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Synthesis of Bridged Azacycles and Propellanes via Nitrene/Alkyne Cascades

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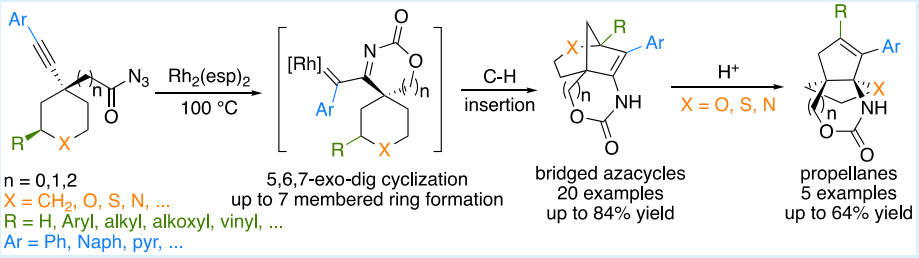

ABSTRACT: A nitrene/alkyne cascade reaction terminating in C−H bond insertion to form functionalized bridged azacycles from carbonazidates is presented. Due to an initial Huisgen cyclization, all carbonazidates reacted with the alkyne in an exo mode in contrast to the use of sulfamate esters, which react predominately in an endo mode. Substrates with different ring sizes as well as different aryl and heteroaryl groups were also explored. Variation of the nitrene tether showed that 7-membered rings were the maximum ring size to be formed by nitrene attack on the alkyne. Examples incorporating stereocenters on the carbonazidate's tether induced diasteroselectivity in the formation of the bridged ring and two new stereocenters. Additionally, propellanes containing aminals, hemiaminals, and thioaminals formed from the bridged azacycles in the same reaction via an acid-promoted rearrangement.

Oxygen- and nitrogen-containing polycycles are common structural motifs present in natural products, many of which possess significant biological activities.[1,2] Strategies for the construction of bridged polycycles that have been explored in total syntheses include cycloadditions,[3] cyclizations,[4] carbocation rearrangements,[5] and multistep reactions. A substrate-controlled, general strategy to construct bridged polycyclic isomers from easily accessible precursors would facilitate the rapid construction of these targets. To that end, many research groups, including our own, are in pursuit of carbene/alkyne and nitrene/alkyne cascades to build multiple C−C and C−N bonds and multiple rings of the target polycycles in a single transformation.[6,7]

Nitrene/alkyne cascades could be utilized for the formation of polycyclic azacycles. For example, Blakey's group developed a series of metallonitrene/alkyne cascade reactions initiated by endocyclization with Rh-nitrenes to generate cation/metal-loenamine intermediate **2**, followed by intramolecular cyclopropanation, aromatic substitution, or oxygen-ylide formation followed by [2,3]-Wittig rearrangement to build the fused bisheterocyclic products **3** (Scheme 1a).[8] Recently, Shi and coworkers reported a substrate-dependent cascade reaction of alkynyl-tethered sulfamates **5** (Scheme 1b).[9] In the case of sulfamates bearing a cyclopropyl or cyclobutyl group, oxidative amination and cyclization formed cyclobutane-containing heterocycles **7** and **8**. Alternatively, with 5- or 6-membered cyclic sulfamates, only a direct C−H bond insertion reaction occurred to give the fused bicyclic products **4**.[9a] Sulfamate-based nitrenes almost exclusively reacted in an exolike mode with alkynes.

The *exo*-cyclization of alkynyl nitrenes to form α-iminocarbenes like **16** has been significantly more difficult to implement. Instead, α-diazoimines and α-iminocarbenes were generated via triazole formation and subsequent ring opening in the presence of transition metal catalysts (see **14** and **15**).[10] Our group reported that intermediates **10** were generated from silyl alkynylcarbonazidates **9** via triazole formation, and dediazotization provided the exolike product of nitrene/alkyne cyclization (Scheme 1c).[6f] Unfortunately, azasilacyclopentenes **11** were formed as the major products via an unusual α-silyl C−H bond insertion due to triplet carbene reactivity. The targeted bridged tricyclic product **12** was observed only as a minor product, and to the best of our knowledge, no group has successfully selectively synthesized nitrogen-containing bridged tricycles via nitrene/alkyne cascades.

