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Intramolecular rhodium-catalyzed activation of α-amino C–H bonds: decisive influence of conformational factors in the synthesis of bicyclic aminals from *N*-sulfamoyloxyacetyl azacycloalkanes

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Abstract—The activation of α-amino C–H bonds in azacycloalkanes by way of intramolecular rhodium-catalyzed amination is reported. In this study, the 'activating' sulfamoyloxy group is attached to the endocyclic nitrogen atom with an appropriate linker. The influence of various structural parameters was studied. Results obtained demonstrate the remarkable conformational control that is possible with such azacycloalkane systems. This work leads to the first example of a successful intramolecular catalyzed amination of a tertiary sulfamic ester, a substrate known to be highly prone to elimination and/or nucleophilic displacement.

The direct and selective transformation of unactivated C–H bonds is expected to have a profound impact on many areas of chemistry, from reaction design to the synthesis of pharmaceuticals and complex organic molecules.[1] The high prevalence of nitrogen-based functional groups in natural and synthetic products has stimulated the development of efficient catalytic methods for the amination of unactivated C–H bonds.[2,3] One of the major advances in this field has recently involved Rh-catalyzed intramolecular C–H insertion reactions using sulfamic ester substrates.[3–5] This highly diastereo- and regioselective process leads generally to the formation of the corresponding six-membered ring insertion product (Fig. 1).[3]

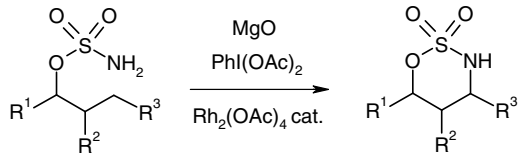
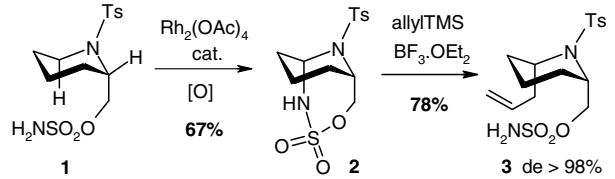


Figure 1. Rh-catalyzed oxidative cyclization of sulfamic esters.

Electronic effects were found to have a dramatic influence on the regioselectivity of the intramolecular amination reaction. Benzylic, allylic and tertiary C–H bonds as well as sites adjacent to electron-donating groups are generally favoured.[3] In a study performed in the piperidine series, we recently reported the first examples of 7-membered and 8-membered ring obtained by way of intramolecular catalyzed amination of C–H bonds (Scheme 1).[6,7]

Based on results obtained with various test substrates, it was shown that the unusual regioselectivity observed in nitrogen-containing systems could be rationalized by subtle conformational factors.[6] The major synthetic interest of this process is to functionalize a C–H bond in 1,7- or 1,8-relationship with respect to the activating



Scheme 1.

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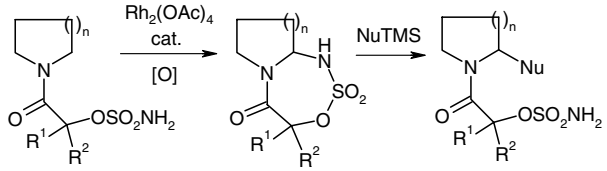
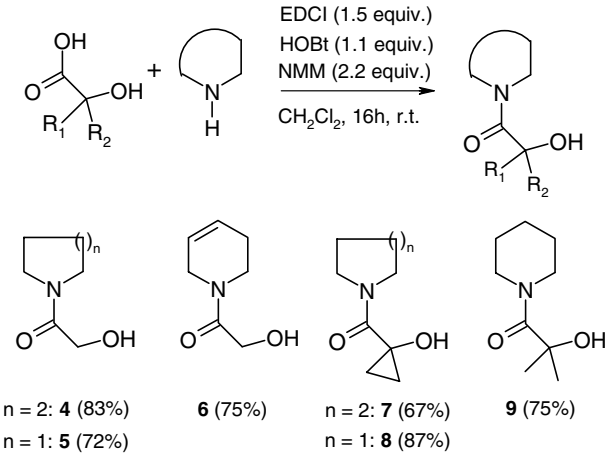
group to afford a reactive aminal function. Addition of various nucleophiles to the *N*-tosyliminium ion precursor **2** leads to the stereoselective formation of a new C–C bond and regenerates the sulfamic ester that may be used again for further C–H amination of the piperidine ring (Scheme 1).[6,8] These results open the way to unique strategies for the iterative multifunctionalization of unactivated C–H bonds in nitrogen-containing heterocycles. To study the feasibility of this new concept and increase its synthetic flexibility, we decided to explore azacycloalkane systems in which the sulfamoyloxymethyl group would be attached to the endocyclic nitrogen with an appropriate linker (Scheme 2).

