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Lewis-Acid-Catalyzed Asymmetric Alkynylation of Alkynyl 1,2-Diketones: Controllable Formation of 3(2*H*)-Furanones and *α*-Hydroxy Ketones

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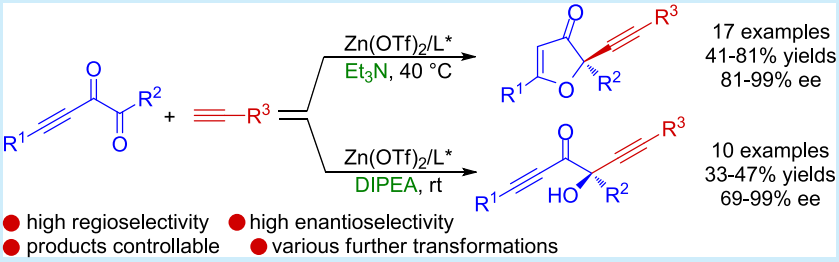

ABSTRACT: We report the highly regio- and enantioselective alkynylation of alkynyl 1,2-diketones under Lewis acid catalysis, leading to the formation of a series of biologically important 3(2*H*)-furanones with high to excellent ee values. Moreover, a slight change of the reaction conditions produces a range of highly functionalized *α*-hydroxy ketones with a high level of enantioselectivity. A variety of further transformations can be easily achieved, demonstrating the synthetic potential of this protocol.

Developing synthetic protocols that can provide enantioenriched substances with structural diversity through the minor modification of reaction conditions is challenging but highly valuable, since it can significantly improve the efficiency and economy of the whole process by avoiding the frequent alteration of reaction reagents and reducing the steps of preparing different starting materials.[1] For instance, the asymmetric alkynylation of ketones has been well established as a reliable method to afford propargylic tertiary alcohols, and various catalytic systems have been developed to achieve this goal (Scheme 1a).[2] On the other side, 3(2*H*)-furanones widely exist as substructures in a large amount of natural products and biologically active molecules such as hyperolactone A/B/C and jatrophone,[3] but only few catalytic asymmetric methods have been reported using reactions of nucleophilic (2*H*)-furanones and different electrophiles (Scheme 1b).[4] Nevertheless, they represent two thoroughly different reaction types, and no single protocol has been developed to afford both tertiary alcohols and 3(2*H*)-furanones to the best our knowledge, thus making such a protocol very challenging but highly valuable and desirable.

We have been interested in disclosing the unique reactivities of conjugated 1,2-diketones.[5] During our recent study in the asymmetric alkynylation of alkynyl diketones, we found that, under Lewis acid catalysis, a series of 3(2*H*)-furanones with quaternary stereocenters were obtained in high regio- and enantioselectivity. Moreover, through simply changing the base, the reaction can afford a range of enantioenriched *α*-hydroxy ketones, which are also highly useful building blocks

