Synthesis and Crystal Structure of Unexpected (1*S*,4*R*,5*R*,6*S*)-4-cyano-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonan-6-yl acetate

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The reaction of (-)-β-pinene with KCN under a mild bridged Ritter reaction gave (1*S*,5*R*,6*S*)-2,2,6-trimethyl-3-aza-bicyclo[3.3.1]non-3-en-6-yl acetate that subsequently reacted to provide an unexpected (1*S*,4*R*,5*R*,6*S*)-4-cyano-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonane-6-yl acetate. The structure of the compound was determined by HRMS, IR, NMR and confirmed by single crystal X-ray crystallography. The compound crystallises in the monoclinic $P2_1$ space group, with unit cell parameters a = 8.6120 (17), b = 7.4570 (15), c = 11.189 (2) Å, β = 110.16 (3)°.

Introduction

The Ritter reaction describes a one-flask process in which a carbenium ion and nitrile (R–CN) react to form a nitrilium ion. This may be hydrolysed to give an amide product, or undergo intramolecular cyclisation to a heterocycle that contains an imine group. In the bridged Ritter reaction, the nitrile clips across an unsaturated carbenium ion component to generate a product containing a 1-azacyclohexene unit.[1] This process allows for the generation of new heterocycles, closely related in structure to bioactive natural products, such as the *Aristotelia* Alkaloids (Fig. 1) that are based around an azabicyclo[3.3.1]nonane core.[2],[3]

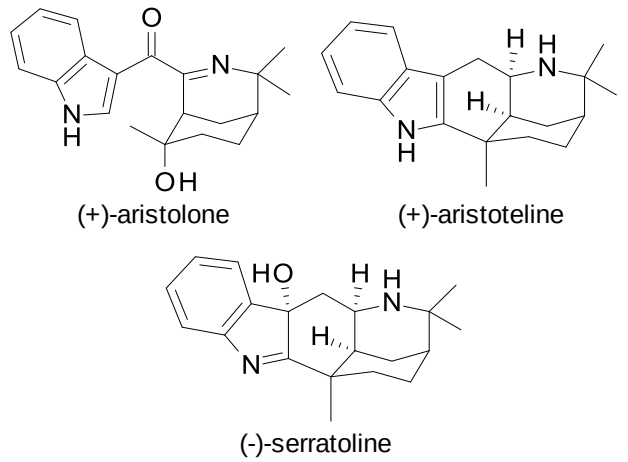
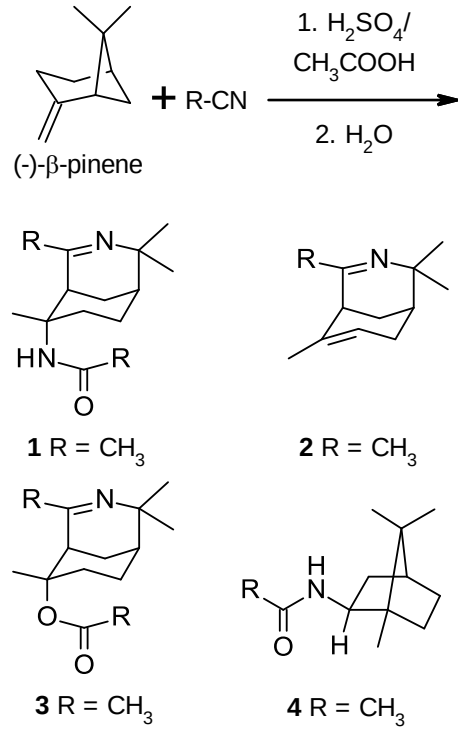
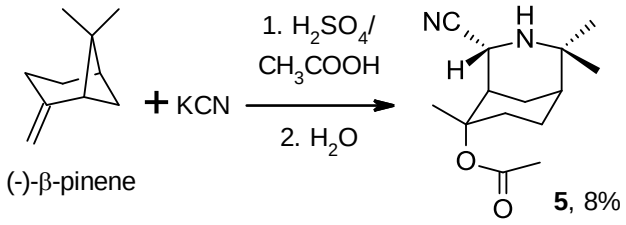


Fig. 1. Structures of known *Aristotelia* Alkaloids.

