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Reactivity of Morita−Baylis−Hillman Adducts in C−H Functionalization of (Hetero)aryl Nitrones: Access to Bridged Cycles and Carbazoles

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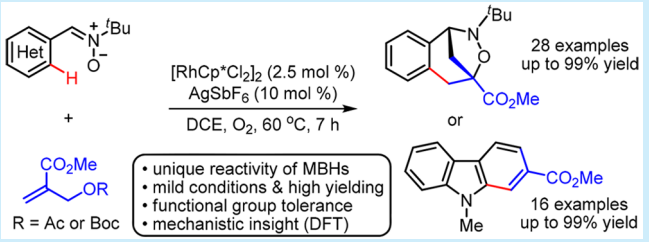
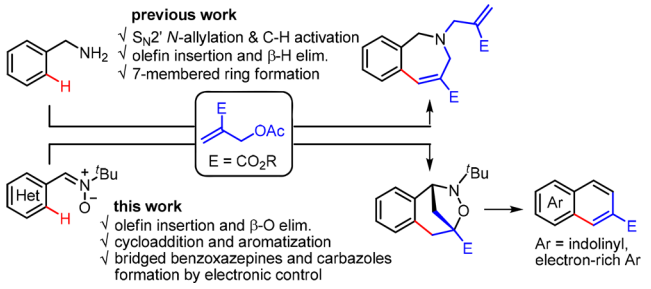
Supporting Information

ABSTRACT: The rhodium(III)-catalyzed cross-coupling of (hetero)aryl nitrones with Morita−Baylis−Hillman (MBH) adducts is described. An allylated intermediate derived from aryl nitrones and MBH adducts allows the formation of bridged cyclic compounds via an exotype [3 + 2] cycloaddition. In sharp contrast, electron-rich indolinyl or aniline substrates were found to couple with MBH adducts to generate naphthalene or carbazole derivatives, respectively.



The Morita−Baylis−Hillman (MBH) reaction is one of the useful C−C bond-forming reactions in organic synthesis.[1] MBH adducts are used as relevant precursors for the formation of highly substituted alkenes by nucleophilic substitution.[2] Very recently, our group first reported the utility of MBH adducts in C−H functionalization reactions for generating 2-benzazepines (Scheme 1).[3] In this report, MBH adducts were employed as both the electrophiles for *N*-substitution and olefin sources for intramolecular C−C bond formation. Although MBH adducts have been widely used in coupling reaction, the integration of C−H functionalization and annulation reactions using MBH adducts have been unexplored. Nitrones have been used as directing groups in C−H functionalization reactions due to the polar nature of the N−O bond and the electrophilicity of the imine moiety.[4] Although nitrones have been utilized for dipolar cycloaddition reactions in organic synthesis,[5] the combination of C−H functionalization and dipolar cycloadditions using nitrones has rarely been explored.[6] Herein, we disclose the unique reactivity of MBH adducts in the C−H functionalization of (hetero)aryl nitrones under Rh(III) catalysis. Notably, depending on the electronic properties of the aryl nitrone, the formation of bridged benzoxazepines, naphthalenes, and carbazoles was exclusively observed.

Scheme 1. C−H Functionalization Using MBH Adducts



Our investigation was initiated by examining the coupling of aryl nitrone **1a** and methyl 2-(acetoxymethyl)-acrylate (**2a**) under rhodium catalysis (Table 1). To our delight, a cationic rhodium(III) catalyst, derived from $[RhCp^*Cl_2]_2$ and $AgSbF_6$, in 1,2-dichloroethane (DCE) at 60 °C for 7 h under air atmosphere was found to promote the C−H functionalization to afford bridged benzoxazepine **3aa** in 88% yield (entries 1 and 2). This observation might be rationalized by the C−H allylation and subsequent exotype [3 + 2] dipolar cycloaddition.[7] Replacing $AgSbF_6$ with $AgNTf_2$ decreased the formation of **3aa** (entry 3). Screening of acetate additives showed that $Cu(OAc)_2$ and LiOAc slightly increased the yield of **3aa** (entries 4 and 5). Interestingly, it was found that molecular oxygen gave an excellent yield (99%) of **3aa** (entry 8). Alternative solvents such as THF and toluene were found to be less effective for this transformation (entries 9 and 10). This process was also compatible with either MBH carbonate **2b** or a preformed $[RhCp^*(MeCN)_3SbF_6]$ catalyst (entries 11 and 12). Finally, this reaction could be conducted with 1 mol % of a Rh(III) catalyst with an extended reaction time (24 h) to furnish **3aa** in 89% yield (entry 13). It should be mentioned that other nitrones such as *N*-methyl-*α*-phenylnitrone and *N*-phenyl-*α*-phenylnitrone were unreactive under the standard reaction conditions.

