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Diverting β-Hydride Elimination of a π-Allyl Pd^{II} Carbene Complex for the Assembly of Disubstituted Indolines via a Highly Diastereoselective (4 + 1)-Cycloaddition

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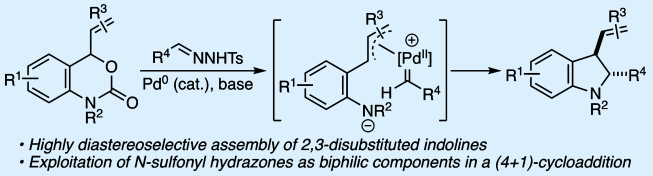
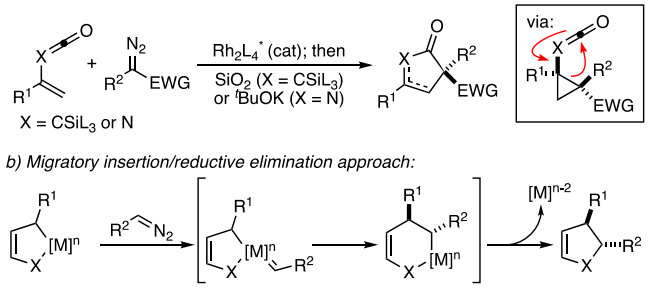
ABSTRACT: A Pd^0-catalyzed formal (4 + 1)-cycloaddition approach to 2,3-disubstituted dihydroindoles is described. The diastereoselective formation of dihydroindoles that is highlighted by a carbene migratory insertion/reductive elimination sequence proceeding via a π-allyl Pd^{II}-species compliments existing methods of indoline assembly.



Although less developed than the (3 + 2) analog,[1] (4 + 1)-cycloadditions offer a powerful, complementary retrosynthetic disconnect for the generation of highly substituted five-membered carbo- and heterocyclic systems.[2] A major challenge in the design and implementation of (4 + 1)-cycloadditions is the identification of compatible C_4- and C_1-atom synthons that provide the desired cycloadduct in a stereoselective fashion with a high degree of functional group compatibility.[3] Recently, we reported on the development of (4 + 1)-cycloaddition strategies that employ diazo compounds as C_1-synthons in the presence of a Rh^{II}−carboxylate catalyst (Scheme 1a).[4] The net cycloaddition occurs via the initial

Scheme 1. Mechanistic Divergence in (4 + 1)-Cycloadditions



cyclopropanation of either a vinyl ketene or vinyl isocyanate followed by a 1,3-carbon migration to provide the corresponding cyclopentenone or lactam, respectively.[4b−d] Enantioselective formation of the cyclopentenone α-quaternary carbon was achieved employing a Davies chiral Rh^{II} −carboxylate complex. Seeking to exploit this synthetic disconnect beyond vinyl ketenes/isocyanates, we speculated that greater architectural diversity could be achieved by altering the mechanistic profile from a ring expansion event (i.e., vinyl cyclopropane rearrangement) to a migratory insertion/reductive elimination sequence reticent of Pd-catalyzed enyne and diene cycloisomerizations (Scheme 1b).[5] Herein, we disclose the successful execution of a Pd-catalyzed (4 + 1)-cycloaddition via the migratory insertion of a Pd^{II}−carbene complex with high levels of diastereoselectivity.

Seminal work by the Wang and Van Vranken groups have revealed the utility of palladium carbenes in a variety of different cross-couplings employing aryl/alkyl halides,[6a−e] boronic acids,[7a−c] and nitrogen/carbon nucleophiles[8a−d] wherein migratory insertion serves as the critical C−C bond forming event. While initial reports focused on migratory couplings of metallocarbenes to η^1-ligands, as demonstrated by Van Vranken's approach to allyl amines (Scheme 2a), inner sphere migrations involving η^3-allyl metal complexes have likewise proven effective. For example, Wang demonstrated that the Pd-catalyzed oxidative addition to allyl acetates and allyl halides in the presence of a diazo ester led to a migratory insertion/β-hydride elimination sequence resulting in 1,3-diene formation (Scheme 2b). We sought to divert β-hydride elimination through the incorporation of an internal nucleophile resulting in a net cycloaddition. To achieve this aim, we speculated that treatment of vinyl benzoxazinone **1** and the diazo compound generated *in situ* from *N*-sulfonyl hydrazone **2** and base in the presence of a Pd^0 catalyst would provide dihydroindole **3** via sequential, intramolecular C−C and C−N bond formations from π-allyl Pd complex **4** (Scheme 2c).[9] An important consideration in our proposed (4 + 1)-cycloaddition was the coordination capability of the pendant