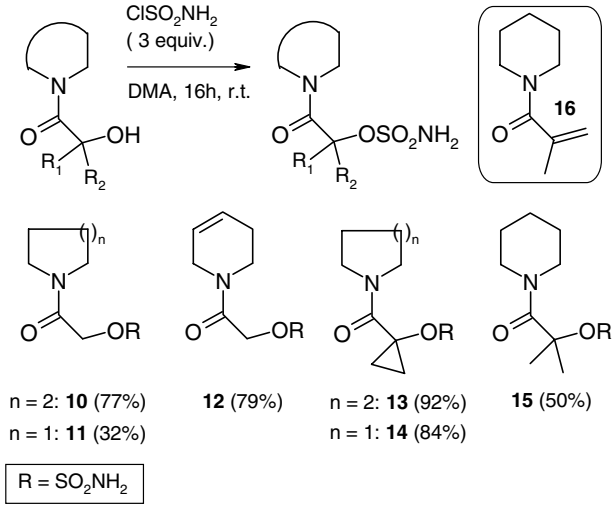
In connection with our ongoing interest in the synthesis of alkaloids related to iminosugars,[9] we focused on pyrrolidine- and piperidine-containing test substrates. The sulfamoyloxymethyl group was linked to the endocyclic nitrogen by way of a carbonyl group to prevent unproductive coordination of the nitrogen lone-pair to the catalyst. In pursuing the design of the 'activating arm', various groups (R^1 and R^2) were introduced to modulate or facilitate the amination reaction, for example, by way of Thorpe–Ingold effect (R^1, R^2 = H, methyl, cyclopropyl).[10] The structure of the test substrates was chosen to study the influence of conformational factors (ring size, *gem*-dialkyl effect) as well as electronic factors (allylic activation) on the amination reaction. The two-step synthesis began with the coupling of cyclic amines to unprotected β-hydroxy carboxylic acids using HOBt and EDCI to produce the expected amides **4**–**9** in 67–87% yield (Scheme 3).[11,12]



Scheme 2.



Scheme 3.



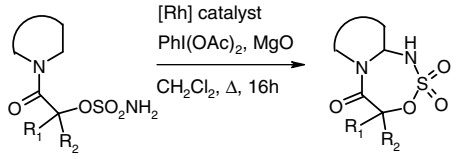
Scheme 4.

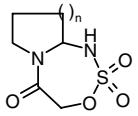
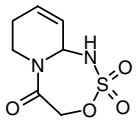
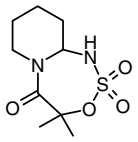
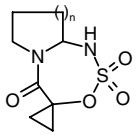
It is noteworthy that direct coupling of piperidine to glycolic acid in refluxing xylene was found to be much less effective as only 25% of the expected product **4** could be isolated.[13] The second step turned out to be more challenging (Scheme 4). Under typical sulfamoylation conditions,[3] reaction of primary alcohol **4** with sulfamoyl chloride and pyridine in CH_2Cl_2 afforded the expected sulfamic ester **10** in only 36% yield. Sulfamoylation of tertiary *gem*-dimethyl alcohol **9** led to the highly favoured formation of the elimination product **16**. It is indeed well-known that tertiary sulfamic esters are intrinsically unstable because of the activating nature of the sulfamoyl group for elimination and/or nucleophilic displacement.[3]

