

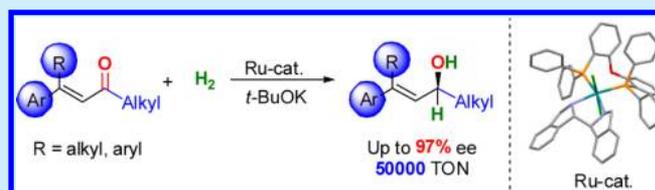
# Highly Enantioselective Hydrogenation of Steric Hindrance Enones Catalyzed by Ru Complexes with Chiral Diamine and Achiral Phosphane

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## S Supporting Information

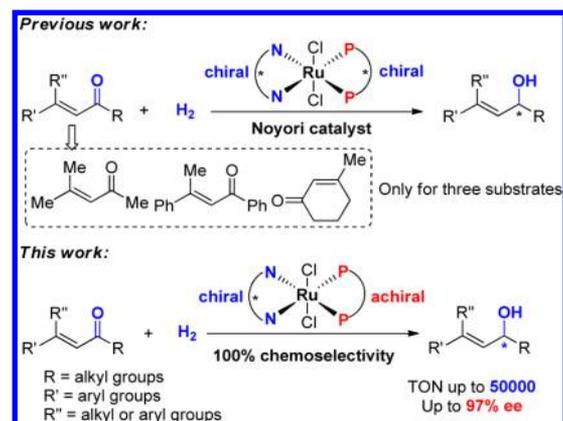
**ABSTRACT:** An asymmetric hydrogenation of sterically hindered  $\beta,\beta$ -disubstituted enones has been well-established by using a ruthenium complex composed of an achiral diphosphane and a chiral diamine as catalyst, wherein the carbonyl group was selectively hydrogenated to give a wide range of chiral allylic alcohols with high levels of enantioselectivity and complete chemoselectivity.



Chiral allylic alcohols are key structural subunits of natural products and serve as prevalent building blocks in the synthesis of numerous valuable pharmaceuticals and agrochemicals with a wide range of biological activities.<sup>1</sup> As a result, both academia and industry have paid much attention to developing efficient methods to access these compounds for decades, especially with regard to the enantioselective 1,2-reduction of enones.<sup>2</sup> In this context, the catalytic asymmetric hydrogenation has demonstrated excellent versatility and efficiency, providing a reliable synthetic platform to chiral compounds.<sup>3</sup> Among the transition-metal catalysts developed, the chiral ruthenium diphosphane/diamine catalytic system, pioneered by Noyori and co-workers, represents the most reliable approach to the synthesis of chiral alcohols.<sup>4</sup> Nowadays, a wide variety of cyclic and acyclic enones including simple aryl vinyl ketones and  $\alpha$ -substituted enones has been hydrogenated by using this type of catalyst to give the corresponding chiral allylic alcohols with both high chemoselectivity and excellent enantioselectivity.<sup>5,6</sup> However, the asymmetric hydrogenation of  $\beta,\beta$ -disubstituted enones is still a challenging task because of the steric hindrance at the  $\beta$ -position. To the best of our knowledge, only a few  $\beta,\beta$ -disubstituted enones, such as 4-methylpent-3-en-2-one, 1,3-diphenylbut-2-en-1-one, and 3-methylcyclohex-2-enone (Scheme 1), have been successfully hydrogenated with Noyori-type catalysts at relatively harsh reaction conditions to give the corresponding allylic alcohols with good enantioselectivity.<sup>6</sup> On the other hand, although highly efficient iridium catalysts for the asymmetric hydrogenation of sterically hindered enones have been reported by Zhou and Xie, a substituent in the  $\alpha$ -position is needed.<sup>7</sup> In contrast, the catalytic asymmetric hydrogenation of  $\beta$ -aryl- and  $\beta$ -alkyl-substituted vinyl alkyl ketones remains unexplored,<sup>8</sup> despite the fact that chiral  $\beta$ -aryl- and  $\beta$ -alkyl-substituted allylic alcohols are core intermediates for the synthesis of a number of drug agents such as isoaminile.<sup>9</sup>