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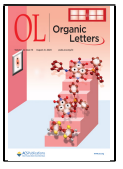

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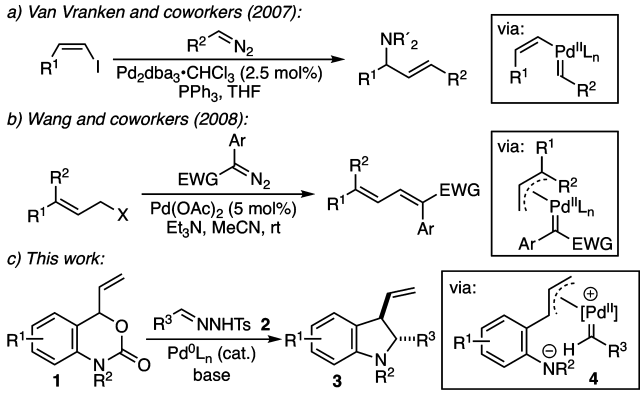
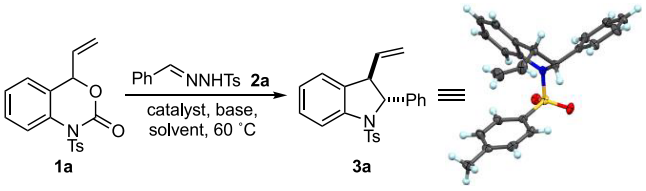
Scheme 2. Selected Pd−Carbene Migratory Insertions



sulfonamide upon oxidative addition to the vinyl benzoxazinone, and whether this secondary ligation would inhibit diazo decomposition. Additionally, the presence of a phosphine ligand to facilitate π-allyl Pd^{II} formation could diminish the capability of accommodating a metallocarbene, thereby leading to catalyst inhibition.

In an effort to assuage these initial concerns, we began our study by examining the Pd-catalyzed (4 + 1)-cycloaddition of vinyl benzoxazinone **1a** with hydrazone **2a** (Table 1). Our

Table 1. Optimization of Reaction Conditions[a]



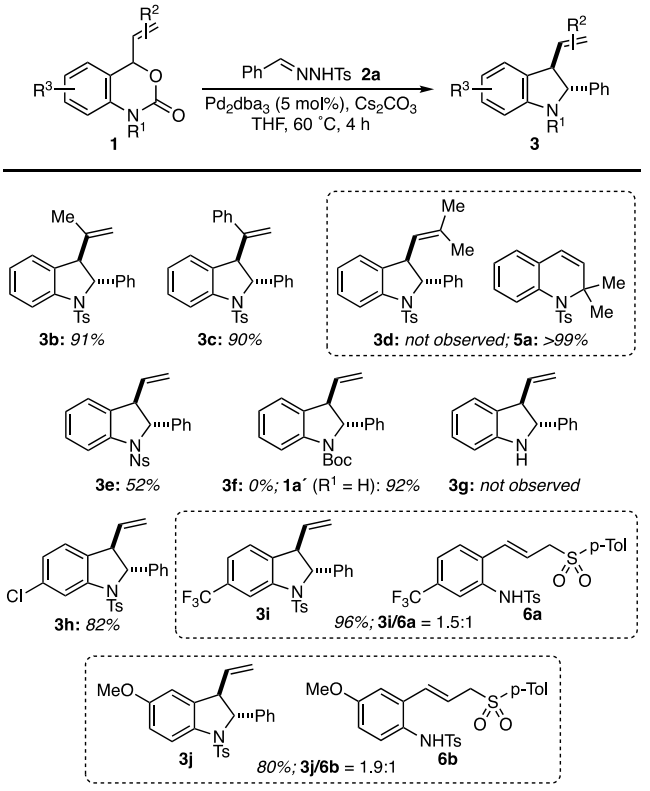
Entry	Catalyst	Ligand	Base	Solvent	Yield (%)
1	Pd_2dba_3·$CHCl_3$	–	^{t}BuOK	THF	69
2	Pd_2dba_3·$CHCl_3$	–	^{t}BuOK	DMF	5
3	Pd_2dba_3·$CHCl_3$	–	^{t}BuOK	PhMe	32
4	Pd_2dba_3	–	^{t}BuOK	THF	74
5	*Pd_2dba_3*	–	*Cs_2CO_3*	*THF*	*87(77)*[b]
6	$Pd(PPh_3)_4$	–	^{t}BuOK	THF	<5
7	$[Pd(allyl)Cl]_2$	P(furyl)$_3$	^{t}BuOK	THF	29
8	$Pd(OAc)_2$	P(furyl)$_3$	^{t}BuOK	THF	19
9	$Pd(OAc)_2$	dppe	^{t}BuOK	THF	40

