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Catalytic asymmetric addition of thiols to silyl glyoxylates for synthesis of multi-hetero-atom substituted carbon stereocenters†

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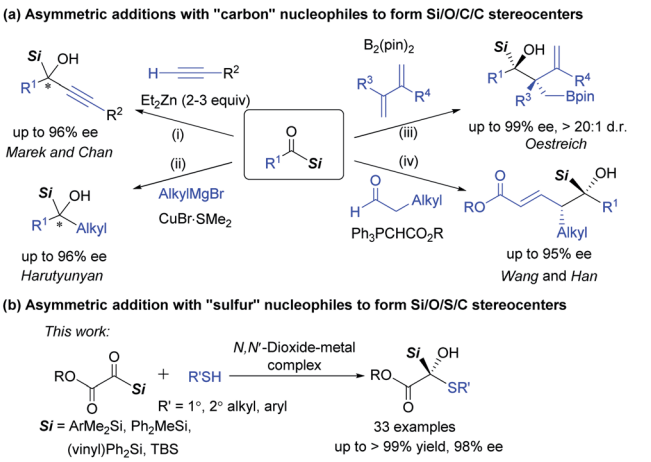
A chiral Lewis acid-catalyzed enantioselective addition of thiols to silyl glyoxylates was developed. The reaction proceeds well with a broad range of thiols and acylsilanes, affording the target tertiary chiral α-silyl–α-sulfydryl alcohols with multi-hetero-atom carbon stereocenters in excellent yields (up to 99%) and enantioselectivities (up to 98% ee). A series of control experiments were conducted to elucidate the reaction mechanism.

Introduction

Heteroatoms are prevalent in numerous organic compounds. As a significant subset of heteroatom-containing compounds, organosilanes are important skeletons of many known drugs and provide an opportunity to control pharmacokinetic properties.[1] They have been also widely applied in modern organic synthesis due to their unique properties. Particularly, optically active α-hydroxysilanes, containing a carbon stereocenter linked with a silicon atom and an oxygen atom simultaneously, are highly useful reagents in stereoselective C–C bond formation and rearrangement reactions for delivering various chiral molecules.[2] As a result, catalytic asymmetric preparation of chiral α-hydroxysilanes attracts much attention.

Enantioselective access to α-silyl alcohols could be obtained from nucleophilic addition of organosilanes to carbonyl compounds,[3] or from reduction[4] and addition reactions[5–9] of acylsilanes, which represent a class of unusual and fascinating carbonyl compounds.[10] The addition of highly reactive (pro) nucleophilic organometallic reagents to acylsilanes has emerged for the construction of α-hydroxysilanes bearing two saturated or unsaturated hydrocarbyl groups. For example, Marek's[5] and Chan's[6] group reported zinc-catalyzed enantioselective alkynylations of acylsilanes to give alkyl substituted α-silyl alcohols (Scheme 1a, path i). Harutyunyan[7] later extended the nucleophiles to a series of alkyl Grignard reagents in the presence of a copper ferrocenyl diphosphine complex catalyst (path ii), and the competing Meerwein–Ponndorf–Verley reduction could be largely suppressed by using an equivalent mixture of $CeCl_3$ and $BF_3 \cdot Et_2O$. Recently, Oestreich developed the stereoselective addition of chiral allylic copper intermediates (*in situ* generated from boron nucleophile and 1,3-dienes) to acylsilanes (path iii).[8] Alternatively, Wang, Han and co-workers realized an organocatalytic (vinylogous) aldol reaction with carbonyl compounds as nucleophiles (path iv).[9] The advance in synthesis of chiral α-silyl alcohols by using "carbon" nucleophiles intrigued us to investigate enantioselective construction of multi-hetero-atom-bearing carbon stereogenic centers by using hetero-atom nucleophiles.[11]

The asymmetric construction of a carbon–sulfur (C–S) bond plays a prominent role for the synthesis of valuable chiral organosulfur compounds.[12] Significant progress has been



Scheme 1 Enantioselective nucleophilic addition reactions of acylsilanes for the construction of chiral tertiary α-silyl alcohols.

