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# Bimetallic tandem catalysis-enabled enantioselective cycloisomerization/carbonyl–ene reaction for construction of 5-oxazoylmethyl $\alpha$ -silyl alcohol†

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A bimetallic tandem catalysis-enabled enantioselective cycloisomerization/carbonyl–ene reaction was developed. The reaction proceeded well with a broad range of *N*-propargylamides and acylsilanes, affording the target chiral 5-oxazoylmethyl  $\alpha$ -silyl alcohols in up to 95% yield and 99% ee under mild conditions. Importantly, this facile protocol was available for the late-stage modification of several bioactive molecules. Based on the mechanistic study and control experiments, a possible catalytic cycle and transition state are proposed to elucidate the reaction process and enantioinduction.

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## Introduction

Organosilicon compounds are widely applied in synthetic chemistry, pharmaceutical chemistry and materials science because of their unique physicochemical properties.<sup>1</sup> For instance, the incorporation of silicon into bioactive molecules may increase the lipophilicity and potency in comparison to the parent (Fig. 1).<sup>1b,2</sup> The related discovery and evaluation have been demonstrated by Schreiber and others.<sup>2</sup>

As a special subset, chiral tertiary  $\alpha$ -silyl alcohols serve as important building blocks in versatile transformations for the construction of complex molecules.<sup>3</sup> Asymmetric

nucleophilic addition to acylsilanes<sup>4</sup> containing an  $sp^2$  carbon atom binding to both a silicon and an oxygen atom is one of the most direct and efficient accesses to optically active  $\alpha$ -silyl alcohols (Scheme 1a),<sup>4</sup> and has attracted considerable attention in the past two decades. A series of intriguing studies were realized by several groups, wherein highly active nucleophilic reagents, such as organometallic reagents,<sup>5a–e,h</sup>

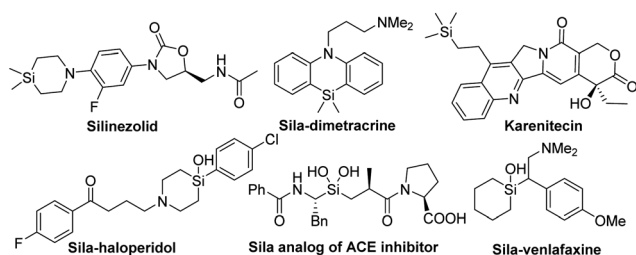
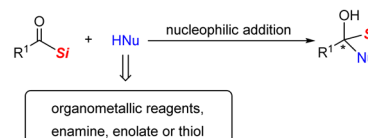


Fig. 1 Selected examples of silicon-containing bioactive molecules and drugs.

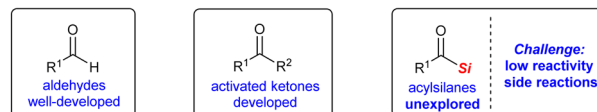
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† Electronic supplementary information (ESI) available: <sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H} and <sup>19</sup>F{<sup>1</sup>H} NMR, HPLC spectra. X-ray crystallographic data for C20 (CIF). CCDC 2207796. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc01048a>

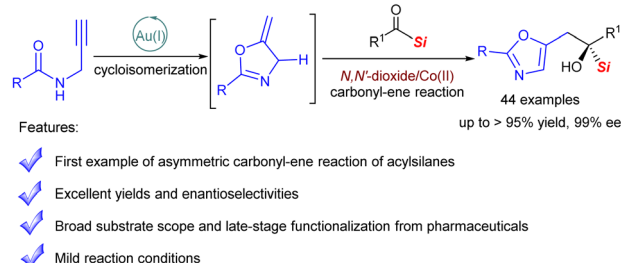
(a) Asymmetric nucleophilic addition of acylsilanes accessing to chiral tertiary  $\alpha$ -silyl alcohols



(b) The research status of enantioselective carbonyl–ene reactions



(c) **This work:** Asymmetric carbonyl–ene reaction of acylsilanes promoted by Au/chiral Co<sup>II</sup> catalysis



Scheme 1 Catalytic asymmetric reactions of acylsilanes for the construction of chiral  $\alpha$ -silyl alcohol and the research status of enantioselective carbonyl–ene reactions.