Scheme 1. Research Background

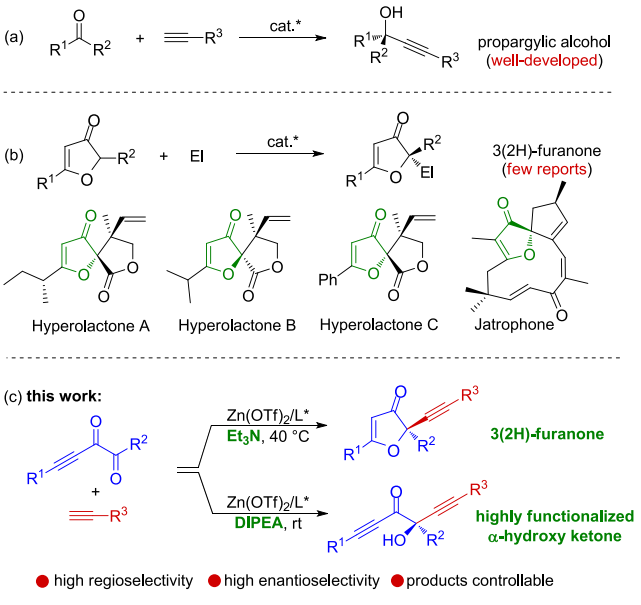

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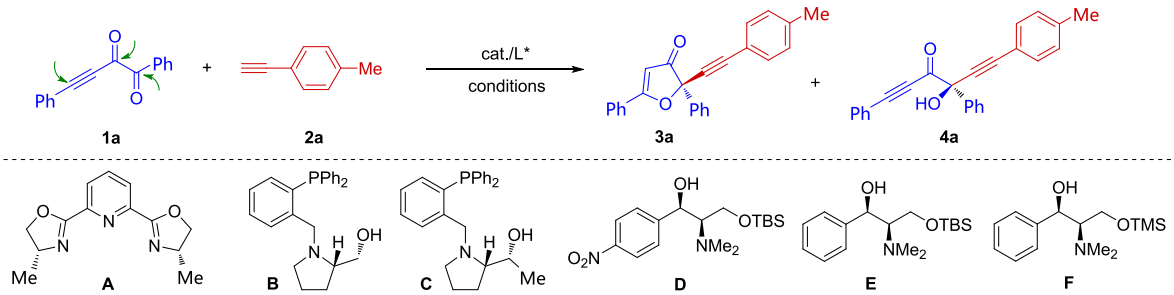
Table 1. Reaction Condition Optimization



							yield (%)		ee (%)	
entry	cat. (mol %)	ligand (mol %)	base (equiv)	solvent	temp	time	**3a**	**4a**	**3a**	**4a**
1[a]	CuCl (10)	**A** (11)	Et_3N (1.0)	toluene	rt	12 h	0	0		
2[a]	CuCl (10)	**B** (11)	K_2CO_3 (0.3)	toluene	rt	12 h	0	0		
3[a]	CuCl (10)	**B** (11)	K_2CO_3 (0.3)	*i*PrOH	rt	12 h	30	24	73	70
4[a]	CuCl (10)	**B** (11)	K_2CO_3 (0.3)	*t*BuOH	rt	12 h	12	40	61	75
5[a]	CuCl (10)	**C** (11)	K_2CO_3 (0.3)	*i*PrOH	rt	12 h	35	trace	80	
6[a]	CuCl (10)	**C** (11)	K_2CO_3 (0.3)	*i*PrOH	0 °C	12 h	39	trace	81	
7[a]	$Zn(OTf)_2$ (20)	**D** (22)	Et_3N (0.3)	toluene	rt	12 h	0	0		
8[b]	$Zn(OTf)_2$ (20)	**D** (22)	Et_3N (0.3)		rt	12 h	0	0		
9[b]	$Zn(OTf)_2$ (20)	**D** (22)	Et_3N (0.5)		rt	24 h	40	<15	86	
10[b]	$Zn(OTf)_2$ (20)	**D** (22)	Et_3N (1.0)		rt	24 h	50	trace	87	
11[b]	$Zn(OTf)_2$ (20)	**D** (22)	Et_3N (1.0)		40 °C	24 h	70	0	93	
12[b]	$Zn(OTf)_2$ (20)	**D** (22)	Et_3N (1.0)		40 °C	18 h	70	0	93	
13[b]	$Zn(OTf)_2$ (20)	**D** (22)	Et_3N (1.2)		40 °C	18 h	70	0	93	
14[b]	$Zn(OTf)_2$ (20)	**D** (22)	DBU (1.0)		40 °C	18 h	0	0		
15[b]	$Zn(OTf)_2$ (20)	**D** (22)	DIPEA (1.0)		40 °C	18 h	0	32		93
16[b]	$Zn(OTf)_2$ (20)	**E** (22)	DIPEA (1.0)		40 °C	18 h	0	25		
17[b]	$Zn(OTf)_2$ (20)	**F** (22)	DIPEA (1.0)		40 °C	18 h	0	18		
18[b]	$Zn(OTf)_2$ (20)	**D** (22)	DIPEA (1.0)		50 °C	18 h	0	32		92
19[b]	$Zn(OTf)_2$ (20)	**D** (22)	DIPEA (1.0)		rt	18 h	0	37		90
20[b]	$Zn(OTf)_2$ (20)	**D** (22)	DIPEA (1.0)		rt	24 h	0	44		93
21[b]	$Zn(OTf)_2$ (20)	**D** (22)	DIPEA (1.0)		rt	36 h	0	44		92
22[b,c]	$Zn(OTf)_2$ (20)	**D** (22)	DIPEA (1.0)		rt	24 h	0	44		93

