

Cite this: *Chem. Sci.*, 2022, 13, 11648

All publication charges for this article have been paid for by the Royal Society of Chemistry

# Organocatalytic asymmetric azidation of sulfoxonium ylides: mild synthesis of enantioenriched $\alpha$ -azido ketones bearing a labile tertiary stereocenter†

Wengang Guo,<sup>ID</sup>\*<sup>a</sup> Feng Jiang,<sup>a</sup> Shijia Li<sup>bc</sup> and Jianwei Sun<sup>ID</sup>\*<sup>abc</sup>

Disclosed here is a catalytic asymmetric azidation reaction for the efficient synthesis of  $\alpha$ -azido ketones bearing a labile tertiary stereocenter. With a superb chiral squaramide catalyst, a mild asymmetric formal H–N<sub>3</sub> insertion of  $\alpha$ -carbonyl sulfoxonium ylides proceeded with excellent efficiency and enantioselectivity. This organocatalytic process not only complements the previous  $\alpha$ -azidation approaches for the formation of quaternary stereocenters and mostly for 1,3-dicarbonyl compounds, but also has advantages over the well-known metal-catalyzed asymmetric carbene insertion chemistry using  $\alpha$ -diazocarbonyl compounds. Detailed mechanistic studies *via* control reactions and NMR studies provided important insights into the reaction pathway, which features reversible protonation and dynamic kinetic resolution. The curiosity in mechanism also led to the development of a simplified alternative protocol with a cheaper HN<sub>3</sub> source.

Received 25th June 2022

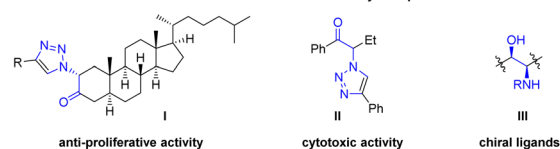
Accepted 6th September 2022

DOI: 10.1039/d2sc03552a

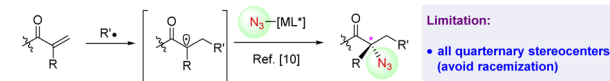
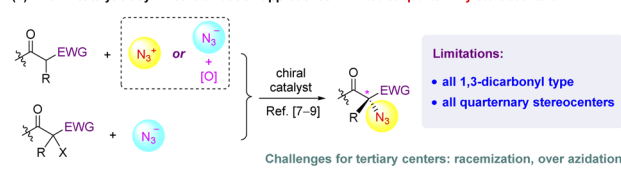
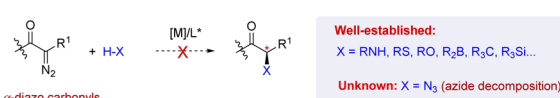
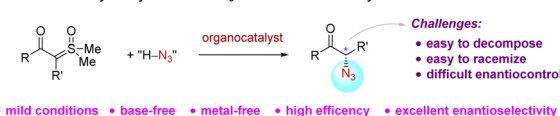
rsc.li/chemical-science

## Introduction

Organic azides are valuable molecules with broad applications in different disciplines, including chemical biology, material science, and drug discovery.<sup>1,2</sup> They are also important building blocks for the synthesis of other useful compounds, such as amines, nitrenes, and iminophosphoranes.<sup>1,3</sup> Specifically,  $\alpha$ -azido carbonyl compounds represent a special class of azides with unique applications.<sup>4</sup> The proximal azide and carbonyl functionalities enable them to serve as useful precursors toward biologically important molecules, heterocycles, and chiral ligands (*e.g.*, I–III, Scheme 1a).<sup>4,5</sup> As a result, a wide range of racemic or achiral methods have been developed for their synthesis.<sup>1,6–12</sup> However, their asymmetric synthesis remains a challenge. Among the few methods, catalytic asymmetric  $\alpha$ -azidation of carbonyl compounds represents an attractive one, but it was implemented with only limited success (Scheme 1b). These include electrophilic azidation,<sup>7</sup> oxidative nucleophilic

(a) Selected useful molecules derived from chiral  $\alpha$ -azido carbonyl compounds

(b) Known catalytic asymmetric azidation approaches: Limited to quaternary stereocenters

(c) Asymmetric insertion to diazocarbonyls? Powerful, but not suitable for H–N<sub>3</sub> insertion(d) This work: Catalytic asymmetric "H–N<sub>3</sub>" insertion with sulfur ylides toward  $\alpha$ -azido ketones

Scheme 1 Introduction to asymmetric  $\alpha$ -azidation of carbonyl compounds.