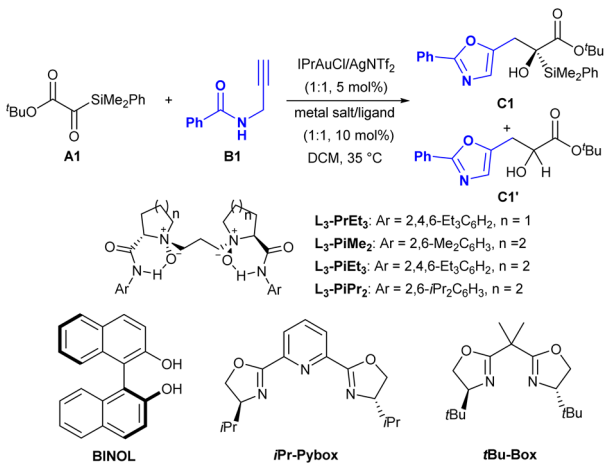


enamine,<sup>5f</sup> enolate,<sup>5g</sup> or thiol,<sup>5i</sup> were commonly employed to offset the poor reactivity of the acylsilanes.

As we know, the catalytic asymmetric carbonyl-ene reaction<sup>6</sup> between a carbonyl compound and an alkene bearing an allylic hydrogen is a powerful and stereocontrolled approach to prepare chiral homoallyl alcohols through a six-membered pericyclic process. Along this line, the carbonyl-ene reaction of acylsilanes, a type of unusual carbonyl compound (the enophile), may provide an ideal route to functionalized chiral tertiary  $\alpha$ -silyl alcohols. Nevertheless, to the best of our knowledge, although remarkable advances concerning the substance scope of aldehydes and activated ketones have been achieved, few examples of acylsilanes are found, which is highly challenging due to the low reactivity arising from the steric and electron-donating effects of the bulky trisubstituted silyl (Scheme 1b).<sup>7</sup> Meanwhile, side reactions may occur, including competing [1,2]-Brook rearrangement<sup>3e,4f,8</sup> and possible generation of carbenes<sup>4f,p,9</sup> from acylsilanes. On the other hand, in view of the importance of the oxazole skeleton,<sup>10</sup> we envisioned that the carbonyl-ene reaction of alkylideneoxazoline with acylsilanes may be favorable by means of the driving aromatization of the former and the assistance of a chiral Lewis acid catalyst lowering the LUMO energy of the latter. Herein, we report the first example of an enantioselective carbonyl-ene reaction of acylsilanes with easily available *N*-propargylamides in one-pot catalyzed by the bimetallic catalyst system consisting of Au(i) and chiral *N,N'*-dioxide/Co(ii) complex,<sup>11,12</sup> producing a chiral 5-oxazoylmethyl  $\alpha$ -silyl alcohol framework with high yield and enantioselectivity under mild conditions (Scheme 1c).