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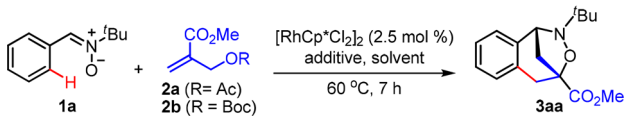
Table 1. Optimization for Reaction Conditions[a]

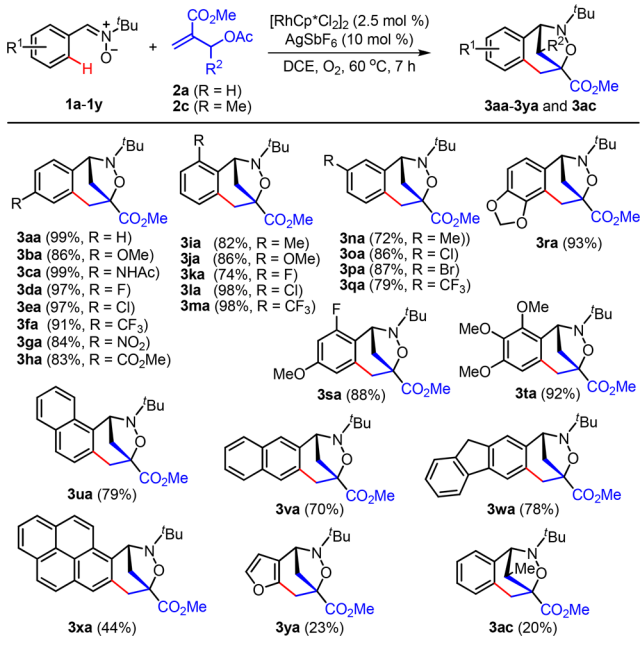


entry	MBH	additive (mol %)	solvent	yield (%)[b]
1[c]	**2a**		DCE	N.R.
2[c]	**2a**	$AgSbF_6$ (10)	DCE	88
3[c]	**2a**	$AgNTf_2$ (10)	DCE	75
4[c]	**2a**	$AgSbF_6$ (10), $Cu(OAc)_2$ (50)	DCE	92
5[c]	**2a**	$AgSbF_6$ (10), LiOAc (50)	DCE	90
6[c]	**2a**	$AgSbF_6$ (10), NaOAc (50)	DCE	55
7[c]	**2a**	$AgSbF_6$ (10), AgOAc (50)	DCE	72
8	**2a**	$AgSbF_6$ (10), O_2 (1 atm)	DCE	99
9	**2a**	$AgSbF_6$ (10), O_2 (1 atm)	THF	40
10	**2a**	$AgSbF_6$ (10), O_2 (1 atm)	toluene	45
11	**2b**	$AgSbF_6$ (10), O_2 (1 atm)	DCE	99
12[d]	**2a**	$AgSbF_6$ (10), O_2 (1 atm)	DCE	98
13[e]	**2a**	$AgSbF_6$ (10), O_2 (1 atm)	DCE	89

[a]Reaction conditions: **1a** (0.2 mmol), **2a** or **2b** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive, solvent (1 mL) at 60 °C for 7 h in pressure tubes. [b]Isolated yield. [c]Air atmosphere. [d]$[RhCp^*(MeCN)_3SbF_6]$ (5 mol %). [e]$[RhCp^*Cl_2]_2$ (1 mol %) and $AgSbF_6$ (4 mol %) for 24 h.