To avoid α-silyl C−H bond insertion in the cascade reaction, phenylethynyl carbonazidate **19** was prepared in just two steps from the parent ketone **18** (80% yield overall). A

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Scheme 1. Nitrene-Initiated Cascade Reactions

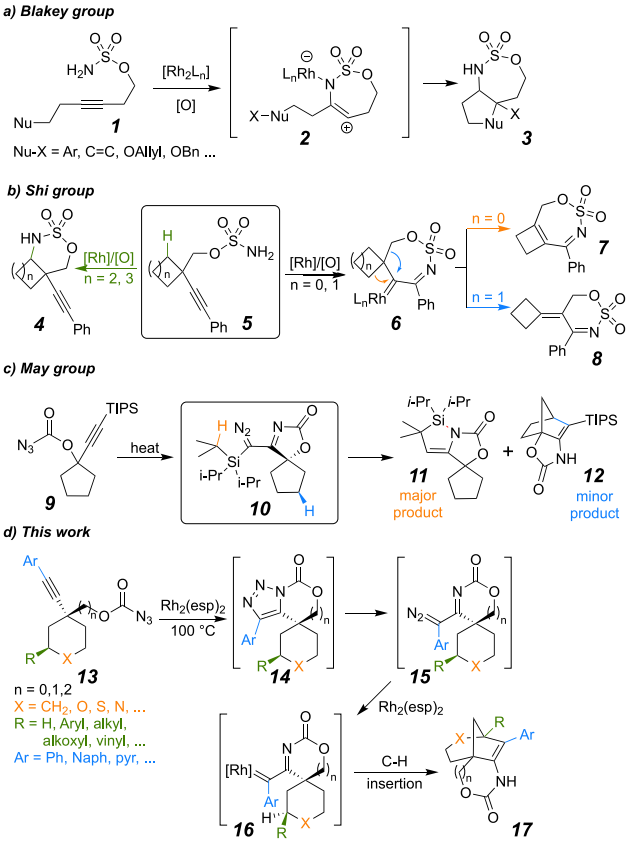
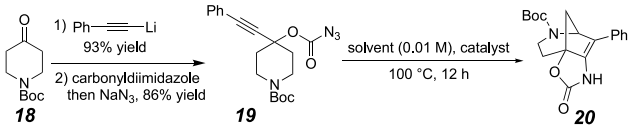


Table 1. Formation of Bridged Azacycle



entry	solvent	catalyst	yield of **17**[a]
1	benzene	none	10%
2	1,4-dioxane	none	13%
3	cyclohexane	none	20%
4	*n*-hexane	none	25%
5	*i*-PrOAc	none	35%
6	***i*-PrOAc**	**$Rh_2(esp)_2$ (1 mol %)**	**55%**
7	EtOAc	$Rh_2(esp)_2$ (1 mol %)	47%
8	*t*-BuOAc	$Rh_2(esp)_2$ (5 mol %)	43%
9		$Rh_2(esp)_2$ (1 mol %)	43%
10		$Rh_2(esp)_2$ (1 mol %)	34%
11	*i*-PrOAc	$Rh_2(pfb)_4$ (5 mol %)	35%
12	*i*-PrOAc	$Rh_2(cap)_4$ (5 mol %)	33%
13	*i*-PrOAc	$Rh_2(TPA)_4$ (5 mol %)	40%

[a]Yield based on ^{1}H NMR peak integration relative to methyl-4-nitrobenzoate. See the Supporting Information for more details.

range of aprotic solvents were examined at 0.01 M. Saturated hydrocarbon solvents provided better yields than benzene or 1,4-dioxane (Table 1, entries 1−4). Isopropyl acetate (*i*-PrOAc) was also examined due to its common use in industry as well as in carbene reactions. To our delight, it afforded a better yield (35%) than that from nonpolar solvents (entry 5). To reduce side reactions, a rhodium(II) catalyst was added to promote intramolecular C−H insertion. Gratifyingly, after adding $Rh_2(esp)_2$, the yield of the bridged azacycle **20** increased significantly. As a result, *i*-PrOAc with $Rh_2(esp)_2$ (1 mol %) provided the best conditions for this nitrene/alkyne cascade reaction and gave the bridged azacycle **20** in 55% yield (entry 6). With different ester solvents, the yields were less than those from *i*-PrOAc (entries 7−9). Dimethyl carbonate was also examined, but the yield was not improved (entry 10). Some other dirhodium catalysts were also examined (entries 11−13),[11] but did not improve the yields.