Our investigation of the carbonyl-ene reaction began with silyl glyoxylates **A1** and *N*-propargylamide **B1** as model substrates to optimize the reaction conditions (Table 1). The reaction exhibited low reactivity in dichloromethane (DCM) at 35 °C and afforded the desired chiral 5-oxazoylmethyl-substituted  $\alpha$ -silyl alcohol **C1** with 7% yield by using IPrAuCl/AgNTf<sub>2</sub> (1 : 1, 5 mol%) as the catalyst (Table 1, entry 1). Next, a multi-metallic catalyst system *via* the combination of IPrAuCl/AgNTf<sub>2</sub> and a chiral Lewis acid catalyst was investigated. The screening of Lewis acids coordinating with an L-proline-derived chiral *N,N'*-dioxide ligand<sup>13</sup> **L<sub>3</sub>-PrEt<sub>3</sub>** showed that Sc(OTf)<sub>3</sub> and Fe(OTf)<sub>2</sub> gave extremely low yields and ee values (Table 1, entries 2 and 3), but Zn(OTf)<sub>2</sub> promoted this reaction resulting in 65% yield with 96% ee (Table 1, entry 4), and the Co(OTf)<sub>2</sub>/**L<sub>3</sub>-PrEt<sub>3</sub>** complex provided the best result (Table 1, entry 5, 84% yield with 99% ee). The chiral *N,N'*-dioxide ligands were then evaluated (Table 1, entries 6–8, see Table S4 in the ESI for details†); a higher yield (88%) and the same ee value were obtained with the use of the L-pipecolic acid-derived **L<sub>3</sub>-PiPr<sub>2</sub>**, which possessed larger steric hindrance at the 2,6-position of the phenyl group of the amide unit (Table 1, entry 8). Comparatively, when other representative chiral ligands, such as chiral **BINOL**, bis(oxazoline) (**tBu-BOX**), and pyridine-2,6-bis(oxazoline) (**iPr-Pybox**) were used instead, only moderate yields with no more than 4% ee were achieved (Table 1, entries 9–11). On decreasing the temperature to 20 °C, a reduced yield (74%) was observed (Table 1, entry 12). When the reaction was

Table 1 Optimization of the reaction conditions<sup>a</sup>



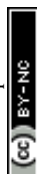
Entry	Metal salt	Ligand	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	—	—	7	0
2	Sc(OTf) <sub>3</sub>	<b>L<sub>3</sub>-PrEt<sub>3</sub></b>	49	32
3	Fe(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PrEt<sub>3</sub></b>	25	39
4	Zn(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PrEt<sub>3</sub></b>	65	96
5	Co(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PrEt<sub>3</sub></b>	84	99
6	Co(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PiEt<sub>3</sub></b>	85	99
7	Co(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PiMe<sub>2</sub></b>	74	99
8	Co(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PiPr<sub>2</sub></b>	88	99
9	Co(OTf) <sub>2</sub>	<b>BINOL</b>	56	0
10	Co(OTf) <sub>2</sub>	<b>iPr-Pybox</b>	14	0
11	Co(OTf) <sub>2</sub>	<b>tBu-Box</b>	39	4
12 <sup>d</sup>	Co(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PiPr<sub>2</sub></b>	74	99
13 <sup>e</sup>	Co(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PiPr<sub>2</sub></b>	N.R.	—
14 <sup>f</sup>	Co(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PiPr<sub>2</sub></b>	48	99
15 <sup>g</sup>	Co(OTf) <sub>2</sub>	<b>L<sub>3</sub>-PrEt<sub>3</sub></b>	46 (3)	99

<sup>a</sup> Unless otherwise noted, all reactions were performed with metal salt/ligand (1 : 1, 10 mol%), IPrAuCl/AgNTf<sub>2</sub> (1 : 1, 5 mol%), **A1** (0.10 mmol), **B1** (0.12 mmol) in DCM (1.0 mL) at 35 °C for 5 h. <sup>b</sup> Yield of the isolated product. <sup>c</sup> Determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> At 20 °C. <sup>e</sup> Without IPrAuCl/AgNTf<sub>2</sub>. N.R. = no reaction. <sup>f</sup> Without AgNTf<sub>2</sub>. <sup>g</sup> With 10  $\mu$ L H<sub>2</sub>O. The data in parenthesis indicate the yield of the byproduct **C1'**.

performed without IPrAuCl/AgNTf<sub>2</sub>, the reaction would not happen (Table 1, entry 13), and the yield decreased significantly in the absence of AgNTf<sub>2</sub> (Table 1, entry 14), suggesting the important roles of Au(i) and the counterion NTf<sub>2</sub><sup>−</sup>.<sup>14</sup> It is worth mentioning that the [1,2]-Brook rearrangement product **C1'** (3%) was detected and the yield of **C1** decreased significantly in the presence of a small amount of water (Table 1, entry 15). Other reaction parameters, including the solvent, additive and so on were also explored, no better results were obtained (see the ESI for details†).