[a]Conditions: **3a** (0.05 mmol), **4a** (0.06 mmol), base (0.06 mmol), Pd catalyst (5 mol %), solvent (0.5 mL). [b]Performed on 3 mmol scale.

initial attempts at facilitating the (4 + 1)-cycloaddition of benzoxazinone **1a** with *N*-tosylhydrazone **2a** focused on assessing the feasibility of conducting the reaction under essentially ligandless conditions by employing Pd_2dba_3·$CHCl_3$ (5 mol %) and ^{t}BuOK in THF. While conducting the reaction at room temperature resulted only in recovered benzoxazinone **1a**, conducting the reaction at 60 °C provided the 2,3-*anti* dihydroindole **3a** in 69% yield after 4 h as a single diastereomer (entry 1). The relative stereochemistry was assigned by X-ray crystallography. Variation of the solvent provided the formal cycloadduct in diminished yields (entries 2 and 3). While employing Pd_2dba_3 with ^{t}BuOK increased the yield of **3a** to 74%, using Cs_2CO_3 to generate the desired diazo compound improved the yield to 87% (entries 4 and 5). These conditions also proved tolerable on a 3 mmol scale, providing the desired dihydroindole in 77% yield and >20:1 dr. Employing $Pd(PPh_3)_4$ led to only trace amounts of **3a**, while the addition of P(furyl)$_3$, a common phosphine employed in Pd-carbene cross-couplings, to $[Pd(allyl)Cl]_2$ or $Pd(OAc)_2$ provided **3a** in 29% and 19% yield, respectively (entries 6−8).[6b,10,11a−c] The bidentate phosphine dppe also failed to improved the yield of **3a** (entries 9; dppp: **3a** = 28%).

With optimized conditions in hand, we turned our attention toward evaluating the architectural limitations of vinyl benzoxazinone **1** in a Pd-catalyzed (4 + 1)-cycloaddition with *N*-tosyl phenylhydrazone **2a** (Scheme 3). Olefin R^2-alkyl

Scheme 3. Structural Variations on Vinyl Benzoxazinone 3



and -aryl substitution at C2 provided dihydroindoles **3b** and **3c** in 91% and 90% yield, respectively. However, olefin 1,1-dimethyl substitution failed to yield the anticipated dihydroindole **3d**, but favored C−N reductive elimination to give dihydroquinoline **5a** in quantitative yield. However, substitution of the benzylic position and 1,2-substitution of the alkene were not tolerated under the optimized reaction conditions. Interestingly, the (4 + 1)-cycloaddition proved sensitive to the *N*-substituent on **1**. For example, the *N*-nosyl benzoxazinone gave **3e** in 52% yield, while the corresponding *N*-Boc benzoxazinone led to selective deacylation of the carbonate to give **1a′** (R^1 = H) in 92% yield. Resubjection of **1a′** to the optimized reaction conditions failed to undergo cycloaddition to **3g**; rather an intractable mixture of byproducts was observed. In contrast, substitution of the arene was well tolerated, but product distribution proved dependent on the electronic impact of the substituent. For example, 5-chloro vinyl benzoxazinone yielded dihydroindole **3h** in 82%, but a CF_3-group at the 5-position led to a 1.5:1 mixture of the (4 + 1)-cycloadduct **3i** and *S*- allylation product **6a** in 96% combined yield. Similarly, 4-methoxy substitution