The scope of carbonazidate reactivity was then explored (Scheme 2). For carbonazidates containing a heteroatom-activated methylene, bridged products **20** and **21**−**24** were formed in useful isolated yields. Similar yields of **20** and **21** illustrated that the electron-withdrawing group on the alkynyl phenyl ring had little effect on the outcome. Introducing a methoxy group in the meta position of the phenyl ring decreased the yield to 45% of **22**, which could be due to inductive effects. Electron-rich naphthyl-substituted **23** successfully produced product in 41% yield. *N*-Toluenesulfonyl amide (*N*-Ts) **24** showed similar reactivity as *N*-Boc amide **20**. Sulfur-containing substrate provided less of the bridged azacycle than amides, affording the corresponding product **25** in a lower yield (34%). This could be due to decreased activation of the adjacent C−H bond by sulfur relative to an amide nitrogen. Alternatively, sulfur could also react with the intermediate carbene to form a sulfur ylide,[12] which could potentially shut down the cascade reaction. Interestingly, by introducing a phenyl group in the cyclohexyl 4-position, the conformation of the cyclohexane ring can be controlled. With the alkyne cis to the phenyl group, bridged tricycle **26** was produced. However, with the alkyne trans to the phenyl group, no bridged product was produced. Incorporation of a ketal in the 4-position provided no activation for product formation, giving **27** with only a 29% yield. For the carbonazidates containing tertiary, benzylic, or allylic C−H bonds for insertion, the yields were generally higher than those with an α-heteroatom activated methylenes (see **28**−**31**). Benzylic C−H bonds showed the highest activity for C−H insertion, giving enamine **28** in 84% yield. Both methoxy-activated and methyl-activated tertiary C−H bonds were highly reactive and provided higher yields of product than did C−H insertion at an allylic C−H bond (compare **29**−**31**).

Many pyridine derivatives have intriguing activities against important biological targets.[13] Impressively, when using a cyclohexyl carbonazidate bearing 3-pyridinyl alkynyl substitution, bridged tricycle **32** was obtained in 59% yield. Introducing a methyl group at the 3 position in the ring improved the yield, giving **33** in 68% yield. However, when a 2-pyridinyl alkynyl carbonazidate was tested, only pyridotriazole **34** was formed with or without $Rh_2(esp)_2$ via an electrocyclization from the corresponding diazo intermediate (formed in the first mechanistic cyclization).[14] This product was very thermally stable (tested to 175 °C), and no further transformation was observed.