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), cat. (10 mol %), solvent (1.0 mL), under argon protection. All isolated yields were based on **1a**; ee values were determined via HPLC analysis on a chiral stationary phase. [b]**2a**:**1a** = 5:1. [c]100 mg of $MgSO_4$ was added.

in organic synthesis and the pharmaceutical industry.[6] Therefore, two structurally thoroughly different units can now be accessed via a single protocol, and the previously unmet challenge can be successfully addressed. Herein, we report the results.

As shown in Table 1, easily available alkynyl 1,2-diketone **1a**[7] was selected as the model substrate for the condition optimization. It is worthwhile to mention that **1a** has three reactive sites for the nucleophilic attack, and the control of the regioselectivity is supposed to be difficult. Our initial tests using CuCl and ligands **A**[8] and **B**[8] in toluene were not successful because no conversion was observed (Table 1, entries 1 and 2). However, a mixture of **3a** and **4a** was formed in moderate total yields with moderate ee values when the solvent was changed to *i*PrOH or *t*BuOH (Table 1, entries 3 and 4). The use of ligand **C** can afford **3a** as the major product with good enantioselectivity, but in low yields (Table 1, entries 5 and 6). Then, we resorted to the combination of $Zn(OTf)_2$ and ligand **D**, which was first used by Jiang and co-workers.[9] Unfortunately, 0.3 equiv of Et_3N did not make the reaction occur (Table 1, entries 7 and 8), but we were pleased to find that increased amount of Et_3N and higher temperature were beneficial for the formation of the furanone product (Table 1, entries 9−11); under the optimal conditions, **3a** was produced as the single product in 70% yield with excellent 93% ee (Table 1, entry 12). No change of the outcome was observed when 1.2 equiv of Et_3N was used (Table 1, entry 13), and DBU was found detrimental to the reaction (Table 1, entry 14). To our pleasure, when DIPEA was used as the base, the formation of annulation product **3a** was suppressed, and α-hydroxy ketone **4a** was generated as the major product with excellent 93% ee, albeit in low yield (Table 1, entry 15). Ligands **E** and **F** resulted in lower yields of **4a** (Table 1, entries 16 and 17). Then, using ligand **D**, we screened a series of other conditions (Table 1, entries 18−22), and the best results showed that **4a** can be obtained in 41% yield with 93% ee (Table 1, entry 20); further efforts to improve the yield all failed. Although the yield can currently be obtained in a moderate level, the highly regioselective asymmetric alkynylation of unsymmetrical α-diketones that leads to highly functionalized α-hydroxy ketones has been less studied.[2] It is also worthwhile to mention that, in call cases, no products derived from the attack on another carbonyl group and the alkyne unit were detected, indicating the high regioselectivity of the protocol.

Having obtained the optimal conditions, we then commenced to test the generality and limitation of this reaction. First, we tested a series of alkynes with different aryl substituents. As demonstrated in Scheme 2, we found that the