Our early work found that under mildly acidic conditions, (-)-β-pinene reacted with acetonitrile to produce the azabicyclo[3.3.1nonene derivatives **1** and **2** in the ratio 5:1, the acetate **3**,[4] plus an unexpected isobornylacetamide **4**[5] (Scheme 1). Herein, the X-ray structure of another unexpected product **5** from the reaction in Scheme 2 is reported with a proposed mechanism of formation.



Scheme 1. The bridged Ritter reaction of nitrile with functionality -R and (-)-β-pinene to give bridged products **2** and **3** and the isobornylacetamide **4**.



Scheme 2. The bridged Ritter reaction of potassium cyanide and (-)-β-pinene to give the unexpected acetate **5**.

Experimental

Materials and Physical Measurements

All chemical reagents and analytical grade solvents were obtained from commercial sources such as Sigma-Aldrich, Cambridge Isotope Laboratories Inc. and Merck Millipore. All reactions were monitored using either TLC aluminium oxide 60 F254 neutral or TLC Silica gel 60 F254 with UV detection at 254 nm. ^{1}H NMR and ^{13}C NMR spectra were recorded on an Agilent 500 MHz spectrometer (500 MHz ^{1}H, 125 MHz ^{13}C) in deuterated chloroform ($CDCl_3$). Gas-chromatography

data were obtained using an Agilent 6890GC fitted with a 5% polysilphenylene: 95% polydimethylsiloxane column. The Mass spectral data was obtained using the attached Agilent 5973n MS (EI) spectrometer. High-resolution mass spectra were obtained using an Agilent 6510 Q-TOF Mass Spectrometer (ESI). The infrared spectra were recorded on an Agilent Cary 630 FTIR with a diamond window using 16 background and sample scans. Melting points were measured on a Gallenkamp Melting Point Apparatus equipment and were uncorrected.

Synthesis

(1S,4R,5R,6S)-4-cyano-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonan-6-yl acetate **5**

The reaction was carried out in a two neck round bottom flask, fitted with a condenser with a gas trap at 0 °C and a septum for delivering the H_2SO_4 while keeping the vessel sealed. Sulfuric acid (18 M, 1.2 mL) was slowly added to a stirred solution of potassium cyanide (1.0439 g, 16.03 mmol) and (-)-β-pinene (1.2 mL, 7.62 mmol), in glacial acetic acid (10 mL). The reaction was left to stir for 30 minutes at 0 °C before continuing for 24 hours at room temperature (ca. 21 °C). The reaction mixture was then quenched by the addition of water (30 mL). The resulting mixture was basified with a 4 M solution of NaOH (until pH was > 10). The resulting mixture was then extracted with chloroform (2 x 20 mL), and the combined extracts were dried over Na_2CO_3. The solvent was removed to give a crude product that was purified by recrstallisation from ethyl acetate to give **5** (0.1480 g, 0.592 mmol, 8%) as a colourless crystal; m.p = 164 °C; $[\alpha]_D^{20}$ +9.76 (c 1.00, $CHCl_3$). IR (neat, cm^{-1}) 3335, 2985, 2956, 2929, 2899, 2869, 2220, 1720, 1497, 1458, 1380, 1361, 1255, 1210, 1193, 1148, 1118, 1020, 969, 928, 817, 727, 693; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.10 (br s, 1H, CH-5), 2.69 (br s, 1H, CH-4), 2.28 (dq, *J* = 13.5, 3.0 Hz, 1H, CH_2-2a), 2.23 (dd, *J* = 14.0, 5.5 Hz, 1H, CH_2-1a), 2.03 (br s, 3H, CH_3-11), 1.96-1.95 (m, 1H, CH_2-1b), 1.92-1.82 (m, 1H, CH_2-2b), 1.81 (dq, *J* = 14.0, 4.5 Hz, 1H, CH_2-8a) 1.65 (tt, *J* = 14.0, 4.5 Hz, 1H, CH_2-8b), 1.56 (br s, 3H, CH_3-9) 1.47-1.46 (m, 1H, CH-7), 1.45 (br s, 3H, CH_3-13), 1.09 (br. s, 3H, CH_3-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7 (C-10), 123.1 (C-12), 83.8 (C-3), 53.6 (C-6), 45.66 (CH-5), 38.6 (CH-4), 35.5 (CH-8), 33.2 (CH_2-1), 30.3 (CH_3-11), 29.1 (CH_3-9), 24.5 (CH_2-4), 24.3 (CH_3-13), 23.4 (CH_2-2), 22.8 (CH_3-14); GC/MS R_t = 14.72 min, *m/z* 223 (M-27), 208, (7), 180 (100), 164 (74), 148 (23), 122 (36), 108 (64), 43 (62%). HRESIMS: $[M+H]^+$, found 251.1754, $C_{14}H_{22}N_2O_2$ required 251.1741.