<sup>a</sup>Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou, China. E-mail: wgguo@cczu.edu.cn

<sup>b</sup>Department of Chemistry and the Hong Kong Branch of Chinese National Engineering Research Centre for Tissue Restoration & Reconstruction, The Hong Kong University of Science and Technology (HKUST), Clear Water Bay, Kowloon, Hong Kong SAR, China. E-mail: sunjw@ust.hk

<sup>c</sup>Shenzhen Research Institute, HKUST, No. 9 Yuxing 1st Rd, Shenzhen 518057, China

† Electronic supplementary information (ESI) available. CCDC 2149693. For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2sc03552a>

azidation,<sup>8</sup> enantioconvergent halogenophilic nucleophilic substitution ( $S_N2X$ ),<sup>9</sup> and radical addition.<sup>10</sup> All these methods were uniformly limited to the formation of quaternary stereogenic centers and the majority were even limited to certain 1,3-dicarbonyl molecules. To the best of our knowledge, catalytic asymmetric  $\alpha$ -azidation of carbonyl compounds to generate a tertiary stereocenter remains unknown,<sup>11</sup> with the exception of a few multi-step approaches from enantioenriched precursors.<sup>12</sup> Adjacent to both carbonyl and azide functionalities, this type of doubly activated tertiary stereocenters are very labile (easy to racemize) and vulnerable to many reaction conditions. Moreover, chemoselectivity issues resulting from this tertiary center (e.g., over-azidation) cause additional challenges.<sup>13</sup> Herein we address this unmet challenge by a new approach, leading to the first asymmetric azidation toward  $\alpha$ -azido ketones bearing a tertiary stereocenter.

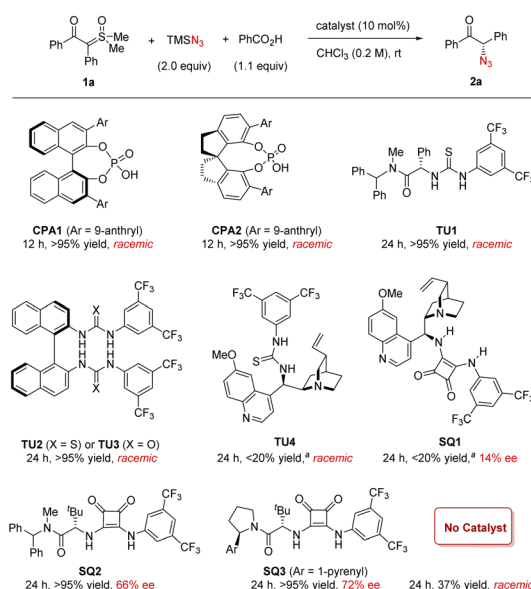
Catalytic asymmetric H–X bond insertion of metal carbenes generated *in situ* from  $\alpha$ -diazocarbonyls represents one of the most powerful approaches to access chiral  $\alpha$ -functionalized carbonyl compounds bearing a tertiary stereocenter (Scheme 1c).<sup>14</sup> However, despite the great success of this chemistry for the installation of a range of functionalities to the carbonyl  $\alpha$ -position, the insertion to a “H–N<sub>3</sub>” bond remains unknown. This is likely due to the potentially facile decomposition of either the azide reagents or the azido carbonyl products triggered by the same metal catalysts employed for carbene insertion (similar to azide reactivity toward nitrene).

Recently,  $\alpha$ -carbonyl sulfur ylides have been developed as powerful surrogates to  $\alpha$ -diazocarbonyl compounds, participating in a range of asymmetric cycloaddition and H–X bond insertion reactions, with the latter still in its infancy.<sup>15–17</sup> The amenability of this chemistry to mild metal-free organocatalytic conditions, combined with our continued interests in this topic,<sup>17</sup> led us to envision that an asymmetric formal H–N<sub>3</sub> insertion of  $\alpha$ -carbonyl sulfoxonium ylides could be possibly achieved.<sup>18</sup> If successful, it would not only eliminate the drawback of the already powerful diazo-based carbene insertion chemistry, but also serve as an important alternative solution to the above challenge in the synthesis of enantioenriched  $\alpha$ -azido carbonyl compounds (Scheme 1d).