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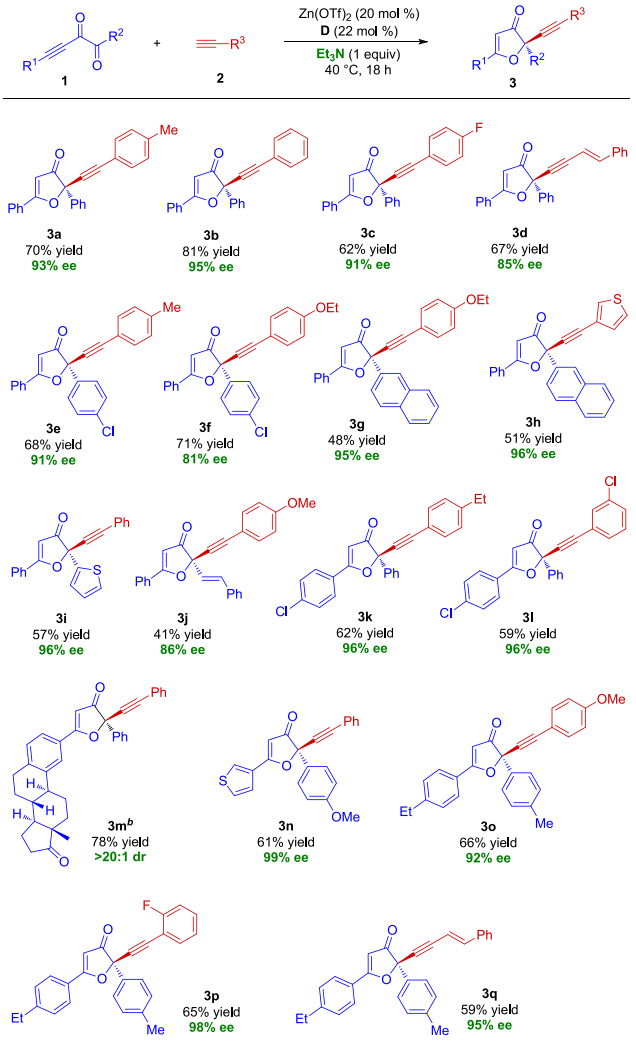
Scheme 2. Scope of 3(2*H*)-Furanone Synthesis[a]



[a]All reactions were run on a 0.5 mmol scale for 18 h; all yields were determined by isolating desired products by column chromatography. ee values were determined via HPLC analysis on a chiral stationary phase. [b]The reaction was run on a 0.5 mmol scale for 36 h.

introduction of both electron-donating and electron-withdrawing groups into the phenyl rings had limited effect on the outcomes, delivering **3a**–**3c** with 91–95% ee (Scheme 2, **3a**–**3c**). The use of 1,3-enyne was also successful, giving **3d** with 85% ee (Scheme 2, **3d**). Then, we found that diketones with a series of different R^2 substituents such as 4-ClC_6H_4, 2-naphthyl, and 2-thienyl could also react smoothly with alkynes, allowing access to **3e**–**3i** with a high level of enantioselectivities (Scheme 2, **3e**–**3i**). Furthermore, when R^2 is a styryl group, the corresponding product **3j** was also formed with good ee, albeit in low yield (Scheme 2, **3j**). The evaluation of different R^1 groups also proved possible, delivering **3k** and **3l** both with 96% ee (Scheme 2, **3k** and **3l**). Diketone derived from steroid worked well, resulting in the formation of **3m** with >20:1 dr (Scheme 2, **3m**). Finally, the simultaneous variation of both R^1 and R^2 groups in diketone substrates proceeded smoothly to give **3n**–**3q** with up to 99% ee (Scheme 2, **3n**–**3q**). Unfortunately, low yields were observed when R^1 or R^2 is an aliphatic group, and no conversion was detected when R^3 is an alkyl substituent. A new catalytic system remains to be developed to solve the issue.

The absolute configuration of the annulation products was determined via the single crystal X-ray structure analysis of **3h**, and other products were assigned by analogy (Figure 1).

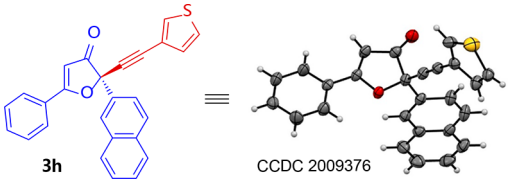
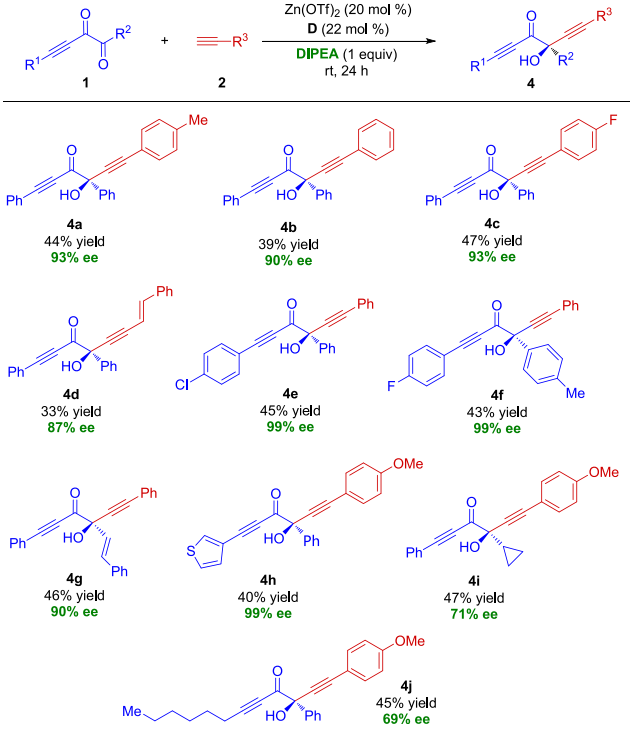