Decisive improvement was obtained by using *N*,*N*-dimethylacetamide (DMA) as solvent, without pyridine, according to the method described by Okada et al.[14] for primary and secondary alcohols. The process was applied successfully to tertiary alcohols **7**–**9** to provide sulfamates **13**–**15** (Scheme 4).[15,16]

Having test substrates **10**–**15** in hand, we first investigated the influence of ring size on the amination reaction outcome (Table 1). Quite surprisingly, following a standard protocol using $PhI(OAc)_2$ (1.1 equiv), MgO (2.3 equiv) and 5 mol % of $Rh_2(OAc)_4$,[6] piperidine **10** was converted into the expected aminal **17** in 20% yield only (entry 1). The amination reaction was then performed with tetrahydropyridine **12**, a close analog of **10**, which was designed to strongly favoured the insertion into the allylic α-amino C–H bond (entries 4 and 5). Even in this case, no improvement was observed and the amination product **19** was obtained in low yields. In contrast, ring size was found to play a key role since pyrrolidine **11** provided the expected aminal **18** in a much better yield of 47% (entry 2). The yield of the reaction was not improved by using $Rh_2(esp)_2$, an efficient C–H amination catalyst (entry 3).[4b] The influence of the *gem*-dialkyl effect (Thorpe–Ingold effect)[10] on the formation of the cyclized amination product was then studied. It is noteworthy that no intramolecular

Table 1. Study of the influence of various structural parameters in C–H insertion of sulfamic esters[a]



Entry	Catalyst	Product		Yield[c] (%)
1 (**10**)[b]	$Rh_2(OAc)_4$		**17** ($n = 2$)	20
2 (**11**)[b]	$Rh_2(OAc)_4$		**18** ($n = 1$)	47
3 (**11**)[b]	$Rh_2(esp)_2$		**18** ($n = 1$)	40
4 (**12**)[b]	$Rh_2(OAc)_4$		**19**	12
5 (**12**)[b]	$Rh_2(esp)_2$		**19**	25
6 (**15**)[b]	$Rh_2(OAc)_4$		**20**	12[d]
7 (**15**)[b]	$Rh_2(oct)_4$		**20**	8[d]
8 (**13**)[b]	$Rh_2(OAc)_4$		**21** ($n = 2$)	24
9 (**14**)[b]	$Rh_2(OAc)_4$		**22** ($n = 1$)	86
10 (**14**)[b]	$Rh_2(esp)_2$		**22** ($n = 1$)	83

[a] All reactions have been carried out in the presence of 2.3 equiv of MgO, 1.1 equiv of $PhI(OAc)_2$ and a catalytic amount of $Rh_2(OAc)_4$ (5 mol %), $Rh_2(esp)_2$ (4 mol %) or $Rh_2(oct)_4$ (4 mol %).
[b] Amination substrate.
[c] Isolated yield.
[d] Elimination product **16** was also isolated (7–10%).

catalyzed amination has been described from tertiary sulfamic ester so far. Not surprisingly, *gem*-dimethyl-containing compound **15** was found to be a poor substrate and the expected aminal **20** was obtained in 8–12% yield, along with an equal amount of the elimination product **16** (entries 6 and 7).

The influence of ring-size and *gem*-dialkyl effect on α-amino C–H insertion could be nicely demonstrated from substrates **13** and **14**. Conversion of cyclopropyl-containing pyrrolidine **14** afforded the desired cyclized product **22**[17] in an excellent yield of 86% whereas no decisive improvement was observed for the corresponding piperidine analog **13** (entries 8–10). To our knowledge, this is the first example of a successful intramolecular catalyzed C–H amination from a tertiary sulfamic ester.[3] Results presented in Table 1 remarkably highlight the decisive influence of conformational effects, which may dominate electronic effects; the introduction of an electronically favoured allylic site was indeed less effective to improve the insertion process (Table 1, entries 4 and 5). The better yields observed for pyrrolidine systems compared to piperidine systems may be explained by the fact that the pyrrolidine five-membered ring is more conformationally flexible and thus better accommodates the transition state for C–H insertion.[18,19]