X-Ray Crystallography

The X-ray diffraction measurements for compound **5** were carried out at MX1 beamline at the Australian Synchrotron Facility, Melbourne. The crystal was mounted on the goniometer using a cryo-loop for diffraction measurements, was coated with paraffin oil and then quickly transferred to the cold stream using Cryo stream attachment. Data were collected using Si<111> monochromated synchrotron X-ray radiation (λ = 0.71023 Å) at 100 K and were corrected for Lorentz and polarization effects using the XDS software.[6] The structure was solved by direct methods, and the full-matrix

least-squares refinements were carried out using SHELXL[7] with the program Olex-2.[8] The non-hydrogen atoms were refined anisotropically. The molecular graphics were generated using Mercury.[9] Key crystallographic data and refinement details are presented in Table 1.

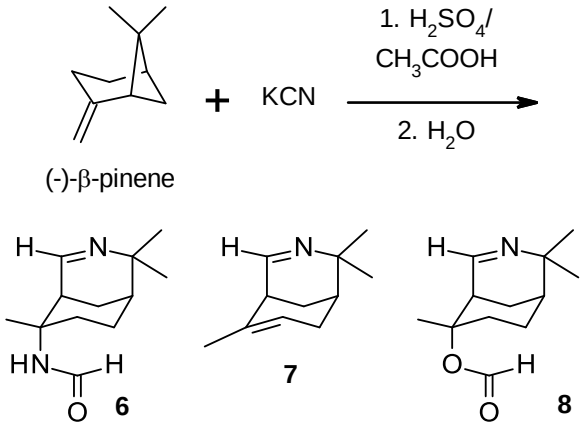
Table 1. Experimental details for compound **5**.

Crystal Data	
Chemical formula	$C_{14}H_{22}N_2O_2$
M_r	250.33
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, *b*, *c* (Å)	8.6120 (17), 7.4570 (15), 11.189 (2)
β (°)	110.16 (3)
V (Å^3)	674.5 (3)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	0.08
Crystal size (mm)	0.04 × 0.02 × 0.02
Data collection	
Diffractometer	Australian Synchrotron
Absorption correction	–
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	11209, 3006, 2935
R_{int}	0.024
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.659
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.039, 0.102, 1.14
No. of reflections	3006
No. of parameters	171
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.30, −0.21
Absolute structure	Flack x determined using 1310 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.3 (3)
CCDC deposition Number	1454979

Results and Discussion

Using the toxic and low boiling H–CN is a safety limitation when performing the Ritter reaction, however, alternative approaches that avoid this dangerous substance are now available.[1] The resulting *N*-alkylformamides from these methods can be hydrolysed comparatively easily, thereby providing an important synthetic route to the corresponding *N*-alkylamine.[10] Unfortunately, these alternative procedures are not applicable to the bridged-Ritter reaction. In fact, clipping H–CN (or its chemical equivalent) across an unsaturated carbenium ion intermediate has not been previously reported.