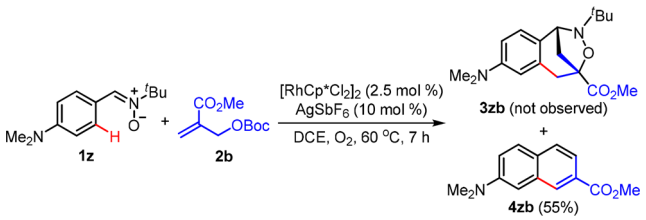
With the optimized reaction conditions in hand, we then examined the scope of aryl nitrones with MBH adducts (Scheme 2). A wide range of *para*-, *meta*-, and *ortho*-substituted aryl nitrones **1a**–**1q** were coupled with MBH acetate **2a** and delivered bridged benzoxazepine derivatives **3aa**–**3qa** in 72–99% yields. The tolerance of the reaction conditions for NHAc, CO_2Me, and NO_2 groups was of interest, as these moieties provide a versatile synthetic handle for further functionalization of the products. Interestingly, piperonyl nitrone **1r** exclusively underwent the C–H functionalization on the *ortho*-position of oxygen atom to give **3ra** in 93% yield, presumably due to the higher acidity of C–H bond and secondary directing effect.

Scheme 2. Scope of Aryl Nitrones



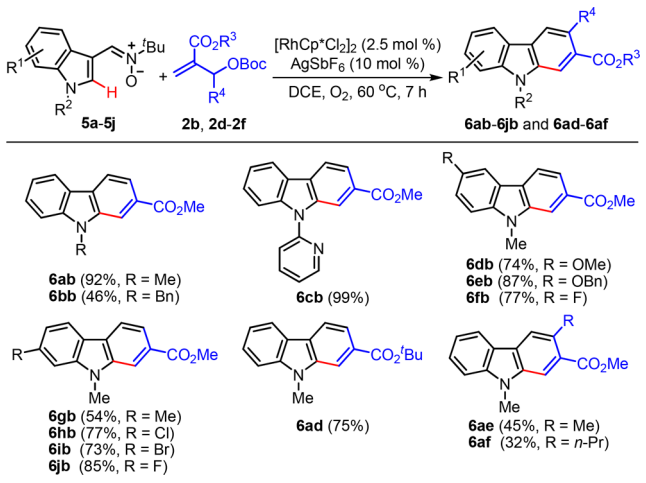
This reaction also tolerated di- and trisubstituted aryl nitrones **1s** and **1t** and afforded the desired products **3sa** and **3ta** in high yields. In addition, reaction of 1- and 2-naphthyl nitrones **1u** and **1v** with **2a** proceeded smoothly to afford bridged cycles **3ua** and **3va** in good yields. Polycyclic nitrones were also favored in this transformation, furnishing the corresponding products **3wa** (78%) and **3xa** (44%), respectively. Heterocyclic nitrone **1y** was also applied for the formation of bridged benzoxazepine **3ya**. Finally, α-substituted MBH adduct **2c** showed a significantly lower yield of **3ac**. In sharp contrast, an electron-rich functional group (NMe_2) on aryl nitrone **1z** led to the construction of naphthalene **4zb** (55%) without formation of bridged benzoxazepine adduct **3zb** (Scheme 3).

Scheme 3. Reaction of Electron-Rich Aryl Nitrone



Inspired by these results, we focused on the C–H functionalization of the electron-rich nitrones, e.g. indolinyl nitrones, with MBH adducts (Scheme 4). Gratifyingly, *N*-methyl indolinyl nitrone **5a** was coupled with MBH acetate **2a** to give carbazole **6ab** in 64% yield. After replacing MBH acetate **2a** with MBH carbonate **2b**, a significantly improved yield (92%) of **6ab** was observed. In addition, *N*-benzyl indolinyl nitrone **5b** displayed decreased reactivity under the reaction conditions. It should be noted that *N*-pyridinyl indole derivative **5c** was also compatible with the annulation process, providing **6cb** in 99% yield. C5- and C6-substituted indoles **5d**–**5j** containing electron-rich and electron-deficient functional groups smoothly participated in the coupling reaction to deliver corresponding products **6db**–**6jb** in high yields. MBH adduct **2d**, generated from *t*-butyl acrylate with paraformaldehyde, was reacted with **5a** to furnish desired product **6ad** in