## Results and discussion

With the optimized reaction conditions in hand (Table 1, entry 8), the scope of silyl glyoxylate **A** was investigated with **B1** as the ene-reaction precursor. As shown in Table 2,



changing the ester group unit from *tert*-butyl to cyclohexyl and benzyl resulted in an excellent ee value but gradually reduced yields (entries 1–3, **C2**, 81% yield; **C3**, 57% yield). The substituents located at the aryl group of the silyl unit had little effect on the reactivity and enantioselectivity, and the desired nearly optically pure products **C5–C10** were obtained in 77–88% yields (entries 5–10) except for **C4** bearing a methyl group at the 2-position, which might be attributed to the increased steric hindrance (entry 4, 71% yield and 88% ee). The 2-naphthyl substituted silyl glyoxylate also worked well, delivering **C11** in 82% yield with 99% ee (entry 11). Nevertheless, the enantioselectivity decreased dramatically for **A12** containing a Ph<sub>2</sub>MeSi group, giving the corresponding product **C12** in 73% yield with 29% ee (entry 12). By contrast, the alkyl silyl (TBS, TIPS, TES) substituted substrates exhibited poor reactivities and no reactions occurred even at a higher temperature (80 °C, see Fig. S1 in the ESI for details†).

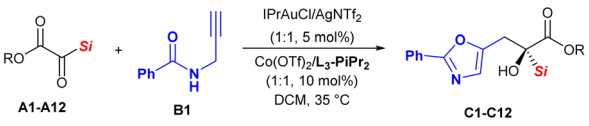
Subsequently, various *N*-propargylamides were evaluated (Scheme 2). Regardless of the electronic effect and steric effect of the substituents on the aryl ring, the *N*-propargylamides were transformed into the corresponding products in high yields with excellent enantioselectivities (**C13–C20**, 76–95% yields, 96–99% ee). A gram-scale experiment was also carried out, providing the product **C20** in 88% yield (1.06 g) with a maintained ee value, and its absolute configuration was determined to be *R* by X-ray crystallography analysis.<sup>15</sup> The 2-naphthyl, ferrocenyl and heteroaromatic substrates worked as well, delivering the optically pure **C21–C25** in 76–90% yields. However, no products were observed when introducing pyridine substituted propargylamides as well as urea, thiourea and guanidine-derived products (see Fig. S2 in the ESI for details†). Extensive examination of a wide range of **B** revealed that the *N*-propargylamides bearing primary, secondary and tertiary alkyl groups were also tolerated without the influence of the stereocontrol (**C26–C33**, 34–84% yields, 88–99% ee). Alkenyl-substituted propargylamide showed high reactivity but with decreased enantioselectivity (**C34**, 92% yield, 83% ee). To further probe the potential utility of this approach, a variety of *N*-propargylamide derivatives from drug molecules were employed for late-stage modification, furnishing the chiral modified products (**C35–C44**) with excellent stereocontrol.

Next, some mechanistic studies were conducted to gain an insight into the tandem reaction process. UV-visible absorption spectroscopy indicated a strong interaction between **A1** and L<sub>3</sub>-PiPr<sub>2</sub>/Co(II) (see Fig. S4 in the ESI for details†). Investigation of the relationship between the ee value of L<sub>3</sub>-PiPr<sub>2</sub> and that of **C1** showed a self-evident linear effect, implying that the catalytically active species was likely to be the monomeric complex of Co(OTf)<sub>2</sub> and L<sub>3</sub>-PiPr<sub>2</sub> (see Fig. S5 in the ESI for details†). Moreover, the alkylideneoxazoline intermediate **D** was prepared and tested with the L<sub>3</sub>-PiPr<sub>2</sub>/Co(OTf)<sub>2</sub> complex as the sole catalyst, the result (92% yield and 99% ee) was similar to that of the one-pot approach (Scheme 3a). Meanwhile, the React IR experiment revealed that intermediate **D** was formed rapidly within the initial ten minutes and decreased gradually over the reaction,