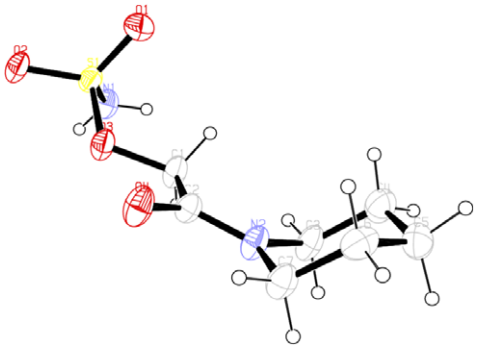


Figure 2. One of the two molecules in the crystal structure of **10**. The asymmetric unit contains two molecules with slightly different conformations. Visualization made with ORTEP-3.0,[23] ellipsoids drawn at 30% probability level.

As supported by X-ray crystallographic analysis of **10** (Fig. 2),[20,21] the piperidine ring of compounds **10**, **13** and **15** is expected to be in a well-defined chair conformation. Additional conformational constraints are introduced by the amide conjugation, which induce a planar arrangement of the NC=O group. This stabilized conformation is likely to place the nitrene centre in an unfavourable position with respect to the more reactive axial C–H bond at C-2 (Fig. 3b).[18] By analogy with the study performed on cyclic ethers by Ingold et al.,[18] we assume that stereoelectronic weakening of the C–H bond adjacent to the amide nitrogen is at a maximum when the dihedral angle, θ, between the C–H bond and the p-type lone pair orbital on the nitrogen is 0° and at a minimum when this angle is 90° (Fig. 3).

The more flexible pyrrolidine five-membered ring may adopt an averaged planar conformation as suggested by X-ray crystallographic and ^{1}H NMR analysis of **14**[16,20,22] (Fig. 4). In this conformation the two geminal α-amino C–H bonds are both activated with an average θ value of ca. 30° (Fig. 3a). The dramatic influence of the replacement of a methylene group by a cyclopropyl group in pyrrolidine systems can be rationalized by the 'reactive rotamer' concept.[10]

As shown by X-ray crystallographic analysis of **14** and **10**,[20] the conformation of both molecules is different. Conformation of compound **14** is much more rigid due to the presence of a strained cyclopropane ring. The aliphatic part of the molecule in compound **10**, which has almost linear conformation, changes strongly in the structure of **14** in which the distance between the sulfamate nitrogen atom and the α-amino C–H bond is remarkably shorter. The dihedral angles N–CO–C–O(–S) are equal to 55.6(3)° in **14** and 21.2(3)° in the cyclized

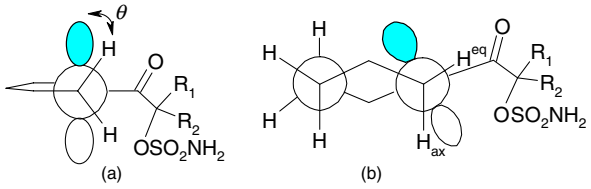


Figure 3.

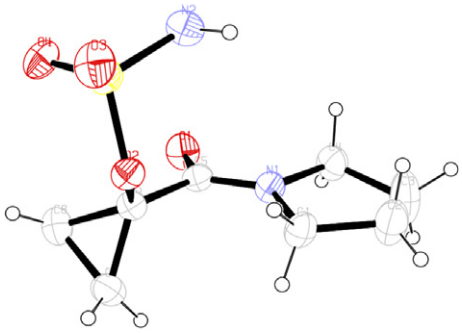


Figure 4. The projection of the asymmetric unit of compound **14**. Visualization made with ORTEP-3.0,[23] ellipsoids drawn at 30% probability level.

product **22** (Figs. 4 and 6).[20,24] In **10**, the values of these angles, which correspond to the above-mentioned linear conformation, are 175.6(2)° and 176.6(2)° for the first and second molecule of the asymmetric unit, respectively. These results suggest that the cyclopropyl group favours a reactive conformation, which places the nitrene precursor in close proximity to the reacting C–H bond. The amination reaction is thus facilitated by a higher population of the reactive rotamer due to the presence of the cyclopropyl group (Fig. 5).