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† Electronic supplementary information (ESI) available: ^1H, $^{13}C\{1H\}$ and $^{19}F\{1H\}$ NMR, and HPLC spectra. X-ray crystallographic data for **3w** (CIF). CCDC 2056433 and 2064772. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc01096d

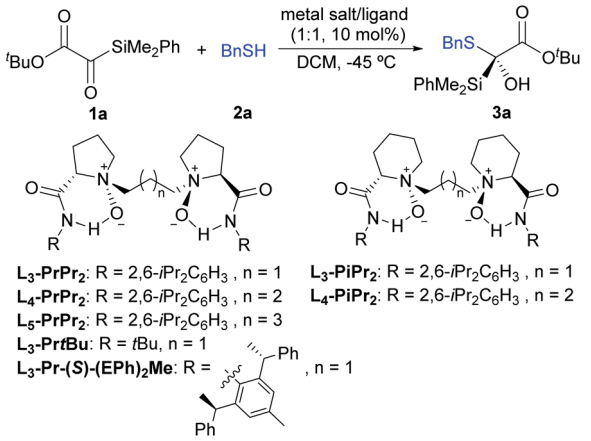
achieved through the addition of "sulfur" nucleophiles to carbon–carbon or carbon–nitrogen double bonds, as well as thiolysis of epoxides or aziridines, and so on. However, the enantioselective addition of thiols to carbonyl compounds is hard to realize, although the corresponding thiohemiacetal and thiohemiketal products are common skeletons in many pharmaceuticals,[13] which are generally considered as unstable structures and prone to racemization.

As a continuation of our interest in asymmetric sulfur-chemistry,[14] we envisaged that chiral *N*,*N*′-dioxide–metal complex catalysts[15] would be potentially useful in asymmetric addition of thiols to silyl glyoxylates,[16] although the reaction was found to be highly reactive in some solvents including water without catalysts.[11a] Herein we report an efficient enantioselective addition of silyl glyoxylates with various thiols as nucleophiles for the formation of chiral tertiary α-silyl alcohols containing a thiohemiketal skeleton (Scheme 1b). The adducts with multi-hetero-atom carbon stereocenters were afforded in excellent yields, and the competing Brook rearrangement[2] products were suppressed.[11]

Results and discussion

Our study commenced with silyl glyoxylate **1a** and benzyl mercaptan **2a** as the model substrates to optimize the reaction conditions (Table 1). Considering the strong background reaction response,[11] the initial attempts focused on exploring various chiral *N*,*N*′-dioxide ligands with $Er(OTf)_3$ (10 mol%) in DCM at a low temperature (−45 °C). To our delight, the $Er(OTf)_3$/**L_3-PrPr$_2$** complex could promote this reaction to afford the desired product **3a** in 85% yield with 49% ee (entry 1). It was found that the chiral backbones, the amide substituents, and the linker of the ligands displayed obvious effects on the enantioselectivity of the reaction (entries 1–6, see Table S1 in the ESI† for details). The amide substituents with the *tert*-butyl group exhibited poor enantioselectivity compared to that with the aryl group (entry 3 *vs.* 1). The investigation of the linker of the ligands revealed that **L_5-PrPr$_2$** provided higher enantioselectivity (87% ee) than **L_4-PrPr$_2$** (81% ee) and **L_3-PrPr$_2$** (49% ee) (entry 6 *vs.* entries 4 and 1). Comparatively, when other representative chiral ligands, such as bis(oxazoline) (BOX), pyridine-2,6-bis(oxazoline) (Pybox), BINAP or chiral phosphoric acid (CPA), were used instead of the *N*,*N*′-dioxide ligand, moderate yields with low ee values were achieved (see Table S9 in the ESI† for details). In view of the high reactivity, lowering the reaction temperature to −60 °C led to an increased ee value slightly to 89% (entry 11). Other reaction parameters including solvent (entries 7–10), additives and the concentration were also explored; unfortunately, no better results were obtained (see the ESI† for details). Notably, when protonic additives were used, the racemic version of the reaction process was increased through hydrogen bonding catalysis,[11a] leading to reduced enantiomeric excess. We next chose **L_5-PrPr$_2$** as a chiral ligand to screen the metal salts. $La(OTf)_3$ could provide 88% yield with moderate enantioselectivity (51% ee, entry 12). Nevertheless, $Y(OTf)_3$ led to a slight improvement of enantioselectivity with quantitative yield (99% yield, 91% ee, entry 13). In addition, excellent yield (96%) and enantioselectivity (90% ee) could still be achieved when the catalyst loading was reduced to 2 mol% (entry 14).