Scheme 4. Scope of Indolinyl Nitrones



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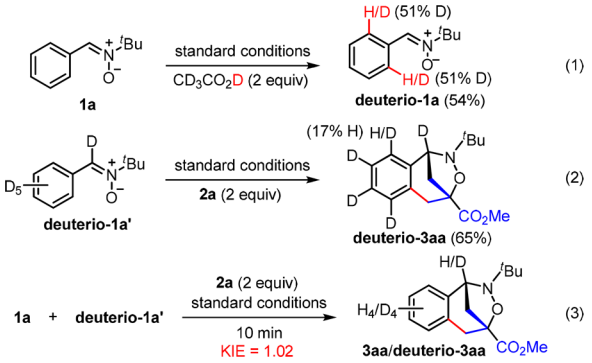
75% yield. Furthermore, α-substituted MBH adducts **2e** and **2f** tolerated in this transformation to afford C3- and C4-disubstituted carbazoles **6ae** (45%) and **6af** (32%), respectively.

To gain mechanistic insight into this process, a series of deuterium-labeling and kinetic isotope effect (KIE) experiments was performed (Scheme 5). First, treatment of **1a** with

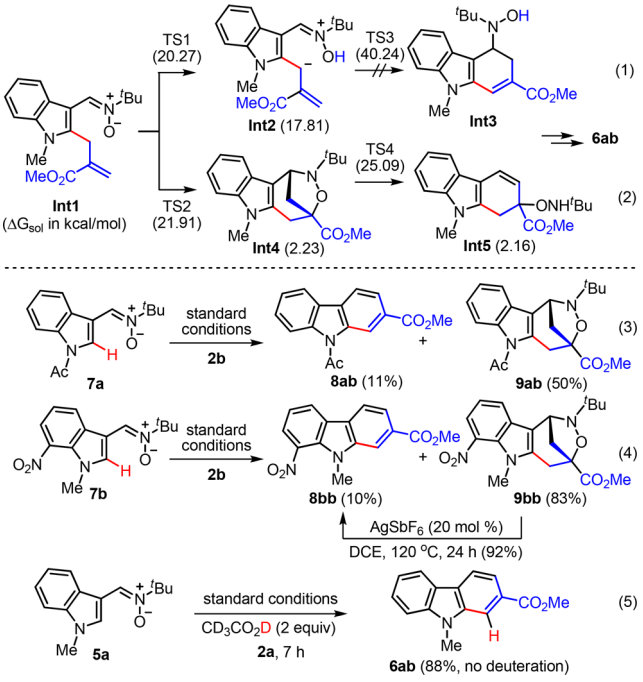
Scheme 5. Deuterium-Labeling and Kinetic Isotope Effect Experiments



CD_3CO_2D resulted in a remarkable H/D exchange (51% D incorporation) at the *ortho*-position of recovered **deuterio-1a**, indicating that the C−H cleavage step might be reversible (eq 1). In addition, the reaction of **deuterio-1a′** with **2a** gave **deuterio-3aa** in 65% yield, and no scrambling of benzylic deuterium was observed. Partial hydrogenation (17% H) at the *ortho*-position on the aryl ring suggests the reversibility of the C−H activation (eq 2). Next, the intermolecular competition reaction between **1a** and **deuterio-1a′** in the presence of **2a** resulted in a KIE value of 1.02, suggesting that the C−H cleavage might not be involved in the turnover-limiting step (eq 3).