In conclusion, rhodium-catalyzed C–H amination of cyclic amines leading to bicyclic aminals is reported. In this original system, the 'activating' sulfamoyloxy group is attached to the endocyclic nitrogen with an appropriate linker. The results obtained further demonstrate the remarkable conformational control that is possible in azacycloalkane derivatives. This work leads to the first example of a successful intramolecular catalyzed amination of a tertiary sulfamic ester and to the first example of α-C–H substitution in azacycloalkane by a group linked to the endocyclic nitrogen. Further studies to explore the potential of this chemistry are currently underway in our laboratory.

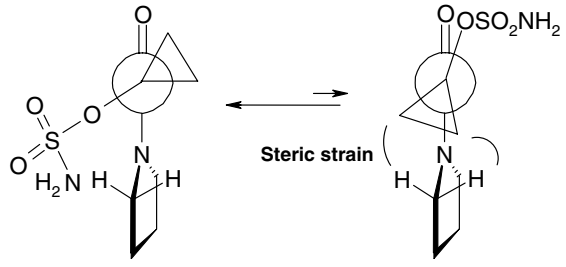


Figure 5.

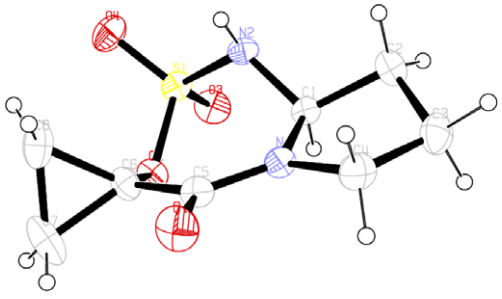


Figure 6. The projection of the asymmetric unit of compound **22**. Visualization made with ORTEP-3.0,[23] ellipsoids drawn at 30% probability level.

Acknowledgments

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12. *Typical amidation procedure*: To a 0.3 M solution of β-hydroxy carboxylic acid (1.5 equiv) in anhydrous CH_2Cl_2,

were added successively the cyclic amine (1 equiv), HOBt (1.1 equiv), *N*-methylmorpholine (NMM, 2.2 equiv) and EDCI (1.5 equiv) at room temperature under argon. The solution was stirred overnight. The reaction mixture was quenched with a solution of NH_4Cl and diluted with water and CH_2Cl_2. The mixture was extracted with CH_2Cl_2 (three times). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification on silica gel (CH_2Cl_2/acetone 95/5) afforded the expected amide.