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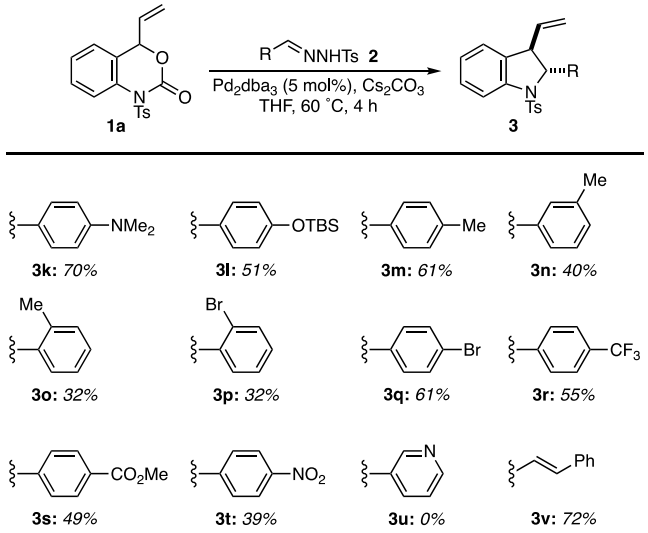
gave cycloadduct **3j** and S-allyl sulfone **6b** in a ratio of 1.9:1 and 80% yield.

In general, varying the structural and electronic properties of *N*-tosyl hydrazone **2** in the (4 + 1)-cycloaddition of vinyl benzoxazinone **1a** resulted in moderate to good yields of the corresponding cycloadducts **3** (Scheme 4). Alkyl hydrazones

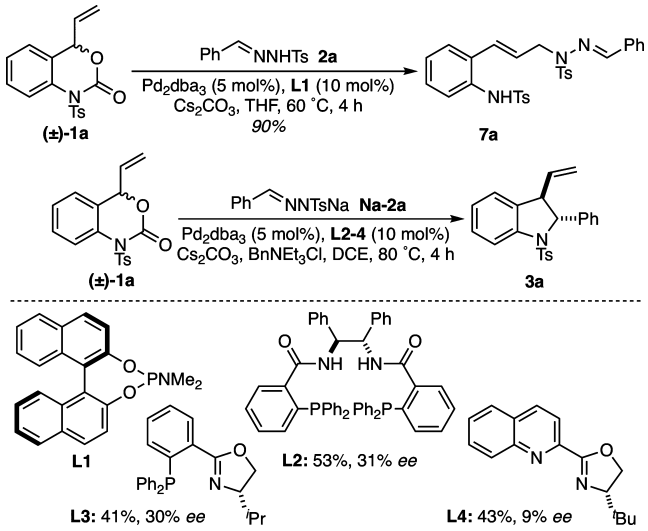
Scheme 4. Structural Variations on the *N*-Tosylhydrazone 2



were not tolerated under the reaction conditions; however, aryl hydrazones bearing the resonance electron donating groups 4-*N*,*N*-dimethylamino and 4-silyloxy gave cycloadducts **3k** and **3l** in 70% and 51% yields, respectively. Alkyl substitution of the aryl hydrazone at the *para*, *meta*, and *ortho* positions led to cycloadducts **3m**−**o** in 32−61% yields, where the more sterically demanding 2-methyl aryl hydrazone was the least efficient substrate of this series, giving the corresponding dihydroindole **3o** in 32% yield. Similarly, the 2-bromo aryl hydrazone led to cycloadduct **3p** in 32%, while the 4-bromo analog yielded adduct **3q** in 61% yield. Notably, no side products resulting from oxidative addition to the Ar−Br bond were detected. Additionally, the 4-CF_3, 4-CO_2Me, and 4-NO_2 substituted aryl hydrazones underwent cycloaddition in 39−55% yield providing **3r**−**t**. In contrast, the 3-pyridyl hydrazone was not tolerated under the reaction conditions, resulting in complete recovery of **1a**. Whether this lack of reactivity is a result of catalyst inhibition by the pyridine ring or inefficient diazo decomposition is unclear at this time. The cinnamyl derived hydrazone also underwent (4 + 1)-cycloaddition with **1a** to provide the anticipated dihydroindole **3v** in 72% yield.