We considered several plausible pathways. One involved allylated intermediate **Int1** undergoing deprotonation to form anionic species **Int2**, which would undergo intramolecular addition to the iminium moiety to give hydroxyamine **Int3** (Scheme 6, eq 1). The difficulty in this pathway lies in the high energy barrier of the annulation under the experimentally developed conditions (see the Supporting Information for details). As an alternative reaction pathway (eq 2), it is conceivable that the carbazole product could be formed from the [3 + 2] bicyclic adduct **Int4**, and the enamine-like reactivity of the indole could trigger further C−N bond cleavage of bridged bicyclic intermediate. To test our hypothesis, a series of control experiments was carried out. We found that *N*-acetyl indolinyl nitrone **7a** was coupled with MBH carbonate **2b** to furnish a separable mixture of carbazole **8ab** (11%) and bridged bicycle **9ab** (50%) (eq 3). A similar phenomenon was observed when using C7-nitro indolinyl nitrone **7b**, which afforded **8bb** (10%) and **9bb** (83%) (eq 4). Intriguingly, **9bb** can be converted into **8bb** upon treatment with $AgSbF_6$ as a Lewis acid in the absence of a Rh(III) catalyst. Furthermore, a kinetic reaction profile between **8bb** and **9bb** was determined by monitoring the conversion of **9bb** into **8bb** under the standard reaction conditions (Figure S1). Within 2 h, bicyclic product **9bb** was formed (approximately 95%), and carbazole **8bb** was subsequently generated with concomitant disappearance of **9bb**, which indicates the intermediacy of **9bb** in the overall process. Interestingly, no

Scheme 6. Possible Pathways and Electronic Effect for the Formation of Carbazoles



deuterium was incorporated into product **6ab** (eq 5), which is in good agreement with our initial calculations that anionic species **Int2** may not be involved in the carbazole formation process.

Preliminary mechanistic studies indicate that the [3 + 2] cycloaddition adducts are initially formed as common intermediates, and only electron-rich indolinyl or aniline substrates can undergo subsequent C−N bond cleavage of the bridged bicyclic intermediate. We sought to better understand the origin of this unusual reactivity through density functional theory (DFT) studies and the energy profiles comparing the different substrates (Scheme 7). We started with allylated intermediates **A1**, **B1**, and **C1** generated from Rh-catalyzed C−H activation and migratory insertion. The energy barriers for the [3 + 2] cycloaddition were less than 22 kcal/mol, indicating that bridged bicyclic intermediates can be readily formed in all cases. The main reaction energy pathway continues to the formation of AcOH complexes **A3**, **B3**, and **C3**, which were located at 3.6, 0.6, and −2.5 kcal/mol, respectively. To push the reaction forward and form aromatic rings, **A3**, **B3**, and **C3** should proceed through the C−N bond cleavage, followed by deprotonation by the acetate anion to give intermediates **A4**, **B4**, and **C4**. Whereas the transition state for this step, **C3-TS** is found at 34.4 kcal/mol, resulting in a barrier of 38.4 kcal/mol as highlighted in red, the analogous transition states **A3-TS** and **B3-TS** are located at 25.1 and 22.7 kcal/mol, giving rise to barriers of 22.9 and 26.1 kcal/mol, respectively (see the Supporting Information for details). Once intermediates **A3** and **B3** are formed, the reaction pathways become essentially irreversible, leading to the construction of carbazole and naphthalene after facile elimination of the nitroso group and aromatization. In the case of indolinyl and aniline substrates, the electron-rich enamine systems in **A3** and **B3** could trigger the C−N bond cleavage of the bridged bicyclic intermediate. In accordance with the experimental observations that the

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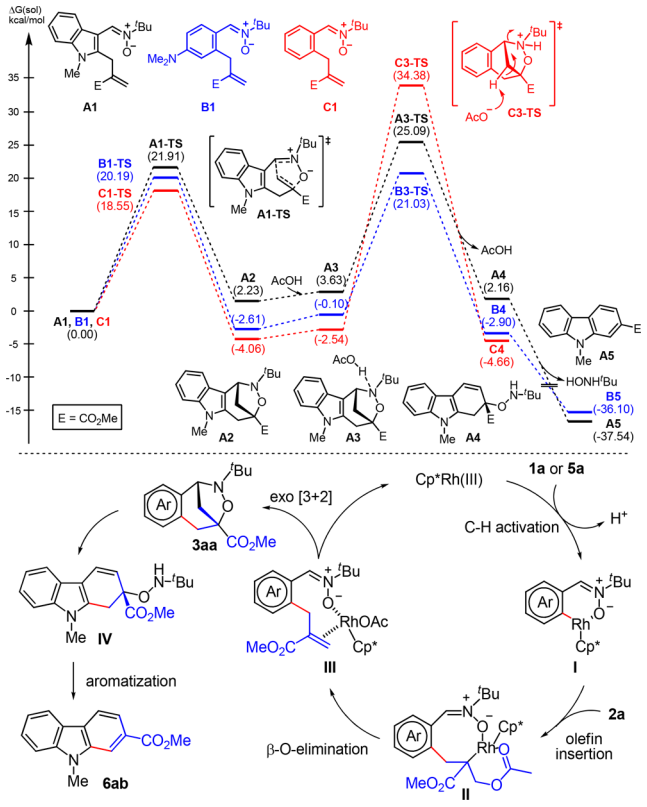
Scheme 7. Energy Profile Diagram and Plausible Reaction Mechanism