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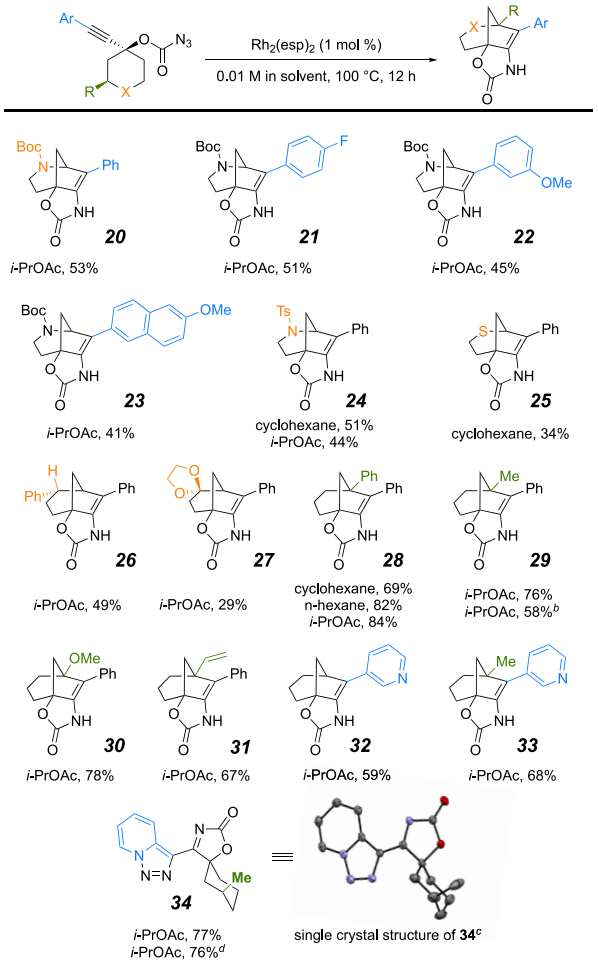
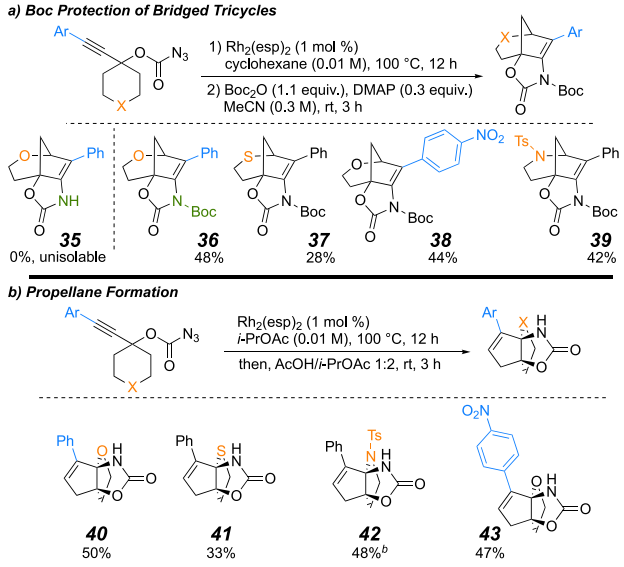
Scheme 2. Formation of Bridged Azacycles[a]



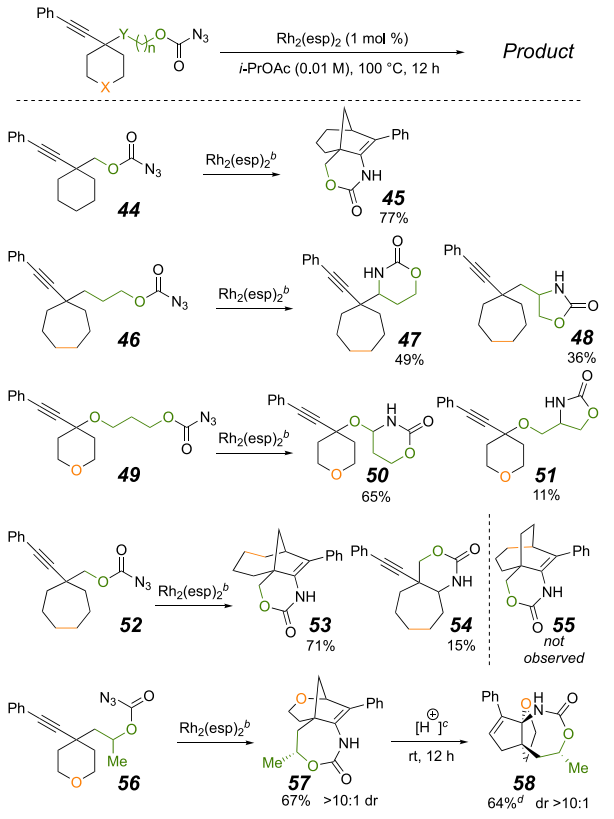
[a]All yields are isolated yields (average of 2 runs). [b]Overall yield of two steps from the propargylic alcohol. See the Supporting Information for more details. [c]ORTEP diagram for **34**. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms have been omitted for clarity. [d]Without $Rh_2(esp)_2$.

Scheme 3. Boc Protection of Bridged Azacycles and Propellane Formation[a]



[a]All yields are isolated yields (average of 2 runs). [b]Trifluoroacetic acid used instead of acetic acid.