Recently, we designed and synthesized a series of rigid chiral diamine ligands (BIDN), which demonstrated excellent chiral-

## Scheme 1. Asymmetric Hydrogenation of $\beta,\beta$ -Disubstituted Enones



induced abilities in asymmetric Michael addition of malonate esters as well as asymmetric Michael/Michael/Henry tandem sequence for constructing functionalized cyclohexanes with six contiguous stereocenters.<sup>10</sup> Ding and co-workers developed efficient ruthenium catalysts with achiral phosphanes for highly enantioselective hydrogenation of aromatic ketones.<sup>11</sup> Inspired by these works, we have also constructed efficient Ru catalysts for the asymmetric hydrogenation of aromatic ketones with our chiral BIDN ligands and commercially available inexpensive achiral phosphane ligands.<sup>12</sup> Unlike in the structure of the classical [RuCl<sub>2</sub>(BINAP)(DPEN)],<sup>4c</sup> where the two *trans*-located and free-rotated phenyl groups of the DPEN lead the equatorially oriented *N,N'*-ligated five-membered ring to be more crowded, the stair-like rigid chiral cyclic BIDN crafts a flat and open chiral environment at the *N,N'*-ligated portion of the

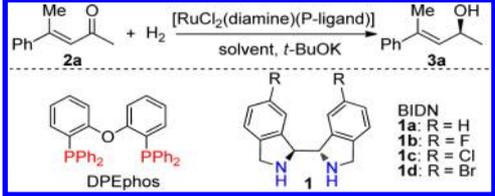
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corresponding Ru-phosphane-amine complexes.<sup>12b</sup> This orientation could lead to the sterically hindered enones entering the chiral pocket easily. Fascinated and inspired by this unique feature, we envisioned that the Ru complexes generated from BIDN and some phosphane ligands could be utilized as effective catalysts for the asymmetric hydrogenation of the sterically hindered  $\beta,\beta$ -disubstituted alkyl vinyl ketones. Herein, we report the first successful enantioselective hydrogenation of sterically hindered  $\beta,\beta$ -disubstituted vinyl alkyl ketones and other enones via asymmetric catalysis by using a ruthenium catalyst generated from a chiral BIDN and achiral diphosphane (DPEphos).

Initially, a series of  $[\text{RuCl}_2(\text{diamine})(\text{P-ligand})]$  catalysts were prepared according to the reported procedure with  $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$  as the catalyst precursor. (*E*)-4-Phenylpent-3-en-2-one **2a** was employed as a standard substrate for the asymmetric hydrogenation reaction. All reactions were carried out at room temperature for 12 h under 10 atm of  $\text{H}_2$ ; *t*-BuOK was used as a base, and the catalyst loading was 0.1 mol %. To explore an effective Ru catalyst, we first turned our attention to the Ru(II) complex generated from chiral diamine **1a** and simple  $\text{PPh}_3$ , which gave promising results in the hydrogenation of **2a** at room temperature in *i*-PrOH (30% yield, 88% ee for *S*-isomer, Table 1, entry 1). We undertook a survey of achiral phosphane

Table 1. Optimization of the Reaction Conditions<sup>a</sup>



entry	diamine	P ligand	yield (%) <sup>b</sup>	ee (%) <sup>b</sup>
1	<b>1a</b>	$\text{PPh}_3$	30	88
2	<b>1a</b>	BIPHEP	NR	ND
3	<b>1a</b>	DPPE	23	5
4	<b>1a</b>	DPPP	56	17
5	<b>1a</b>	DPPHex	84	10
6	<b>1a</b>	DPPPF	15	84
7	<b>1a</b>	Xantphos	6	ND
8	<b>1a</b>	DPEphos	99	93
9 <sup>c</sup>	<b>1a</b>	DPEphos	92	92
10 <sup>d</sup>	<b>1a</b>	DPEphos	96	91
11	<b>1b</b>	DPEphos	99	89
12	<b>1c</b>	DPEphos	98	86
13	<b>1d</b>	DPEphos	99	92