Figure 1. Single crystal X-ray structure of **3h**.

Having obtained a variety of 3(2*H*)-furanones with high enantioselectivities, we then focused on the generation of highly functionalized *α*-hydroxy ketones. Alkynes with differently substituted aryl groups were tolerated under the optimal conditions, affording **4a**–**4c** all with excellent ee values (Scheme 3, **4a**–**4c**). 1,3-Enyne worked well to produce **4d**

Scheme 3. Scope of *α*-Hydroxy Ketone Synthesis[a]



[a]All reactions were run on a 0.5 mmol scale for 24 h; all yields were determined by isolating desired products by column chromatography. ee values were determined via HPLC analysis on a chiral stationary phase.

with 87% ee (Scheme 3, **4d**), and a range of diketones with different combinations of R^1 and R^2 were all viable for the reaction, delivering **4e**–**4h** with up to 99% ee (Scheme 3, **4e**–**4h**). To our pleasure, diketones with aliphatic substituents reacted smoothly, leading to the formation of **4i** and **4j** with moderate ee (Scheme 3, **4i** and **4j**).

To our pleasure, the reaction can be scaled up, and the diverse functional groups within the products enable facile and valuable further transformations. For instance, the reaction using 1.17 g of **1a** led to the formation of **3b** in 60% yield with 96% ee, and the selective chlorination and bromination of **3b**

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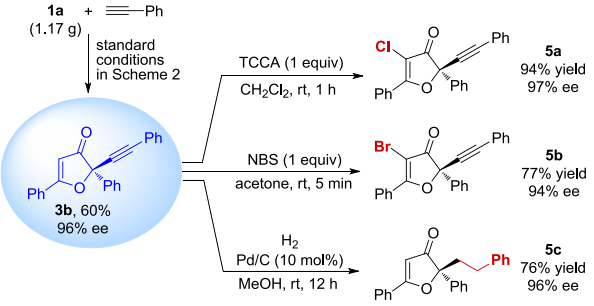
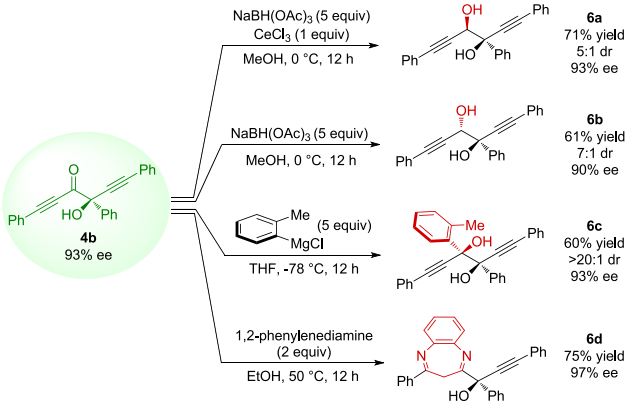
afforded **5a** and **5b** in 94% and 77% yields, respectively, both with excellent ee (Scheme 4, **5a** and **5b**). The selective

Scheme 4. Derivatizations of Product 3b



hydrogenation of **3b** provided **5c** in good yield without erosion of the ee (Scheme 4, **5c**). Furthermore, the diastereoselective reduction of **4b** led to *cis*-diol **6a** and *trans*-diol **6b**, respectively (Scheme 5, **6a** and **6b**).[10] The selective nucleophilic attack of