Scheme 4. Variation of Tether Length and Ring Sizes[a]



[a]All yields are isolated yields. [b]General conditions: 0.01 M of carbonazidate in *i*-PrOAc with 1 mol % $Rh_2(esp)_2$, 100 °C, 12 h. [c]1:2 AcOH/*i*-PrOAc, rt, 3 h. [d]Yield is calculated for two steps from **56**, with a 95% yield from **57**.

In general, the rearrangement of the bridged tricyclic products with heteroatoms such as oxygen, nitrogen, or sulfur connected to the newly formed bridgehead carbon occurs fairly easily, even as a purified solid. Therefore, those bridged products were difficult to purify by chromatography. In particular, oxacycles such as **35** could not be isolated despite multiple techniques attempted (Scheme 3). To avoid rearrangement and isolate these products in a form with a significantly longer shelf life, the relatively more stable *N*-Boc protected bridged tricycles **36**–**39** were synthesized by a one-pot sequence (Scheme 3a). Furthermore, by simply adding acetic acid (AcOH) after the cascade reaction and before any workup, the propellane products **40**–**43** could be generated from bridged tricycles via rearrangement (Scheme 3b).

A larger ring fused to the bridged tricycle could be accessed by lengthening the tether to the carbonazidate (Scheme 4). Both 6- and 7-exo-dig cyclizations produced cyclourethane fused bridged tricycles (**45** and **57**), and no fused bicycles were formed via direct C–H insertion into the cyclohexyl or pyran ring of **44** or **56**, respectively. It appears that 6- and 7-exo-dig cyclization were both more facile than 5-exo-dig cyclizations as evidenced by higher isolated yields (compare **45** and **57** to **36**), which would be an unusual scenario.[15] Alternatively, the conformation of the carbene intermediates after the 6- and 7-exo-dig cyclizations might be more favorable for the

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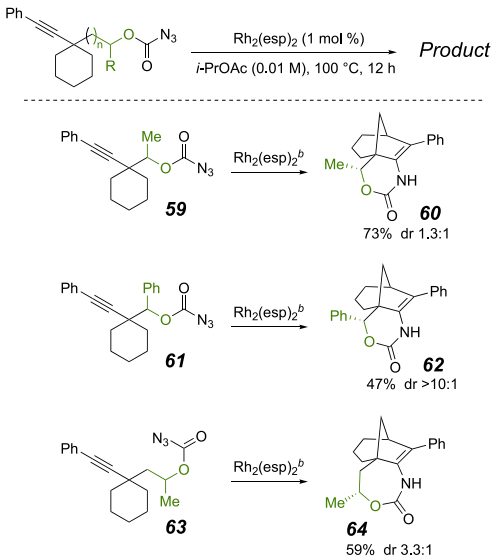
subsequent C−H insertion than the conformation of the 5-exo-dig product. These outcomes are important, because even with the larger rings the initial [3 + 2] cycloaddition to form the triazole intermediate controls the sense of cyclization to give exocyclization-derived carbene reactivity, whereas sulfamate-derived nitrenes give endocyclization-derived carbene reactivity. Unsurprisingly, further extension of the carbonazidate-bearing side chain resulted in only direct C−H insertion on the tether rather than medium ring formation. The cyclization generally favored the formation of a 6-membered ring over a 5-membered ring. This produced a ratio of about 1.5:1 when the tether between the alkyne and the carbonazidate was extended to three atoms (see **47** and **48**), and a ratio of ∼6:1 for an oxygenated four atom tether (see **50** and **51**). The improvement in the selectivity in the latter example was likely due to the oxygen activating the adjacent C−H bonds. Cycloheptane **52** produced the bicyclo[4.2.1]nonane core in **53** in 71% yield, and no bicyclo[3.2.2]nonane **55** was detected. A minor amount of the fused bicyclic product **54** was also observed. Impressively, when methyl substituted secondary carbonazidate **56** was tested, diastereomer **57** was obtained with greater than 10:1 dr. Rearrangement to the propellane was also performed, producing the corresponding diastereomer **58** in 64% overall yield from **56**. The ability to control the stereoselectivity of C−C bond formation via easy to access enantioenriched secondary alcohols[16] will be highly useful in stereocontrolled synthesis.