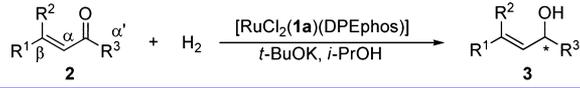
<sup>a</sup>Reaction conditions: **2a** (1.5 mmol),  $[\text{RuCl}_2(\text{diamine})(\text{diphosphane})]$  (0.1 mol %), *t*-BuOK (1 mol %),  $\text{H}_2$  (10 atm) in *i*-PrOH (1.5 mL) at 25 °C for 12 h. <sup>b</sup>Isolated yields were obtained, and ee values determined by HPLC. <sup>c</sup>MeOH as the solvent. <sup>d</sup>*n*-PrOH as the solvent.

ligands in the asymmetric hydrogenation of the model substrate **2a** (Table 1, entries 1–7). Contrary to our previous work on hydrogenation of simple aromatic ketones,<sup>9</sup> most of the phosphane ligands examined here gave us disappointing results (Table 1, entries 2–6). For example, the DPPPF showed good enantioselectivity but exhibited lower activity (Table 1, entry 6). However, a breakthrough result was obtained with DPEphos as a phosphane ligand. This system gave rise to complete conversion, delivering the expected allylic alcohol in complete chemoselectivity and 93% ee (Table 1, entry 8). Different solvents were

then screened, and *i*-PrOH turned out to be the best for this asymmetric hydrogenation (Table 1, entries 9 and 10). Screening of other diamines **1b–d** revealed that the diamines, which have different electronic properties, did not affect the product enantioselectivity and catalyst activity significantly (Table 1, entries 11–13). The chiral induction observed here resulted from the chiral diamines alone, and (*S,E*)-4-phenylpent-3-en-2-ol was obtained as a major isomer in all cases.

With the best reaction conditions established, the scope of the hydrogenation was then investigated by using different  $\beta,\beta$ -disubstituted enones as substrates. As summarized in Table 2, a

Table 2. Scope for the  $\beta$ -Substituted Unsaturated Ketones<sup>a</sup>



entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield (%)	ee (%)
1	Ph	Me	Me	<b>3a</b> (99)	93
2	Ph	Me	<i>n</i> -hexyl	<b>3b</b> (97)	94
3 <sup>b</sup>	Ph	Me	Ph	<b>3c</b> (97)	52
4 <sup>c</sup>	Ph	Et	<i>n</i> -hexyl	<b>3d</b> (83)	93
5 <sup>c</sup>	Ph	<i>i</i> -Pr	<i>n</i> -hexyl	<b>3e</b> (80)	97
6 <sup>d</sup>	Ph	Ph	<i>n</i> -hexyl	<b>3f</b> (97)	91
7	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> -hexyl	<b>3g</b> (98)	95
8	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> -hexyl	<b>3h</b> (92)	93
9	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> -hexyl	<b>3i</b> (98)	93
10 <sup>e</sup>	3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Me	<i>n</i> -hexyl	<b>3j</b> (78)	82
11	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> -hexyl	<b>3k</b> (85)	93
12	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	Me	<i>n</i> -hexyl	<b>3l</b> (90)	92
13	2-thienyl	Me	<i>n</i> -hexyl	<b>3m</b> (91)	97
14	2-naphthyl	Me	<i>n</i> -hexyl	<b>3n</b> (99)	92
15 <sup>f</sup>	Me	Ph	<i>n</i> -hexyl	<b>3c</b> (96) <sup>h</sup>	93 <sup>f</sup>
16 <sup>f</sup>	Me	2-naphthyl	<i>n</i> -hexyl	<b>3n</b> (86) <sup>i</sup>	93 <sup>f</sup>
17 <sup>f</sup>	Me	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>n</i> -hexyl	<b>3l</b> (92)	92
18				<b>3o</b> (99)	97
19 <sup>f</sup>	Ph	Me	Me	<b>3a</b> (99)	93