suggesting that the ene-reaction may be involved in the rate-determining step (see Fig. S6 in the ESI for details†). In addition, to make clear the formation of Brook rearrangement product **C1'**, the conversion experiment of carbonyl–ene product **C1** was performed, and it was found that no **C1'** was observed with or without addition of H<sub>2</sub>O (Scheme 3b), indicating that the formation of the carbonyl–ene product and the formation of the Brook rearrangement product were competing processes, and **C1'** may be generated through a Prins reaction process (see Fig. S3 in the ESI for details†).<sup>7</sup>

Based on the above experimental results, the absolute configuration of the product and the X-ray single-crystal structure of *N,N'*-dioxide/Co(II) complex,<sup>16</sup> a possible mechanism involving an Au(I) catalytic cycle and a Co(II) catalytic cycle is proposed (Scheme 3c). Initially, IPrAuNTf<sub>2</sub> in situ generated from IPrAuCl and AgNTf<sub>2</sub> served as a π-acid to combine with *N*-propargylamide **B1** and formed the intermediate **E**, which underwent 5-*endo*-dig cyclization to deliver the (*E*)-vinylgold intermediate **F**. The subsequent protodeauration of **F** would lead to the alkylideneoxazoline **D**. On the other hand, both the oxygen atoms of the amide and *N*-oxide portions of the ligand coordinated with the central Co(II) to form the L<sub>3</sub>-PiPr<sub>2</sub>/Co(OTf)<sub>2</sub> complex in a tetradentate manner, which acted as a chiral Lewis acid catalyst to activate the silyl glyoxylates **A1** via bidentate coordination with the two oxygen atoms of the carbonyl groups. Mechanistically, the carbonyl–ene reaction considered as a concerted, pericyclic reaction with a six-membered ring transition state occurred. The intermediate **D** approached from the *Si* face of **A1** because the *Re* face was shielded by the 2,6-diisopropylphenyl group of the ligand, producing (*R*)-**C1** and regenerating the L<sub>3</sub>-PiPr<sub>2</sub>/Co(OTf)<sub>2</sub> catalyst.