Table 1 Optimization of the reaction conditions[a]

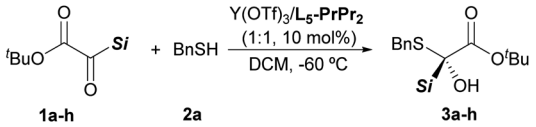


Entry	Ligand	Metal salt	Solvent	Yield[b] (%)	ee[c] (%)
1	**L_3-PrPr$_2$**	$Er(OTf)_3$	DCM	85	49
2	**L_3-PiPr$_2$**	$Er(OTf)_3$	DCM	88	55
3	**L_3-Pr^{t}Bu**	$Er(OTf)_3$	DCM	74	12
4	**L_4-PrPr$_2$**	$Er(OTf)_3$	DCM	86	81
5	**L_4-PiPr$_2$**	$Er(OTf)_3$	DCM	99	77
6	**L_5-PrPr$_2$**	$Er(OTf)_3$	DCM	87	87
7	**L_5-PrPr$_2$**	$Er(OTf)_3$	CH_3CN	86	0
8	**L_5-PrPr$_2$**	$Er(OTf)_3$	THF	85	10
9	**L_5-PrPr$_2$**	$Er(OTf)_3$	Et_2O	NR	—
10	**L_5-PrPr$_2$**	$Er(OTf)_3$	Toluene	NR	—
11[d]	**L_5-PrPr$_2$**	$Er(OTf)_3$	DCM	95	89
12[d]	**L_5-PrPr$_2$**	$La(OTf)_3$	DCM	88	51
13[d]	**L_5-PrPr$_2$**	$Y(OTf)_3$	DCM	99	91
14[d,e]	**L_5-PrPr$_2$**	$Y(OTf)_3$	DCM	96	90

[a] Unless otherwise noted, all reactions were performed with a metal salt/ligand (1 : 1, 10 mol%), **1a** (0.10 mmol), **2a** (0.10 mmol) in DCM (1.0 mL) at −45 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Run at −60 °C. [e] The reaction was performed with 2 mol% of $Y(OTf)_3$/**L_5-PrPr$_2$** for 12 hours.

With the optimized reaction conditions in hand (Table 1, entry 13), the silyl glyoxylate scope was next investigated (Table 2). Good substrate compatibility was observed with this Lewis acid catalysis system, and $PhMe_2Si$, Ph_2MeSi and Ph_2(vinyl)Si substituted silyl glyoxylate (entries 1–3) could be transformed into the corresponding products smoothly with excellent yields and enantioselectivities (**3a–3c**, 97–99% yields, 91–96% ee). The substituents of the phenyl group have little influence on the activity and enantioselectivity (entries 4–6). The aromatic silyl glyoxylate bearing methyl or fluoro groups at the *para*-position provided the desired α-silyl–α-sulfydryl alcohols with decreased yields and enantioselectivities (**3d**, 88% yield with 85% ee; **3e**, 76% yield with 80% ee). Delightedly, the silyl glyoxylate with the 4-chloro group attached to the phenyl ring could be converted into **3f** with 84% yield and 91% ee (entry 6). The alkyl silyl group (TBS) substituted silyl glyoxylate was also tolerated in this

Table 2 Substrate scope of silyl glyoxylates[a]