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15. *Typical sulfamoylation procedure*: To a 0.6 M solution of the alcohol substrate in *N*,*N*-dimethylacetamide (DMA) was added $ClSO_2NH_2$ (3 equiv) at 0° C under argon. The solution was stirred overnight at room temperature. Water and EtOAc were added and the mixture was extracted with EtOAc (three times). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. After the removal of DMA by coevaporation with toluene in vacuo, purification of the residual product on silica gel (CH_2Cl_2/acetone 99/1 to 90/10) afforded the expected sulfamic ester.
16. *Selected data for sulfamic ester* **14**: ^{1}H NMR (400 MHz, acetone-d_6): δ 1.24 (m, 2H); 1.38 (m, 2H); 1.81 (m, 2H); 1.91 (m, 2H); 3.36 (t, 2H, $J = 6.8$ Hz); 3.72 (t, 2H, $J = 6.4$ Hz); 6.93 (s, 2H); ^{13}C NMR (75 MHz, acetone-d_6): δ 11.7; 24.1; 26.7; 47.2; 47.3; 63.3; 166.4; IR (neat) 3406, 1633, 1462, 1373, 1136 cm^{-1}; HRMS (ESI) *m*/*z* 257.0566 $[M+Na]^+$ ($C_8H_{14}N_2O_4NaS$ requires: 257.0572).
17. *Selected data for aminal* **22**: ^{1}H NMR (400 MHz, acetone-d_6): δ 1.27–1.37 (m, 2H); 1.47–1.60 (m, 2H); 1.85–2.02 (m, 3H); 2.39 (m, 1H); 3.46–3.55 (m, 2H), 5.47 (t, 1H, $J = 6.0$ Hz); 8.06 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6): δ 14.8; 15.6; 21.7; 33.5; 48.0; 64.1; 68.5; 166.8. IR (neat) 3442, 1628, 1466, 1373, 1192, 1148 cm^{-1}; HRMS (ESI) *m*/*z* 255.0408 $[M+Na]^+$ ($C_8H_{12}N_2O_4NaS$ requires: 255.0415).
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19. Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462, and references cited therein.
20. The crystals of compounds **10**, **14** and **22** were transparent, white colour and stable in the air. Suitable crystals were obtained after crystallization from acetone/water (2/1) via slow evaporation of the solvent at room temperature. The intensity measurements for crystals of all presented structures were carried out on a Nonius KappaCCD diffractometer using MoKα radiation ($\lambda = 0.7107$ Å) at 293(2) K. The phase problem was solved with direct methods with SIR92[25] for **10** and **14**, and with SHELXS-97[26] for **22**. All structures were refined by full-matrix least-squares on F^2 (SHELXL-97).[26] All non-hydrogen atoms were refined anisotropically. The positions of all hydrogen atoms were found in the difference Fourier map. The hydrogen atoms were refined with isotropic displacement parameter equal 1.2 times that of the parent atom with the use of the riding model. Crystallographic data (excluding structure factors) for structures **10**, **14** and **22** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary Publication Nos. CCDC 653256, CCDC 653257 and CCDC 655724, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
21. *Crystal data for compound* **10**: Moiety formula $C_7H_{14}N_2O_4S$, crystal size: $0.28 \times 0.20 \times 0.13$ mm^3, $M = 222.26$, monoclinic, space group $P2_1/c$, $\alpha = 9.6309(1)$ Å, $b = 20.4516(3)$ Å, $c = 10.4859(1)$ Å, $\beta = 94.9689(6)°$, $V = 2057.62(4)$ Å^3, $Z = 8$, $D_c = 1.435$ g/cm^3, μ(MoKα) = 0.31 mm^{-1}, $F(000) = 944$; theta range: 1.00–27.48°, 66,982 collected reflections, 9446 independent (R(int) = 0.048). The refinement parameters are $R_1 = 0.039$ for reflections with $F^2 > 2\sigma(F^2)$, $wR_2 = 0.095$, $S = 1.04$.
22. *Crystal data for compound* **14**: Moiety formula $C_8H_{14}N_2O_4S$, crystal size: $0.20 \times 0.13 \times 0.05$ mm^3, $M = 234.27$, triclinic, space group $P\bar{1}$, $a = 7.4825(1)$ Å, $b = 8.1228(2)$ Å, $c = 9.4670(2)$ Å, $\alpha = 79.1433(9)°$, $\beta = 81.5618(9)°$, $\gamma = 73.5428(9)°$, $V = 539.27(2)$ Å^3, $Z = 2$, $D_c = 1.443$ g/cm^3, μ(MoKα) = 0.30 mm^{-1}, $F(000) = 248$; theta range: 1.00–27.48°, 12,821 collected reflections, 2479 independent (R(int) = 0.051). The refinement parameters are $R_1 = 0.048$ for reflections with $F^2 > 2\sigma(F^2)$, $wR_2 = 0.121$, $S = 1.03$.
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24. *Crystal data for compound* **22**: Moiety formula $C_8H_{12}N_2O_4S$, crystal size: $0.30 \times 0.22 \times 0.05$ mm^3, $M = 232.26$, orthorhombic, space group *Pbca*, $a = 8.3408(1)$ Å, $b = 14.9800(2)$ Å, $c = 16.2865(3)$ Å, $V = 2034.92(5)$ Å^3, $Z = 8$, $D_c = 1.516$ g/cm^3, μ(MoKα) = 0.31 mm^{-1}, $F(000) = 976$; theta range: 1.00–27.48°, 62,691 collected reflections, 9288 independent (R(int) = 0.038). The refinement parameters are $R1 = 0.042$ for reflections with $F^2 > 2\sigma(F^2)$, $wR_2 = 0.101$, $S = 1.08$.
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