, 128.8, 128.7, 128.4, 128.3, 128.1, 127.8, 115.6, 114.8, 114.1, 113.3, 72.0, 67.2, 55.1, 44.5; Anal. Calcd for $C_{29}H_{25}NO_3$: C, 79.97; H, 5.79; N, 3.21%; Found: C, 80.04; H, 5.73; N, 3.17%.
18. Crystal data for **7b**: Empirical formula, $C_{29}H_{25}NO_3$; formula weight, 435.50; colourless, block crystals; monoclinic; $P2_1/n$; $a = 12.945(1)$ Å, $b = 9.746(1)$ Å, $c = 18.642(3)$ Å; $\alpha = 90°$, $\beta = 94.97(1)°$, $\gamma = 90°$; $V = 2343.1(5)$ Å^3; $Z = 4$; $\rho_{Calcd} = 1.235$ Mg/m^3; μ(Mo-Kα) = 0.080 mm^{-1}; full matrix least-square on F^2; $R_1 = 0.0442$, $wR_2 = 0.1023$ for 2550 reflections $[I > 2\sigma(I)]$; $T = 293(2)$ K; GOF = 1.012. Crystallographic data (excluding structure factors) for the structure **7b** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 604667.