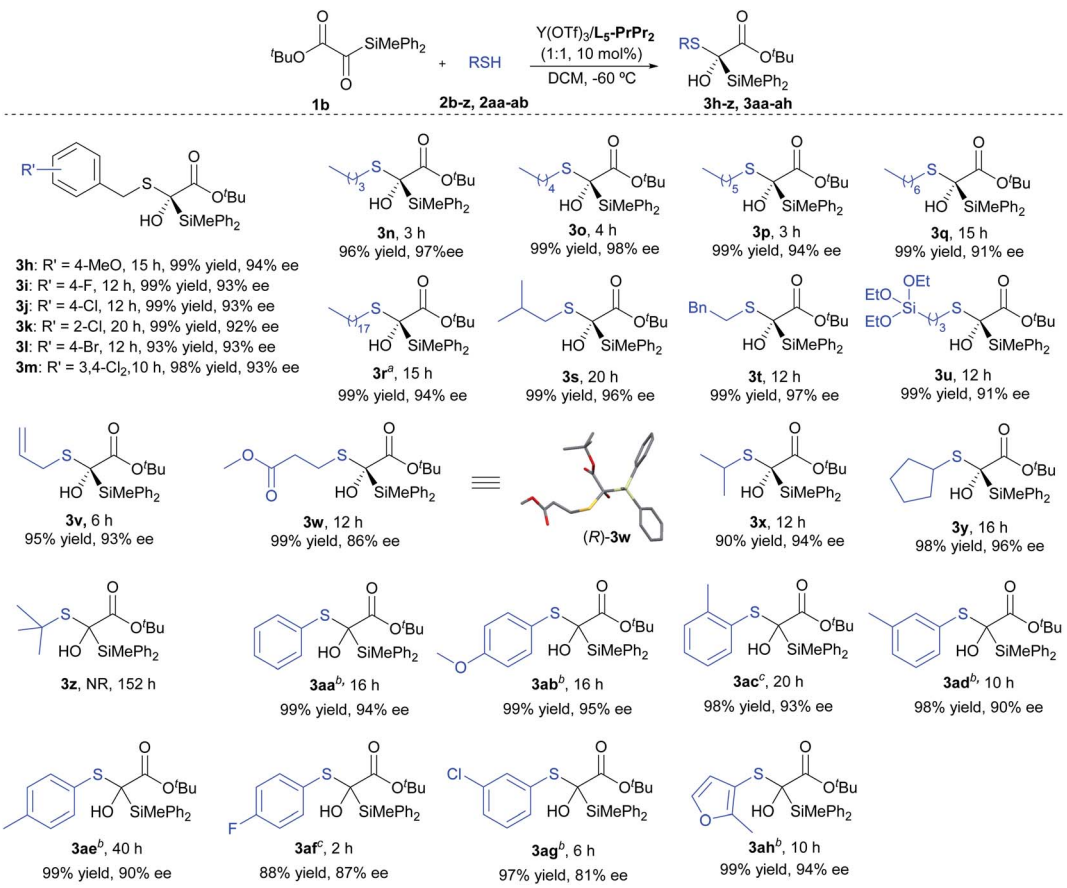
1a-h 2a 3a-h

Entry	*Si*	Yield[b] (%)	ee[c] (%)
1	$PhMe_2Si$	99 (**3a**)	91
2	Ph_2MeSi	99 (**3b**)	95
3	$Ph_2(vinyl)Si$	97 (**3c**)	96
4	(*p*-Tolyl)-Me_2Si	88 (**3d**)	85
5	(4-Fluorophenyl)-Me_2Si	76 (**3e**)	80
6	(4-Chlorophenyl)-Me_2Si	84 (**3f**)	91
7[d,e]	$^tBuMe_2Si$	87 (**3g**)	80

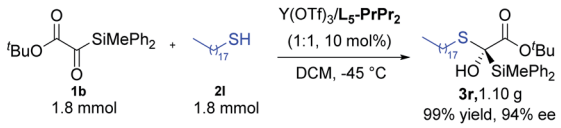
[a] Unless otherwise noted, all reactions were performed with $Y(OTf)_3$/**L_5-PrPr$_2$** (1 : 1, 10 mol%), **1** (0.10 mmol), **2a** (0.10 mmol) in DCM (1.0 mL) at −60 °C. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] **L_3-Pr-(*S*)-EPh$_2$Me** was used instead of **L_5-PrPr$_2$**. [e] Run at −45 °C.

reaction and produced the product **3g** in 87% yield with 80% ee by switching the ligand **L_5-PrPr$_2$** to **L_3-Pr-(*S*)-EPh$_2$Me** (entry 7). However, when less sterically hindered groups, such as the TMS and TES group, were introduced into the silyl glyoxylate, poor results were obtained (see Table S10 in the ESI† for details).