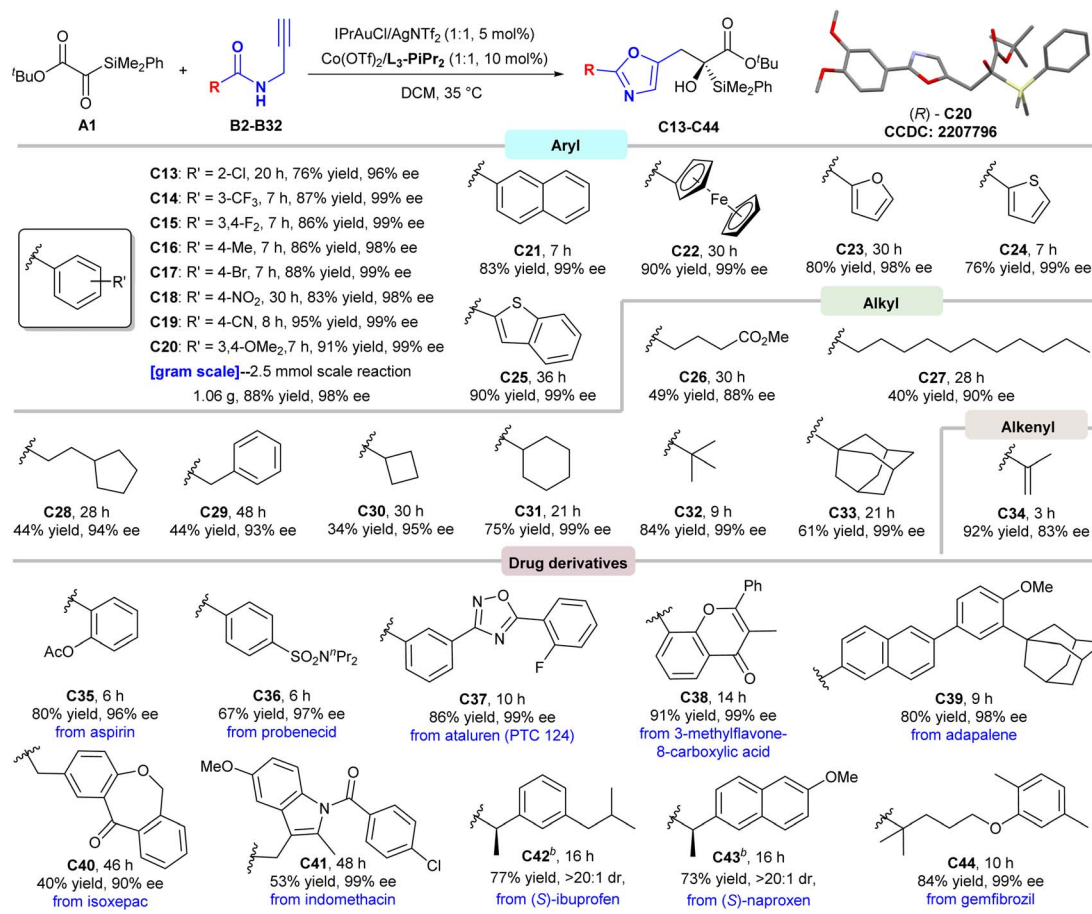
Table 2 Substrate scope of silyl glyoxylates<sup>a</sup>



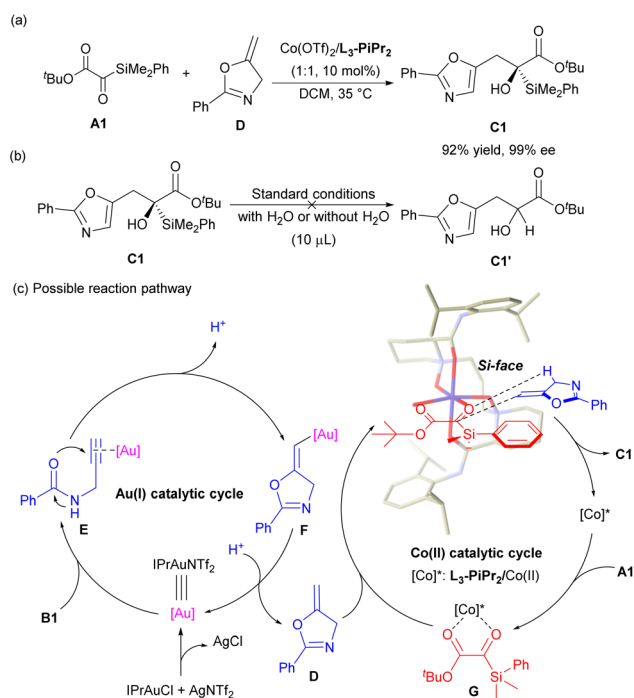
Entry <sup>a</sup>	Si/R	<i>t</i> (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	PhMe <sub>2</sub> Si/ <sup>i</sup> Bu	5	88 ( <b>C1</b> )	99
2	PhMe <sub>2</sub> Si/Cy	4	81 ( <b>C2</b> )	99
3	PhMe <sub>2</sub> Si/Bn	6	57 ( <b>C3</b> )	99
4	(2-MeC <sub>6</sub> H <sub>4</sub> )-Me <sub>2</sub> Si/ <sup>i</sup> Bu	33	71 ( <b>C4</b> )	88
5	(3-MeOC <sub>6</sub> H <sub>4</sub> )-Me <sub>2</sub> Si/ <sup>i</sup> Bu	5	81 ( <b>C5</b> )	99
6	(3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )-Me <sub>2</sub> Si/ <sup>i</sup> Bu	5	82 ( <b>C6</b> )	99
7	(4-MeC <sub>6</sub> H <sub>4</sub> )-Me <sub>2</sub> Si/ <sup>i</sup> Bu	5	83 ( <b>C7</b> )	99
8	(4-FC <sub>6</sub> H <sub>4</sub> )-Me <sub>2</sub> Si/ <sup>i</sup> Bu	5	88 ( <b>C8</b> )	99
9	(4-ClC <sub>6</sub> H <sub>4</sub> )-Me <sub>2</sub> Si/ <sup>i</sup> Bu	5	77 ( <b>C9</b> )	99
10	(4-BrC <sub>6</sub> H <sub>4</sub> )-Me <sub>2</sub> Si/ <sup>i</sup> Bu	4	83 ( <b>C10</b> )	99
11	(Naphthalen-2-yl)-Me <sub>2</sub> Si/ <sup>i</sup> Bu	5	82 ( <b>C11</b> )	99
12	Ph <sub>2</sub> MeSi/ <sup>i</sup> Bu	5	73 ( <b>C12</b> )	29