## Results and discussion

### Reaction development

We began our study by employing sulfoxonium ylide **1a** as the model substrate. The combination of stoichiometric TMSN<sub>3</sub> and PhCO<sub>2</sub>H was used for *in situ* generation of hydrazoic acid (HN<sub>3</sub>) in a safe and user-friendly manner.<sup>19</sup> In hope of inducing enantiocontrol under mild metal-free conditions, we evaluated a diverse range of chiral hydrogen-bonding organocatalysts.<sup>20</sup> Chiral phosphoric acids **CPA1** and **CPA2** were initially tested, as they were the catalysts of choice in our previous amine N–H insertions.<sup>17</sup> The expected azido ketone **2a** was successfully generated in almost quantitative yield, but in racemic form (Scheme 2). We also evaluated a wide range of other chiral phosphoric acids (details in the ESI†), but uniformly without asymmetric induction, suggesting that this azidation process is



**Scheme 2** Preliminary results and catalyst screening. Reaction scale: **1a** (0.1 mmol), TMSN<sub>3</sub> (0.2 mmol), PhCO<sub>2</sub>H (0.11 mmol), **SQ3** (0.01 mmol), solvent (0.5 mL), 24 h. Yield was determined by <sup>1</sup>H NMR spectra of the crude mixture using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. Ee was determined by HPLC on a chiral stationary phase. <sup>a</sup>The reaction gave a messy mixture, likely due to the incompatibility of the reaction with the basic cinchona alkaloid functionality.

drastically distinct from amination. We then screened other hydrogen bonding catalysts, such as chiral (thio)ureas **TU1–4** bearing different chiral motifs (details in the ESI†). However, they also led to no asymmetric induction, although the chemical efficiency could be good. At this point, we realized that PhCO<sub>2</sub>H or the *in situ* generated HN<sub>3</sub> might be sufficient to protonate sulfoxonium ylides and promote the background reaction. Indeed, without catalyst, the reaction did afford the desired product, thus causing an additional challenge in developing the asymmetric variant. The solutions would be either to inhibit the background reaction or to accelerate the asymmetric pathway, with the latter likely being more feasible. With the notion that chiral hydrogen-bond donors (HBDs) can accelerate Brønsted acid-promoted reactions,<sup>21,22</sup> we continued to evaluate another family of HBDs, squaramides, as they feature different acidities and distance between the two HBD motifs from thioureas.<sup>20d</sup> To our delight, when cinchona alkaloid-derived squaramide **SQ1** was used, we started to observe enantiomeric induction (14% ee), albeit low. Subsequent screening indicated that chiral amino acid-derived squaramide **SQ2** was able to substantially improve the enantioselectivity (66% ee). Further considerable screening efforts led to the identification of the best catalyst **SQ3**, giving 72% ee.<sup>23</sup>

We further examined other reaction parameters with **SQ3** as catalyst (Table 1). Less acidic proton sources, such as water, methanol, hexafluoroisopropanol (HFIP), resulted in lower yields and no change in enantioselectivity (entries 1–3). Other carboxylic acids, including AcOH and substituted benzoic acids, gave same results as benzoic acid (entries 4–6). Chiral acids, such as *N*-Boc-L-proline and *N*-Boc-D-proline, did not influence



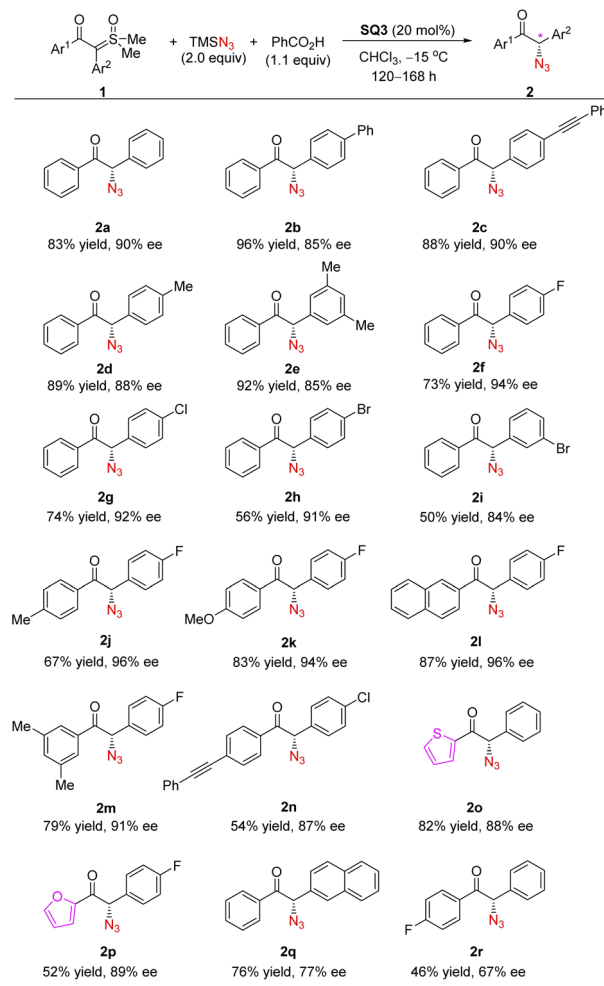
Table 1 Evaluation of reaction conditions<sup>a</sup>