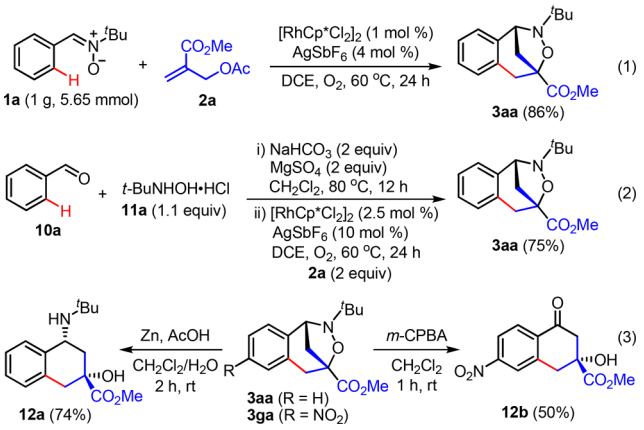


formation of **C5** was not detected, the difficulty in this transformation lies in the aforementioned high C−N bond cleavage barrier under the reaction conditions. With the above mechanistic investigation, the most plausible reaction pathway is outlined, as shown in Scheme 7. Coordination and migratory insertion of MBH adduct **2a** can afford a rhodacyclic intermediate **II**, which can further undergo β-O-elimination to generate allylated intermediate **III**.[8] The exotype [3 + 2] dipolar cycloaddition of **III** can give bridged benzoxazepine **3aa**. In the case of electron-rich indolinyl and aniline nitrones, the dipolar cycloaddition adducts undergo C−N bond cleavage under the reaction conditions to furnish intermediate **IV**. Finally, aromatization leads to the formation of carbazole **6ab**.

To highlight the practicality and versatility of the synthesis of bridged benzoxazepines, we performed the gram-scale and sequential reaction experiments (Scheme 8). To our delight, this transformation was successfully scaled up to 1 g of **1a** with lower loading of a Rh(III) catalyst (1 mol %) to deliver **3aa** in 86% yield (eq 1). In addition, we performed the sequential reaction by using benzaldehyde (**10a**) with hydroxylamine **11a** to afford the corresponding product **3aa** in 75% yield (eq 2). Next, we carried out the reductive cleavage of the N−O bond of **3aa** using Zn powder and AcOH in CH_2Cl_2/H_2O to afford α-hydroxy-γ-amino ester **12a** in 74% yield (eq 3). Treatment of **3ga** with *m*-CPBA led to the formation of tetralone scaffold **12b** in 50% yield.

In conclusion, we disclosed the unique reactivity of MBH adducts in the C−H functionalization of (hetero)aryl nitrones under rhodium(III) catalysis. This protocol provides a facile route for the formation of bridged benzoxazepines and carbazoles in high yields. Mechanistic studies support that [3 + 2] cycloaddition adducts are initially formed as common

Scheme 8. Scale-Up and Sequential Reactions



intermediates, and then electron-rich indolinyl or aniline substrates can undergo C−N bond cleavage of the bridged bicyclic intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01910.

Detailed optimization results; experimental procedures; characterization data; kinetic profile experiment; DFT calculation details; X-ray crystallographic data of **3ga**, **3ac**, and **6ab**; and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

Accession Codes

CCDC 1832365, 1835635, and 1835985 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, 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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