As part of our alkaloid-like drug discovery program, we were interested in synthesising the azabicyclo[3.3.1]nonene derivatives **6**, **7** and **8**. Accordingly, in the likelihood of obtaining products **6**-**8** (Scheme 3), we reacted (-)-β-pinene with HCN generated *in situ* from KCN and H_2SO_4 in acetic acid at 0 °C.[11]



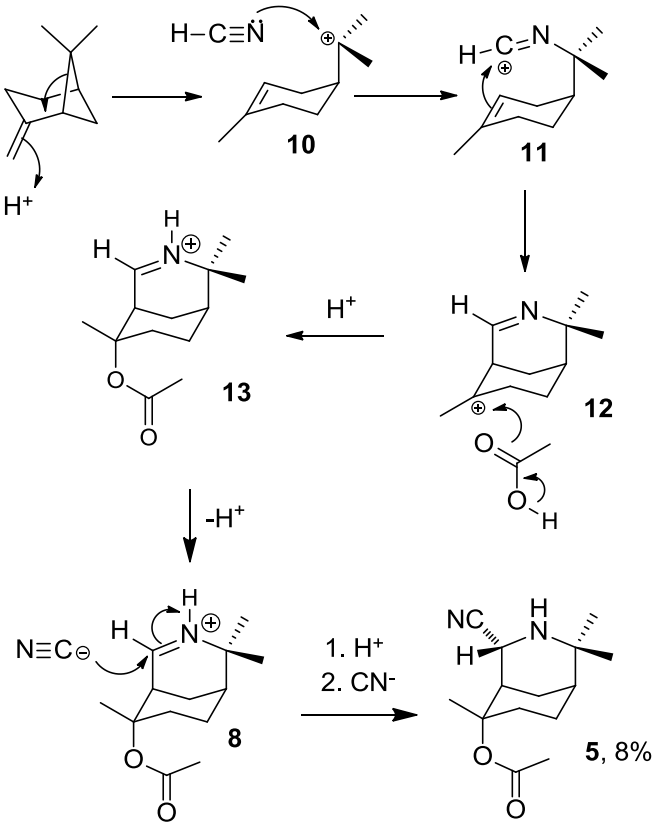
Scheme 3. Expected products from the bridged Ritter reaction of potassium cyanide and (-)-β-pinene.

Compound **5**, shown in Scheme 2, was the only product that was able to be isolated and characterised from this reaction with an 8% yield. Initially, compound **5** was thought to be the expected product **8**, as suggested by HRMS analysis which gave $[M+H]^+$ *m/z* 224.1644 corresponding to formula $C_{13}H_{22}NO_2$, suggesting that the product was (1*S*,5*R*,6*S*)-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-3-en-6-yl acetate. This, however, did not agree with the rest of the spectroscopic analysis and the HRMS analysis was repeated with under neutral conditions by using mobile phase without the ionisation source formic acid. This gave a molecular ion of *m/z* 251.1754 $[M+H]^+$, corresponding to the formula $C_{14}H_{22}N_2O_2$ for compound **5**. This may be explained by the possible elimination of HCN from **5** to form **8** under the acidiic conditions. This unstable nature and HCN elimination have been reported for 1-substituted nitriles of piperidines[12],[13] and has helped propose the suggested mechanism for the reaction below. X-ray analysis of the recrystallized product unequivocally confirm the structure of compound **5**.

Analysis of the initial crude product by GC/MS revealed that the novel expected substances **7** (*m/z* 163, R_t = 11.32 min) was also formed in trace amounts, in addition to a large quantity of rearranged pinene impurities resulting from treatment of the starting material with acid. These compounds were unable to be isolated so no yield could be reported, however, have since been characterised and will be published in future work.

*Proposed Mechanism for the Formation of **5***

The proposed mechanism explaining the formation of **5** is shown in Scheme 4. KCN reacts with H_2SO_4 to generate HCN *in situ*. HCN then reacts with **10** to give the second carbenium ion intermediate **11**, which undergoes intramolecular cyclisation to provide imine **12**. Acetate adds *via* nucleophilic addition to **12**, giving intermediate **13**, which would lose a proton to give **8**. Available CN anions then asymmetrically add to **8** at C-4, from the *Si* face of the imine bond, to give optically active compound **5**.