$1\mathbf{a} + \text{TMSN}_3 + \text{proton source} \xrightarrow[\text{solvent (0.2 M), rt, 24 h}]{\text{SQ3 (10 mol\%)}} 2\mathbf{a}$				
Entry	Proton source	Solvent	Conv. (%)	ee (%)
1	H <sub>2</sub> O	CHCl <sub>3</sub>	30	71
2	MeOH	CHCl <sub>3</sub>	72	71
3	HFIP	CHCl <sub>3</sub>	80	72
4	AcOH	CHCl <sub>3</sub>	>95	71
5	( <i>p</i> -OH)C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	CHCl <sub>3</sub>	>95	70
6	( <i>p</i> -Cl)C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	CHCl <sub>3</sub>	>95	70
7	<i>N</i> -Boc-L-proline	CHCl <sub>3</sub>	>95	71
8	<i>N</i> -Boc-D-proline	CHCl <sub>3</sub>	>95	71
9	PhCO <sub>2</sub> H	DCM	>95	55
10	PhCO <sub>2</sub> H	DCE	>95	41
11	PhCO <sub>2</sub> H	Toluene	45	41
12	PhCO <sub>2</sub> H	THF	25	18
13 <sup>c</sup>	PhCO <sub>2</sub> H	EtOAc	Trace	—
14	PhCO <sub>2</sub> H	MTBE	Trace	—
15 <sup>b,c</sup>	PhCO <sub>2</sub> H	CHCl <sub>3</sub>	>95	84
16 <sup>b,d</sup>	PhCO <sub>2</sub> H	CHCl <sub>3</sub>	>95	83
17 <sup>b,e</sup>	PhCO <sub>2</sub> H	CHCl <sub>3</sub>	>95	84
18 <sup>b,f</sup>	PhCO <sub>2</sub> H	CHCl <sub>3</sub>	>95	89
19 <sup>g</sup>	PhCO <sub>2</sub> H	CHCl <sub>3</sub>	>95 (83)	90

<sup>a</sup> Reaction scale: **1a** (0.1 mmol), TMSN<sub>3</sub> (0.2 mmol), proton source (0.11 mmol), **SQ3** (0.01 mmol), solvent (0.5 mL), 24 h. Yield was determined by <sup>1</sup>H NMR spectra of the crude mixture using CH<sub>2</sub>Br<sub>2</sub> as an internal standard. Yield in parentheses refers to isolated yield. Ee was determined by HPLC on a chiral stationary phase. <sup>b</sup> Run at −10 °C. <sup>c</sup> 96 h. <sup>d</sup> *c* = 0.4 M, 72 h. <sup>e</sup> *c* = 0.1 M, 120 h. <sup>f</sup> Run with 20 mol% of catalyst, 96 h. <sup>g</sup> Run with 20 mol% of catalyst at −15 °C, 120 h.

the enantioselectivity either (entries 7–8). These results indicated that these acids only served as a proton source to generate HN<sub>3</sub>, but did not directly function in the enantiodetermining transition state. It was later found that the yield and enantioselectivity were sensitive to solvents. DCM or DCE resulted in a much lower enantioselectivity (entries 9–10). Toluene and THF led to both low conversion/yield and low enantioselectivity (entries 11–12). Drastically, no reaction was observed in EtOAc and MTBE (entries 13–14). It seemed that coordinating solvents were detrimental to this reaction, presumably due to competing hydrogen bonding interactions. An obvious increase in enantioselectivity was observed at a decreased temperature (−10 °C), though at the expense of reaction time (84% ee, entry 15). Variation of the reaction concentration did not affect the outcome (entries 16–17). The presence of background reaction then prompted us to examine an increased catalyst loading, in hope of enhancing enantiocontrol by accelerating the asymmetric path relative to the background reaction. Gratifyingly, the enantioselectivity was further improved to 89% ee with 20 mol% of catalyst (entry 18). Finally, both excellent yield and enantioselectivity were achieved at −15 °C (90% ee, entry 19). Notably, this is a remarkable result in view of the many unfavorable factors, such as labile tertiary stereogenic center, challenging enantiocontrol (no asymmetric induction with most catalysts) as well as complication by the background reaction.