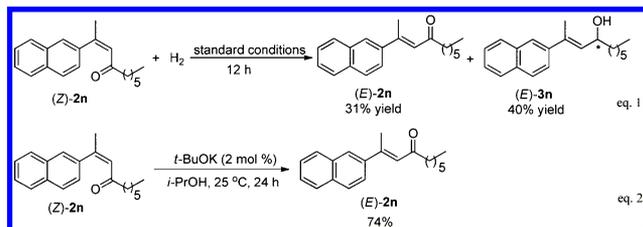
<sup>a</sup>Reaction conditions: **2** (1.0 mmol), Ru-cat (0.1 mol %), *t*-BuOK (1 mol %),  $\text{H}_2$  (10 atm) in *i*-PrOH (1.0 mL) at 25 °C for 12 h. Isolated yields and ee values were determined by HPLC, unless otherwise noted. <sup>b</sup>*t*-BuOK (5 mol %), 12 h. <sup>c</sup>*t*-BuOK (3 mol %), 24 h. <sup>d</sup>Ru-cat (0.2 mol %), *t*-BuOK (5 mol %). <sup>e</sup>*t*-BuOK (0.5 mol %), 24 h. <sup>f</sup>*t*-BuOK (2 mol %), 24 h. <sup>g</sup>*E*-Product. <sup>h</sup>Ratio of *E*-product and *Z*-product was 88:12 determined by <sup>1</sup>H NMR. <sup>i</sup>Ratio of *E*-product and *Z*-product was 91:9 determined by <sup>1</sup>H NMR. <sup>j</sup>TON = 50000, **2a** (1.6 g, 10.0 mmol), Ru-cat (0.002 mol %), *t*-BuOK (1 mol %), at 25 °C for 72 h.

series of  $\beta,\beta$ -disubstituted enones **2** were successfully hydrogenated to the corresponding chiral allylic alcohols **3** in high yields (78–99%) and good to excellent ee (82–97% ee) with  $[\text{RuCl}_2(\mathbf{1a})(\text{DPEphos})]$  as catalyst. The  $\beta$ -phenyl- and  $\beta$ -alkyl-substituted alkyl vinyl ketones containing an alkyl group in the  $\alpha'$ -position could be smoothly hydrogenated to give the corresponding chiral allylic alcohols with high yields and excellent ee (Table 2, entries 1 and 2). Although high yield can be obtained for hydrogenation of 1,3-diphenylbut-2-en-1-one **2c**,<sup>6b</sup> only moderate ee was observed in slightly modified conditions (Table 2, entries 1–3). Hydrogenation of substrates with different  $\beta$ -alkyl substituents, such as ethyl and *i*-propenyl, gave the corresponding allylic alcohols in somewhat lower yields, but consistently high enantioselectivities (93–97% ee) were observed (Table 2, entry 3 vs entries 4 and 5). Interestingly,  $\beta,\beta$ -diphenyl-substituted vinyl alkyl ketone **2f** was also tolerated and

furnished the desired product **3f** in high ee and good yield (Table 2, entry 6). The impact of varying the substituents on the  $\beta$ -aryl ring was then investigated. Both electron-withdrawing and electron-donating groups at the *para*-position of the benzene ring are well-tolerated, giving the corresponding alcohols in high yields and excellent ee (Table 2, entries 7–9). Asymmetric hydrogenation of 3,5-bis(trifluoromethyl)-substituted alkyl vinyl ketone **2j** gave 82% ee with good conversion (Table 2, entry 10). More sterically hindered *ortho*-substituted enones **2k** and **2l** were also subjected to the catalytic system to afford the desired products in 93 and 92% ee, respectively (Table 2, entries 11 and 12). Replacing the  $\beta$ -phenyl substituent with a 2-furyl or 2-naphthyl group also delivered the corresponding allylic alcohols in excellent enantioselectivities (Table 2, entries 13 and 14). It should be noted that when we attempted to hydrogenate the carbonyls of (*Z*)-**2c** and (*Z*)-**2n**, thermodynamically stable (*E*)-**3c** and (*E*)-**3n** were obtained in 93% ee (Table 2, entries 15 and 16). In addition, the thermodynamically stable (*E*)-**3l** can be afforded completely under the same reaction conditions (Table 2, entry 17). Finally, 3-phenylcyclohex-2-enone was also a suitable substrate, affording the desired product in 97% ee with 99% yield (Table 2, entry 18). To evaluate further the catalytic efficiency of the  $[\text{RuCl}_2(\mathbf{1a})(\text{DPEphos})]$  system in asymmetric hydrogenation, hydrogenation of **2a** in the presence of  $[\text{RuCl}_2(\mathbf{1a})(\text{DPEphos})]$  (0.002 mol %, 50000 TON) afforded (*S,E*)-4-phenylpent-3-en-2-ol in 99% yield and 93% ee (Table 2, entry 19).