Using the conversion of racemic benzoxazinone **1a** to indoline **3a**, we sought to evaluate the potential of the Pd-catalyzed (4 + 1)-cycloaddition to provide the formal cycloadducts in optically enriched form via a dynamic kinetic asymmetric transformation (DyKAT). Employing a series of mono- and bidentate chiral ligands **L1**−**L4** known for inducing asymmetry in Pd-catalyzed processes, we surveyed chiral ligands, well-known for their capability to induce asymmetry in Pd-catalyzed transformations. However, the addition of (*R*)-MonoPhos (**L1**) under our optimized reaction conditions resulted in exclusive *N*-allylation of hydrazone **2a** (Scheme 5). In an effort to suppress *N*-allyl hydrazone formation, we modified those conditions shown by Liang and co-workers to minimize hydrazone addition to propagyl-Pd^{II} intermediates.[13]

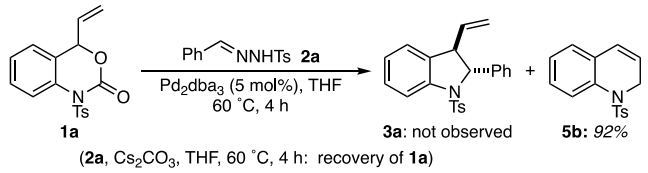
Scheme 5. Synthesis of Optically Enriched Indolines



Thus, exposure of benzoxazinone **1a** and the sodium sulfonate **Na-2a** to Pd_2dba_3 (5 mol %), stilbene diamine ligand **L2** (10 mol %), Cs_2CO_3, and $BnNEt_3Cl$ provided dihydroindole **3a** in 53% yield and 31% *ee*. Employing ligands **L3** and quinox derivative **L4** failed to improve the yield or optical enrichment of **3a**.[14] These results demonstrate the feasibility of inducing asymmetry in 2,3-disubstituted indoline assembly wherein the enantio-determining step is presumably a stereoselective migratory insertion of a Pd^{II}-carbene into a pendant π-allyl ligand. Whether the optical enrichment of dihydroindole **3a** occurs via a DyKAT mechanism or kinetic resolution of the starting racemic benzoxazinone is unclear at the present time.

In an effort to elucidate the role of the catalyst and base in the key C−C and C−N bond forming events, we evaluated the conversion of benzoxazinone **1a** to indoline **3a** while omitting either Pd^0 or base (Scheme 6). Treatment of **1a** and hydrazone

Scheme 6. Elucidating the Role of Pd^0 and Base



2a in the absence of Cs_2CO_3 led to quantitative formation of dihydroquinoline **5b**, presumably arising via reductive elimination of the initial π-allyl Pd^{II} complex formed upon oxidative addition of Pd^0 to **1a**. Not surprisingly, the absence of Pd_2dba_3 resulted in complete recovery of benzoxazinone **1a**. These results would seem to confirm that generation of both an intermediate π-allyl Pd^{II} complex and aryl diazomethane, via a base-induced desulfonylation of hydrazone **1**, are crucial to dihydroindole **3** formation.

Based on our composite findings, in conjunction with work by Wang, Van Vranken, and others, a plausible mechanism for the diastereoselective, (4 + 1)-cycloaddition assembly of 2,3-disubstituted indolines is illustrated in Scheme 7.[6a,7c,15] Oxidative decarboxylation of benzoxazinone **1a** by Pd^0 results in formation of π-allyl Pd^{II} complex **8**,[9a,b] which upon decomposition of phenyl diazomethane **9** arising from desulfonylation of hydrazone **2a** leads to Pd-allyl carbene