The excellent diastereoselectivity from **56** inspired further exploration. Another α-methyl ether in a shorter tether was examined (see carbonazidate **59**). Unfortunately, after 6-exo-dig cyclization, the final C−H insertion gave bridged product **60** with only 1.3:1 dr (Scheme 5). A larger substituent like a phenyl group did increase the diastereoselectivity to be greater than 10:1 dr (**62**). Removing the pyranyl oxygen in **56** to give substrate **63** caused the diastereoselectivity to drop to 3.3:1 dr. These results indicated that the conformation imposed by the tether substituent on the postalkyne-cyclization intermediate could control the stereoselectivity of C−H insertion.

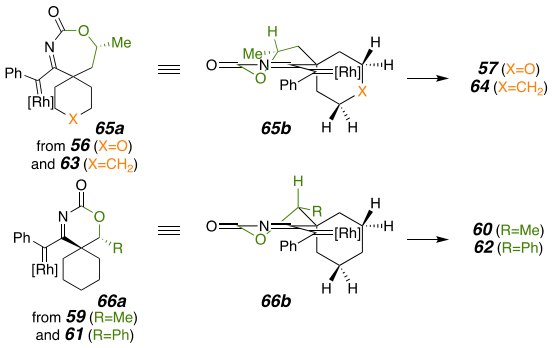
Scheme 5. Diastereoselectivity in the Cascade Reaction[a]



[a]All yields are isolated yields. [b]General conditions: 0.01 M of carbonazidate in *i*-PrOAc with 1 mol % $Rh_2(esp)_2$, 100 °C, 12 h.

The diastereoselectivity above may be explained by considering the carbene intermediate immediately prior to C−H bond insertion (Scheme 6). Huisgen cyclization of

Scheme 6. Potential Origins of Diastereoselectivity



carbonazidates **56** or **63** to form a triazole fused to a 7-membered ring, followed by electrocyclative ring opening to a diazo imine and Rh-catalyzed dediazotization (Scheme 1d), would give carbene intermediates **65**. Similarly, carbonazidates **59** and **61** would give Rh carbenes **66**. Minimizing the conformational energy of the substituted carbamate rings as shown in **65b** and **66b** places the ring substituent in a pseudoequatorial disposition.[3a] In these conformations, the carbene would be placed closer to the methylene on the pseudoequatorial side of the tetrahydropyran ring. In considering **65b**, apparently having a smaller ether oxygen (X = O) allows for a more discriminating carbene approach than the larger methylene (X = CH_2), consequently providing higher disasteroselectivity as well as a higher yield. The control found in conformation **66b** is likely dependent on the size of the R group due to the influence it would exert on the twist-chair conformation, which then controls subsequent insertion selectivity.

In conclusion, nitrene/alkyne cascades synthesized bridged polycyclic compounds chemoselectively from carbonazidates in useful yields. In contrast to our previous approach where bridged products were the minor product, $Rh_2(esp)_2$ catalysis and the use of aromatic alkynes improved the chemoselectivity and gave useful yields of bridged heterocyclic [n.2.1] cores. Aryl and heteroaryl substituents are both readily tolerated. With the abundance of heterocycles in natural and medicinal compounds, this bridged azacycle formation could serve both synthetic and medicinal chemists. By simple modification of the reaction conditions, we were also able to promote rearrangement in the same reaction to propellane structures, which are also present in a considerable number of natural products and medicinally interesting compounds. While endo cyclizations prevailed with the sulfonamide-based substrates, this work shows that 5-, 6-, and 7-exo-dig cyclizations readily occur from carbonazidates as controlled by the initial Huisgen cyclization. Up to 7-membered rings fused to the bridged bicycle can be incorporated. The impact of chiralilty in the carbonazidate tethers on the diastereoselectivity of the cascade reaction has also been explored, with promising transmission of the stereochemistry to the products in several cases. Applications of this methodology to the synthesis of complex targets and additional mechanistic investigations are ongoing.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00798.

Experimental details and compound spectral data (PDF)

Accession Codes

CCDC 1981686 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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