Scheme 4. Proposed mechanism for the formation of **5**.

Spectroscopic Analysis

The IR spectrum of compound **5** revealed bands at 2220, 1720, 1220 and 1017 cm^{-1} corresponding to CN, C=O and C-O stretches that are indicative of cyano and ester functional groups, respectively. ^{13}C NMR showed two resonances at δ 170.7 and 123.1 ppm that confirmed the presence of C=O and CN functional groups. The lack of an imine carbon resonance (≈ 166 ppm in similar compounds from

previous work) and the presence of newly formed CH at 45.7 ppm, further suggest that the imine (C=N) functionality is no longer presence within the structure.

Crystal Structure Analysis

Compound **5** crystallised in the monoclinic $P2_1$ space group. The molecular structure of **5** and the atom-labelling scheme are shown in Fig. 2. Compound **5** adopts a chair-chair conformation. The molecule shows an intramolecular C-H···O interaction in the solid state (Fig. 2). This interaction is commonly observed in these type of bridged compounds, as also shown in our previous work.[4] The crystal and refinement data are given in Table 1. The bond lengths within the azabicyclo[3.3.1]nonane core structure show the evidence for the sp^3 hybridisation at C-5. The N1-C5 bond is 1.451 (3) Å, which is very similar in length to that of N1-C6 (1.479 (3) Å). One would expect the N1-C5 in **8** to be significantly shorter than N1-C6 (1.479 (3) Å). Our previous work on the azabicyclo[3.3.1]nonene system, showed the N1-C5 distance in the imine bond to be in the range of 1.274 (4)-1.259 (11).[12],[15] The presence of cyano group at C-5 is confirmed by the bond lengths of C5-C12 and N2-C12 to be 1.504 (3) and 1.148 (3) Å, respectively, in addition to the bond angle for N2-C12-C5 (178.1 (2)°. These distances and angle are in agreement with the generally accepted values for correlated molecules that contain a cyano group.[16],[17] Moreover, the crystal data of **5** compares well with the results observed in similar azabicyclo[3.3.1]nonane systems found in the literature.[18],[19]

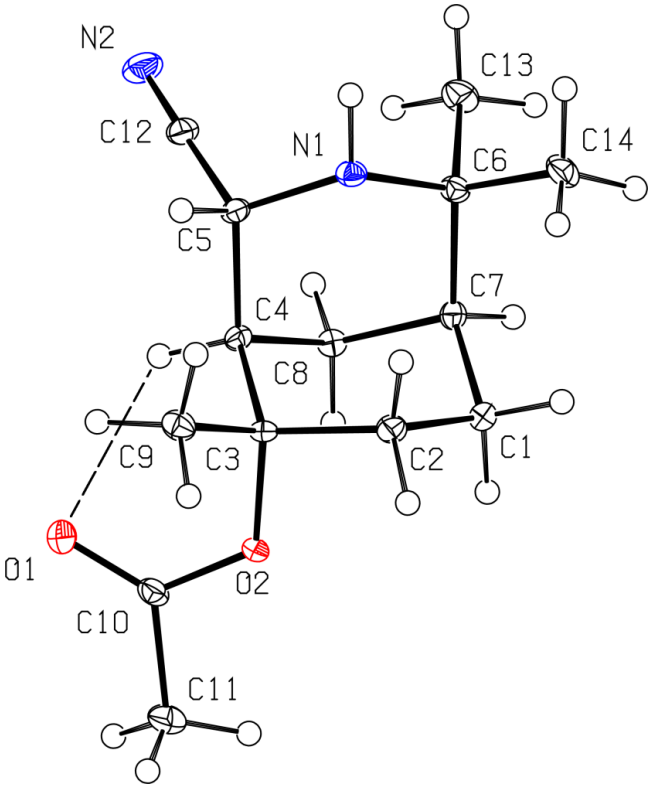


Fig. 2. ORTEP diagram of compound **5**, the intramolecular hydrogen bond is indicated as a dashed line.