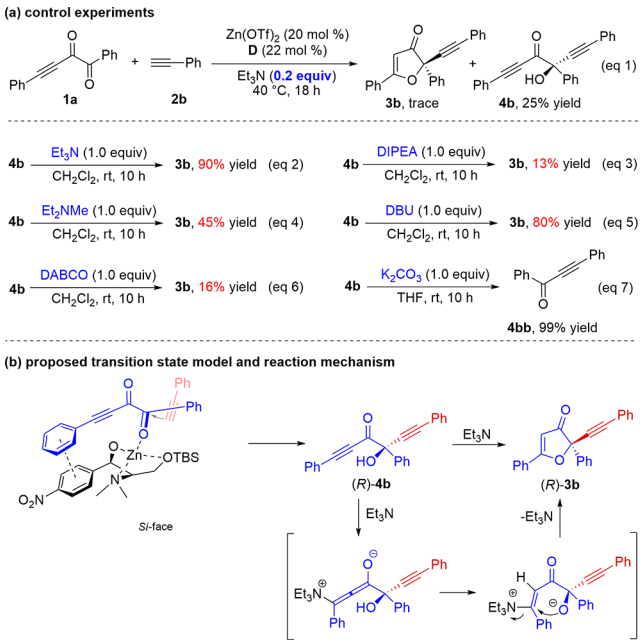
Scheme 5. Derivatizations of Product 4b



4b using Grignard reagent generated **6c** with >20:1 dr and 93% ee (Scheme 5, **6c**), and the condensation of the ynone moiety within **4b** with diamine afforded **6d** with 97% ee (Scheme 5, **6d**).

A series of control experiments were conducted to get more mechanistic insights of the reaction (Scheme 6a). First, using a catalytic amount of Et_3N, only 25% yield of **4b** was formed (eq 1), indicating that stoichiometric Et_3N is necessary. Second, 1.0 equiv of Et_3N was found to facilitate the formation of **3b** using **4b** as the substrate (eq 2), but DIPEA led to poor yield of **4b** under the same conditions (eq 3). Et_2NMe could produce **4b** in moderate yield (eq 4), and DBU proved also beneficial for the reaction (eq 5). In contrast, DABCO was less efficient (eq 6). Furthermore, K_2CO_3 resulted in the cleavage of **4b**, and ynone **4bb** was produced (eq 7). These results show that the basicity of the bases is not the decisive factor in the formation of **3b**, and Et_3N plays profound roles in the reaction, not only in the first step but also in the second step. A tentative transition model for the first step is shown in Scheme 6b: the coordinated zinc complex selectively activates the carbonyl group of the diketone substrate, and the alkyne attacks from the *Si*-face, which results in the (*R*)-configuration of the products. Moreover, a possible $\pi-\pi$ stacking between the aryl rings from the substrates and the ligand may be involved. A mechanism involving the nucleophilic addition of Et_3N to the

Scheme 6. Mechanistic Studies



alkyne unit, followed by proton transfer and nucleophilic substitution, is probably involved for the formation of furanones as shown in Scheme 6b. Although currently it is still ambiguous why only one of the two carbonyls is attacked, we have observed that the catalytic systems and reaction conditions greatly affect the regioselectivities when unsaturated 1,2-diketones are used as the substrates.[11]

In conclusion, we have achieved the asymmetric synthesis of both 3(2*H*)-furanones and α-hydroxy ketones using one protocol of the alkynylation of alkynyl 1,2-diketones through simply changing the reaction conditions. The bases showed critical roles in controlling the product distribution. 3(2*H*)-furanones are valuable units in bioactive substances, and α-hydroxy ketones are useful building blocks in organic synthesis. Furthermore, a series of value-added transformations on the products can be easily realized, showing the synthetic potential of this work. More studies on the unique reactivities of conjugated 1,2-diketones are ongoing in our lab and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02505.

Experimental procedures, spectroscopic data for all new compounds, and crystallographic data for **3h** (PDF)

Accession Codes

CCDC 2009376 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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