To rationalize the configuration isomerization event observed here, control experiments using (*Z*)-**2n** as the substrate were conducted (Scheme 2). When the hydrogenation reaction of

#### Scheme 2. Isomerization of (*Z*)-**2n** to (*E*)-**2n**



(*Z*)-**2n** was conducted under standard conditions and quenched after 12 h, the expected allylic alcohol (*E*)-**3n** was obtained in 40% yield, together with (*E*)-**2n** with 31% yield (eq 1). Furthermore, most of the (*Z*)-**2n** could be isomerized to the corresponding (*E*)-**2n** in the presence of *t*-BuOK (eq 2) at room temperature. These results indicated that the (*Z*)-**2n** might first be isomerized to (*E*)-**2n** in the presence of base, and then (*E*)-**2n** was hydrogenated with the chiral Ru complex under the present catalytic system to afford the corresponding (*E*)-**3n**.

Further studies revealed that our established catalytic system also exhibited good catalytic activity and selectivity for the catalytic asymmetric hydrogenation of  $\beta$ -monosubstituted alkyl vinyl ketones<sup>6a</sup> (Table 3). Various derivatives **4a–4e** from methylenebenzylacetone were selectively hydrogenated, and the desired alcohols **5a–5e** were obtained in high yields and ee values. The results showed that the substituents at the *para*-position of the phenyl ring almost had no significant effect on the enantioselectivity, whereas a slight decreased tendency on product yields was observed along with the increase of their electron-withdrawing abilities (Table 3, entries 1–5). Steric hindrance of the  $\alpha'$ -alkyl substituents showed positive effect on the ee values of the hydrogenated products, although the yields of

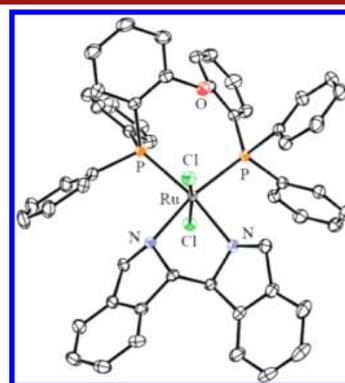
**Table 3. Scope for the Methylenebenzylacetone and  $\alpha'$ -Substituted Unsaturated Ketones<sup>a</sup>**

entry	Ar	R <sup>1</sup>	R <sup>2</sup>	yield (%)	ee (%)
1	Ph	H	Me	<b>5a</b> (99)	95
2	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	H	Me	<b>5b</b> (99)	96
3	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	H	Me	<b>5c</b> (99)	96
4	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	H	Me	<b>5d</b> (93)	95
5	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	Me	<b>5e</b> (90)	94
6	Ph	H	<i>t</i> -Bu	<b>5f</b> (60)	97
7	Ph	H	<i>n</i> -hexyl	<b>5g</b> (98)	95
8	Ph	H	Ph	<b>5h</b> (99)	62
9 <sup>b</sup>	Ph		(CH <sub>2</sub> ) <sub>4</sub>	<b>5i</b> (81)	94
10				<b>5j</b> (99)	95

<sup>a</sup>Reaction conditions: **4** (2 mmol), Ru-cat (0.1 mol %), *t*-BuOK (1 mol %), H<sub>2</sub> (10 atm) in *i*-PrOH (2 mL) at 25 °C for 12 h. Isolated yields were obtained for all the compounds, and ee values were determined by HPLC. <sup>b</sup>*t*-BuOK (0.5 mol %).

the alcohols were decreased (Table 3, entry 6 vs entries 1 and 7). Hydrogenation of chalcone **4h** was also performed in full conversion, but the enantioselectivity was only moderate (Table 3, entry 8). Notably, the benzylidene ketones **4i** and **4j** derived from cyclohexanone and tetralone could be hydrogenated to cyclic allylic alcohols **5i** and **5j** in high yields with 94 and 95% ee, respectively (Table 3, entries 9 and 10).