We next investigated the substrate scope of this formal asymmetric H–N<sub>3</sub> insertion process (Scheme 3). Sulfoxonium



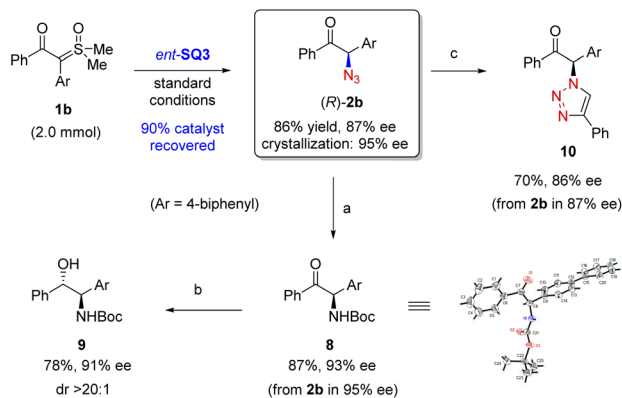
Scheme 3 Reaction scope. Conditions: sulfoxonium ylide **1** (0.20 mmol), BzOH (0.22 mmol), TMSN<sub>3</sub> (0.40 mmol), **SQ3** (0.04 mmol), CHCl<sub>3</sub> (1.0 mL). Isolated yield. ee was determined by HPLC on a chiral stationary phase.

ylides with different substituents (see the ESI for details<sup>†</sup>), both electron-donating and electron-withdrawing ones, at different positions of the aryl rings reacted smoothly under the optimized conditions, leading to a range of enantioenriched α-azido ketones with good to excellent yields and enantioselectivities.<sup>24</sup> It is worth noting that electron-poor arenes on the ylide motif typically reacted at lower reaction rates, but with enhanced enantioselectivity. This might be attributed to less contribution by the background reaction in these cases. Moreover, heterocycles, such as furan and thiophene, could also be incorporated into the azido ketone products with equally good enantioselectivity. These are valuable synthetic precursors to the analogues of monoamine oxidase inhibitors.<sup>25,26a</sup>

### Synthetic application

To demonstrate the practical utility of our process, we carried out a 2 mmol-scale reaction of **1b** using the opposite enantiomer of **SQ3** as catalyst (Scheme 4). Under the standard conditions, product (*R*)-**2b** was obtained with equally good





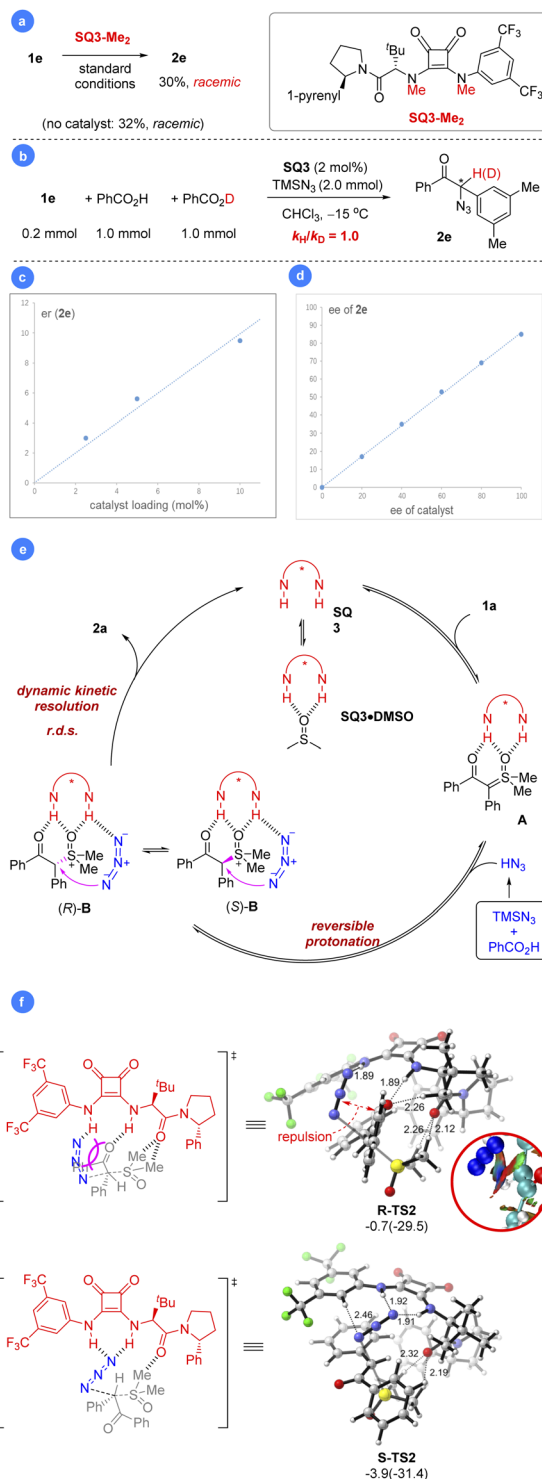
**Scheme 4** Large-scale synthesis of **2b** and product transformations. (a)  $\text{H}_2$ , Pd/C,  $\text{Boc}_2\text{O}$ ,  $\text{EtOAc}$ ,  $0^\circ\text{C}$ , 1 h. (b)  $\text{NaBH}_4$ ,  $\text{MeOH}$ ,  $-20^\circ\text{C}$ , 5 h. (c)  $\text{NaBH}_4$ ;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ,  $\text{PhC}\equiv\text{CH}$ ; DMP.