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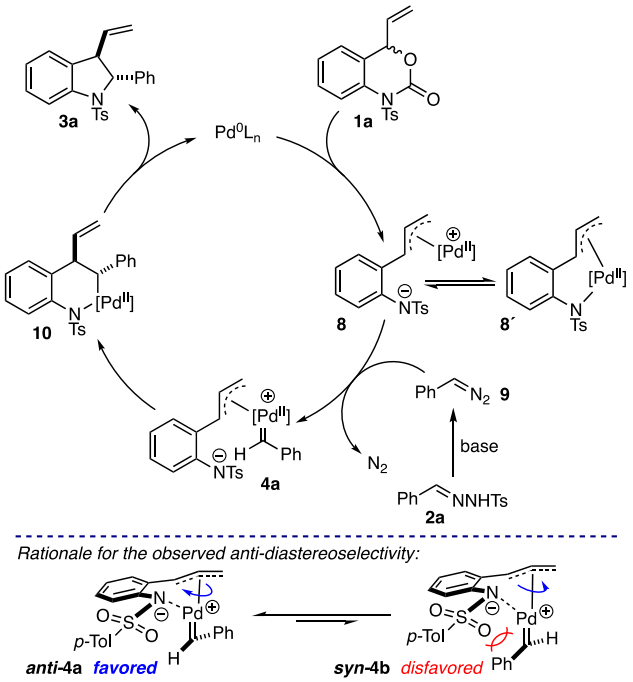
Scheme 7. Proposed Mechanism



4a.[12a,16] A diastereoselective migratory insertion event yields six-membered palladacycle **10**, which upon reductive elimination affords **3a**. While the oxidative addition of Pd^0 to vinyl benzoxinones is relatively well-established,[9] the formation of a π-allyl Pd^{II}–carbene complex and subsequent sequential C–C and C–N bond formations are significantly less precedented. However, the trend we observed wherein aryl hydrazones bearing electron-donating substituents provided the corresponding (4 + 1)-cycloadducts in better yields than their electron-neutral or electron-deficient counterparts is consistent with a mechanism involving Pd^{II}–carbene formation.[12a,b] In contrast, a mechanism involving direct outer-sphere attack on the π-allyl ligand, complementary to the work of Li and Tan, and that of others, involving sulfur ylides, cannot be ruled out.[9b]

While speculative, a rationale for the selective formation of the *anti*-dihydroindole products may result from the alleviation of an unfavorable steric interaction between the aryl substituent on the palladium-stabilized carbene and the *N*-sulfonyl group in intermediate **4a**. Assuming the stereodetermining step is migratory insertion of the carbene center to the π-allyl ligand in **4a**, isomer *anti*-**4a** leads to the observed stereoisomer **10**, whereas *syn*-**4a** would provide the corresponding *syn* stereoisomeric intermediate. The favored *anti*-**4a** positions the hydrogen of the carbene and the *N*-sulfonyl group *syn* thereby minimizing the unfavorable steric interactions present in *syn*-**4b**. The dynamic equilibrium between *anti*-**4a** and *syn*-**4b** may account for the exceptional diastereoselectivity observed in the formation of the *anti*-dihydroindole **3a**.

In conclusion, we were able to demonstrate how the inherent biphilic reactivity of diazo compounds are harnessed in (4 + 1)-cycloadditions by exploiting benzoxazinones as masked 1,4-dipoles in the presence of a Pd^0 catalyst. The resulting 2,3-disubstituted dihydroindoles are obtained in moderate to high yields and exceptional levels of diastereoselectivity (dr >20:1). A series of control experiments indicate the viability of a π-allyl Pd^{II} carbene intermediate followed by sequential C–C and C–N bond formation to construct the indoline core framework. Likewise, the addition of chiral phosphorus-based ligands demonstrates the potential of inducing an enantiodiscriminating migratory insertion/reductive elimination cascade en route to optically enriched cycloadducts. Current studies are focused on the development of an effective enantioselective (4 + 1)-cycloaddition approach toward the construction of highly substituted indolines and elucidating the mechanistic details of the Pd-catalyzed cycloaddition presented herein.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02374.

Experimental procedures, spectroscopic data, and crystallographic data (PDF)

Accession Codes

CCDC 1991894 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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