<sup>a</sup> Unless otherwise noted, all reactions were performed with IPrAuCl/AgNTf<sub>2</sub> (1:1, 5 mol%), Co(OTf)<sub>2</sub>/L<sub>3</sub>-PiPr<sub>2</sub> (1:1, 10 mol%), **A1–A12** (0.10 mmol), **B1** (0.12 mmol) in DCM (1.0 mL) at 35 °C. <sup>b</sup> Yield of the isolated product. <sup>c</sup> Determined by HPLC analysis on a chiral stationary phase.





**Scheme 2** The substrate scope of *N*-propargylamides. <sup>a</sup> Unless otherwise noted, all reactions were performed with IPrAuCl/AgNTf<sub>2</sub> (1:1, 5 mol%), Co(OTf)<sub>2</sub>/L<sub>3</sub>-PiPr<sub>2</sub> (1:1, 10 mol%), A1 (0.10 mmol), B (0.12 mmol) in DCM (1.0 mL) at 35 °C. Yield of the isolated product. Determined by HPLC analysis on a chiral stationary phase. <sup>b</sup> Ent-L<sub>3</sub>-PiPr<sub>2</sub> was used instead of L<sub>3</sub>-PiPr<sub>2</sub>.



**Scheme 3** Control experiments and possible reaction pathway.

## Conclusions

In summary, we reported the first example of enantioselective carbonyl-ene reaction of acylsilanes with *N*-propargylamides, broadening the reaction type of acylsilanes and the substrate scope of the carbonyl-ene reaction, providing the chiral 5-oxazoylmethyl  $\alpha$ -silyl alcohols with high yields and good to excellent enantioselectivities. Importantly, this facile protocol was available for the late-stage modification of several bioactive molecules. A catalytic cycle and transition state were proposed by the mechanistic studies to elucidate the reaction process and enantioinduction. Further investigations of acylsilanes are currently ongoing in our laboratory.

## Data availability

Further details of experimental procedure, <sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H} and <sup>19</sup>F {<sup>1</sup>H} NMR, HPLC spectra, X-ray crystallographic data for C20 are available in the ESI.†

## Author contributions

X. P. S. performed experiments and prepared the ESI† and the paper. Y. H. M. participated in structure characterization and





discussion. S. Y. L. repeated some experiments. W. D. C. and X. H. L. helped with modifying the paper and ESI.† W. D. C. and X. M. F. conceived and directed the project.

## Conflicts of interest

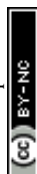
There are no conflicts to declare.

## Acknowledgements

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