In order to gain some insights into the reasons for the observed high enantioselectivities in the present catalytic system, the catalyst precursor  $[\text{RuCl}_2(\text{DPEphos})\{(1S,1'S)\text{-}1,1'\text{-biisoindoline}\}]$  was isolated and fully characterized by NMR and HRMS. In addition, an X-ray crystal structure was obtained (Figure 1).<sup>13</sup> Similar to the structure of  $[\text{RuCl}_2(\text{PPh}_3)_2\{(1S,1'S)\text{-}$



**Figure 1.** Crystal structure of  $[\text{RuCl}_2(\text{DPEphos})\{(1S,1'S)\text{-}1,1'\text{-biisoindoline}\}]$ .

$\text{biisoindoline}\}]$ ,<sup>12b</sup> the classical *trans*-dichloro geometry was also observed in this Ru catalyst precursor and the BIDN ligand assumed a twisted five-membered ring coordination to the Ru center. Unlike the Noyori-type catalyst prepared from BINAP and DPEN, the BIDN presented a stair-like conformation and the two twisted planar conformations make the *N,N'*-ligated portion more flat and open. Furthermore, the P–Ru–P angle (98.85°) of the present Ru complex is notably larger than that of the classical  $[\text{RuCl}_2(\text{BINAP})(\text{DPEN})]$  (92.22°)<sup>4c</sup> and

[RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>(BIDN)] (98.31°),<sup>12b</sup> which forces a close proximity of the phenyl rings of the DPEphos to the chiral center and, therefore, is expected to induce the reactants close to the chiral center. This unique spatial orientation would produce a Bugles-like chiral pocket, which not only facilitates the sterically hindered β,β-disubstituted enone to enter the chiral pocket but also benefits to confine it into the defined chiral environment. As shown in Figure 2, the enone approach to the Ru complex via an

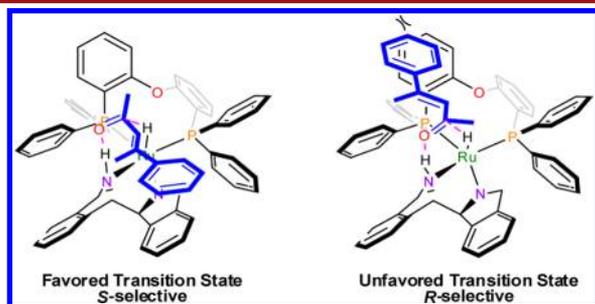


Figure 2. Transition state for asymmetric hydrogenation.

outer-sphere pathway, H<sup>δ+</sup>-N-Ru-H<sup>δ-</sup>, should capture the carbonyl of the ketonic substrate from the *Re* face of enone, delivering the corresponding allylic alcohol with *S*-configuration. In contrast, the *Si* face attack model would lead to large steric hindrance between the phenyl rings that come from the substrate and DPEphos ligand.

In summary, we have demonstrated for the first time that asymmetric hydrogenation of sterically hindered β,β-disubstituted alkyl vinyl ketones to chiral allylic alcohols is feasible. The reaction was catalyzed by a ruthenium catalyst prepared from a simple achiral diphosphane and a rigid chiral diamine, which demonstrated high enantioselectivities (up to 97% ee) and activities (up to 50000 TON) for a wide range of enones. Applications of this type of catalyst in other asymmetric transformations are currently under investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(13) CCDC 995443 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/ci](http://www.ccdc.cam.ac.uk/data_request/ci).