Subsequently, we turned our attention to the scope of mercaptans **2** (Scheme 2). Regardless of the electronic effect or steric hindrance of the substituents on the phenyl ring of benzyl thiols, this asymmetric reaction proceeded smoothly to afford **3h–3m** with efficient yields (93–99%) and ee values (92–94%). For the primary alkyl thiols, the increase of the alkyl chain length did not affect the activity and enantioselectivity of the reaction; the corresponding products (**3n–3r**) were obtained in 96–99% yields with 91–98% ee. Interestingly, functionalized mercaptan reagents, containing silyl, alkenyl or ester groups at the terminal chain of thiols, could be also tolerated, readily yielding the desired products (**3u–3w**) with good results (95–99% yield, 86–93% ee). The absolute configuration of the product **3w** was determined to be (*R*) by X-ray crystallography analysis.[17] It was found that the nucleophilic addition with branched alkyl thiols, such as 2-propanethiol and cyclopentanethiol, proceeded successfully to give **3x** and **3y** in 90% yield with 94% ee and 98% yield with 96% ee, respectively. However, no product was observed when the sterically hindered *t*-butyl mercaptan was used. Apart from the above alkyl mercaptans, aryl mercaptans could also react with silyl glyoxylate **1b** to produce the desired products with high yields and



Scheme 2 Substrate scope of mercaptans. Unless otherwise noted, all reactions were performed with $Y(OTf)_3$/**L_5-PrPr$_2$** (1 : 1, 10 mol%), **1b** (0.10 mmol), and **2** (0.10 mmol) in DCM (1.0 mL) at −60 °C. [a]The reaction was performed at −45 °C. [b]$Eu(OTf)_3$/**L_3-PrPr$_2$** was used instead of $Y(OTf)_3$/**L_5-PrPr$_2$**. [c]$Er(OTf)_3$/**L_3-PrPr$_2$** was used instead of $Y(OTf)_3$/**L_5-PrPr$_2$**.

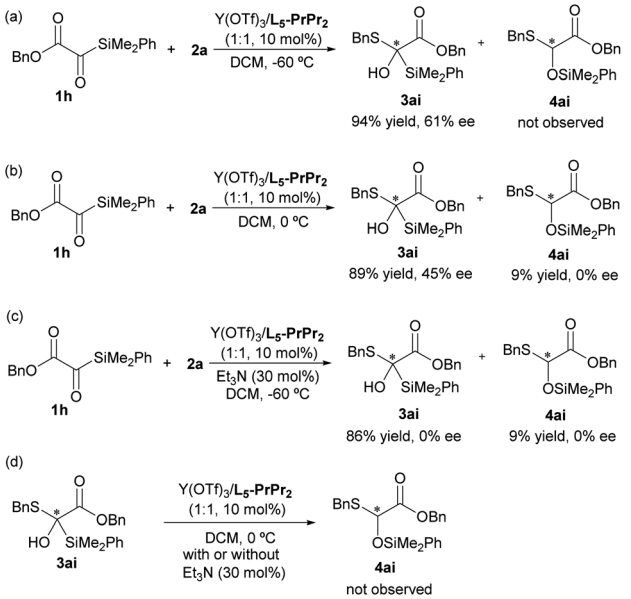


Scheme 3 Gram-scale reaction of **3r**.

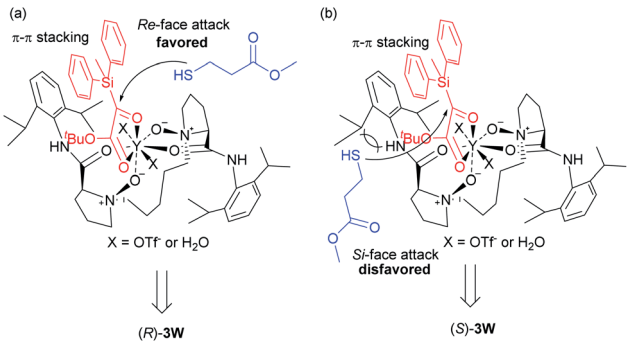
moderate to high enantioselectivities (**3aa–3ah**, 88–99% yields, 81–95% ee).

To evaluate the synthetic value of the catalytic system, a gram-scale synthesis of three-heteroatomic substituted chiral α-silyl–α-sulfydryl alcohol was carried out. **1b** (1.8 mmol) reacted with **2l** (1.8 mmol) under the standard reaction conditions, providing the corresponding product **3r** in 99% yield with 94% ee (Scheme 3).