In the asymmetric crystal packing unit of **5**, two orientations exist. Each of the orientations is stacked as columns parallel to the *b* axis. Columns of each molecule are developed along the *ac* plane, as shown in Fig. 3, where packing of molecules in the crystal lattice are viewed along the *b*-axis.

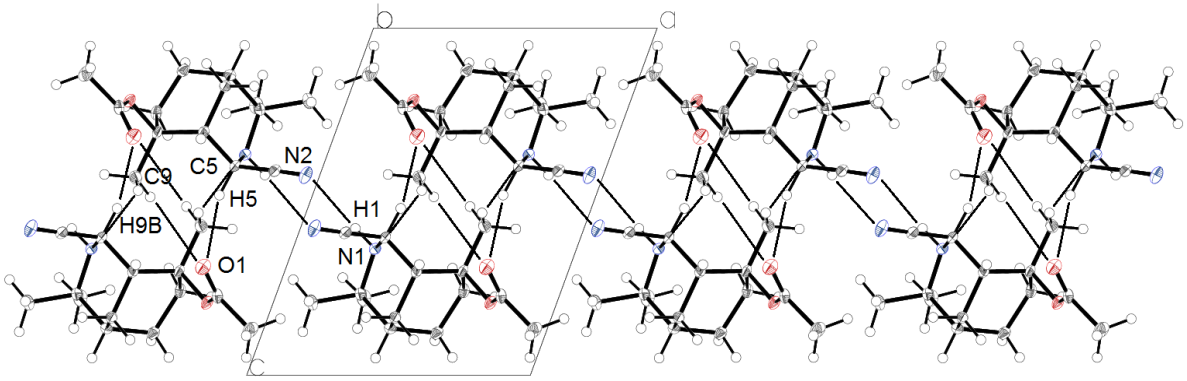


Fig. 3. Packing of molecules viewed along the *b* axis.

Significant intermolecular interactions are recorded in Table 2; interactions clearly seen in this projection are shown and labelled in Fig. 4. Molecular bilayers linked *via* C-H···O and N-H···N are formed parallel to the *ab* plane. Interestingly, these bilayers do not make any significant contacts along the *c* axis. As seen in Fig. 3, the primary extension is along the 21 screw axis where the protruding nitrile group is involved in N-H···N, contacts across 2_1 screw axis, while the rest of the molecule makes several C-H···O interactions, as shown above.

Table 2. Significant intermolecular interactions of compound **5**.

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···N2^{i}	0.94 (4)	2.25 (4)	3.173 (3)	167 (3)
C2—H2*A*···O1^{ii}	0.99	2.86	3.445 (3)	119
C2—H2*A*···N1	0.99	2.51	2.978 (3)	108
C4—H4···O1	1.00	2.34	3.006 (3)	123
C5—H5···O1^{iii}	1.00	2.43	3.347 (3)	152
C8—H8*B*···O2	0.99	2.60	2.945 (3)	101
C9—H9*A*···O1	0.98	2.46	3.005 (3)	114
C9—H9*A*···N1^{iv}	0.98	2.68	3.452 (3)	135

Symmetry codes: (i) −*x*+2, *y*−1/2, −*z*+1; (ii) *x*, *y*−1, *z*; (iii) −*x*+1, *y*−1/2, −*z*+1; (iv) −*x*+1, *y*+1/2, −*z*+1.

Conclusions

This work is not only the first case to report the use of the bridged Ritter reaction with HCN but also demonstrates the usefulness of the products formed from this reaction. Although the yields are low, optimisation could provide useful quantities of the reactive imine intermediate **8** or the reactive product **5**. The ability of the imine in **8** to be susceptible to nucleophilic attack and the ability of the nitrile in **5** to act as a nucleophile, highlights the diverse range of reactions that can be carried out with this scaffold. This window to structural diversity provides a useful handle for the generation of libraries of compounds containing the azabicyclo[3.3.1]nonane core and hence potentially biologically active alkaloid-like compounds, for example, through the introduction of competing nucleophiles added *in situ*.

Supplementary Material

Experimental spectra are available on the journal website.

Acknowledgments

We are grateful to the University of Technology Sydney for providing financial support to this project.

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