To explore the fact that Brook rearrangement products are rarely observed during the reaction, we conducted a series of control experiments. Firstly, the reaction between **1a** and **2a** was performed in the presence of the **L$_5$-PrPr$_2$**/Y(OTf)$_3$ complex at a higher temperature (0 °C); the product of Brook rearrangement was still not detected (see the ESI† for details). When the benzyl 2-(dimethyl(phenyl)silyl)-2-oxoacetate **1h** reacted with **2a** at −60 °C, only addition product **3ai** was observed in 94% yield with 61% ee (Scheme 4a). However, increasing the reaction temperature to 0 °C, a mixture of **3ai** and Brook rearrangement product **4ai** was obtained with a ratio of 10 : 1 (Scheme 4b), suggesting that the Brook rearrangement could be significantly suppressed under low temperature conditions.[11b] Moreover, the result that 45% ee of **3ai** and racemate of **4ai** were observed suggests that oxygen anion **Int-A** generated from **1h** and **2a** facilitated Brook rearrangement to afford the carbon anion **Int-B**, which rapidly underwent racemization before proton transfer due to the existence of the α-ester group (Scheme 4b, see the ESI† for details). Subsequently, the influence of the base was



Scheme 4 Control experiments.



Scheme 5 The proposed working mode.

explored. For the *tert*-butyl 2-silyl-2-oxoacetate **1a**, only racemic addition product **3a** was obtained when Et$_3$N (30 mol%) was added (see the ESI† for details). In contrast, when benzyl 2-silyl-2-oxoacetate **1h** reacted with **2a** under the same conditions, a mixture of addition product and Brook rearrangement product was observed with a ratio of 10 : 1 (Scheme 4c). These experiments suggests that the ester group of substrates and base (Et$_3$N) have an important influence on the Brook rearrangement reaction. In addition, the conversion experiment of addition product **3ai** into Brook rearrangement product **4ai** was also performed with or without addition of Et$_3$N. It was found that no **4ai** was observed (Scheme 4d), which indicates that the formations of the addition product and Brook rearrangement product were competing processes from the oxygen anion **Int-A** (see the ESI† for details).

To further gain insight into the mechanism, the relationship between the ee values of the product **3a** and ligand **L$_5$-PrPr$_2$** was explored. A self-evident linear effect was observed, which indicates that the monomeric catalyst of **L$_5$-PrPr$_2$** and Y(OTf)$_3$ may be the main catalytically active species (see the ESI† for details). Based on the absolute configuration of **3w** and X-ray single-crystal structure of the *N*,*N*′-dioxide/Y^{III} complex,[18] a proposed transition-state model was described in Scheme 5. The four oxygen atoms of ligand *N*,*N*′-dioxide, two oxygen atoms of silyl glyoxylate **1b** and two molecules of the OTf$^-$ anion or a trace amount of H$_2$O in solvent coordinate to Y^{III} in an eight-coordinated manner. In combination with the above experimental results and our previous report,[19] we conjectured that a π–π interaction between the aryl silyl group of the substrate and the aryl group of the ligand exists and is beneficial to the reactivities and enantioselectivities. The *Si*-face of the carbonyl group is blocked by the 2,6-diisopropylphenyl group of the ligand (Scheme 5b), and thus the "sulfur" nucleophile **2q** preferably attacks from the *Re*-face to generate the (*R*)-configured product **3w** (Scheme 5a).

Conclusions

In summary, we have developed the first catalytic asymmetric addition of various thiol nucleophiles to silyl glyoxylates. The corresponding tertiary chiral α-silyl–α-sulfydryl alcohols containing multi-hetero-atom carbon stereocenters were obtained

with high yields and good to excellent enantioselectivities (76–99% yields, 80–98% ee). A series of control experiments were conducted to elucidate the reaction mechanism. The application of this methodology to the modification of protein and pharmaceutical structures needs further research.

Author contributions

M. G. performed experiments and prepared the ESI† and paper. S. W. repeated some experiments. Y. L. helped with crystal growth. W. C. and X. L. helped with modifying the paper and ESI.† X. F. conceived and directed the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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