efficiency and enantioselectivity. Notably, the catalyst could be recovered in 90% yield and reused with equal catalytic activity. The enantiopurity of **2b** could be enhanced by crystallization. The azide functionality in **2b** could be selectively reduced by Pd/C-catalyzed hydrogenation followed by Boc-protection to form  $\alpha$ -amino ketone **8**, whose absolute configuration was confirmed by X-ray crystallography. Further diastereoselective reduction of **8** furnished amino alcohol **9**, representing a family of useful chiral ligands and bioactive molecules.<sup>5,25</sup> Finally, a simple 3-step sequence could convert **2b** to enantioenriched triazole **10** with good overall efficiency.<sup>26b</sup> Notably, in all these transformations, the good enantiopurity remained essentially intact.

### Mechanistic studies

Next, we carried out some control experiments to gain insights into the reaction mechanism. First of all, the *N*-methylated squaramide **SQ3-Me<sub>2</sub>** did not show any catalytic activity (Scheme 5a). Neither rate acceleration (vs. background reaction) nor asymmetric induction was observed, indicating the essential role of the two N-H motifs in the optimal catalyst **SQ3**, likely serving as hydrogen bond donors. Next,  $^1\text{H}$  NMR study was used to probe which reactant is activated by the catalyst (Fig. 1). When a solution of **1a** in  $\text{CDCl}_3$  was treated with **SQ3**, a dramatic high-field shift of the signal at  $\sim 3.6$  ppm (the two methyl groups in **1a**) was observed. Increasing the loading of **SQ3** caused a more pronounced shift, indicating strong but reversible interaction. Such a shift was also observed in the standard reaction mixture. In contrast, mixing **SQ3** with  $\text{HN}_3$  (generated from  $\text{HCl}$  and  $\text{NaN}_3$ ) did not lead to an obvious change in its signal. These observations suggested that the catalyst mainly activates the sulfoxonium ylide partner.

We also carried out a one-pot competition experiment between equal amounts of  $\text{PhCO}_2\text{H}$  and  $\text{PhCO}_2\text{D}$ .<sup>26c</sup> With substoichiometric substrate **1e**, the reaction did not exhibit a primary kinetic isotope effect. Since the product enantiopurity was stable in the presence of  $\text{PhCO}_2\text{H}$ , indicating H/D exchange after product formation was not responsible for this result. Thus, protonation may not be the rate-determining step, which is distinct from the previous S-H insertion (Scheme 5b).<sup>16a</sup> We



**Scheme 5** Mechanistic studies. (a) Catalytic activity of **SQ3-Me<sub>2</sub>**. (b) KIE experiment. (c) Correlation between product *er* value and catalyst loading. (d) Linear correlation between product and catalyst *ee*. (e) Proposed mechanism. (f) Computed geometries of the transition states for azide substitution by employing a simplified **SQ3** catalyst.

believe that the acidity and nucleophilicity of  $\text{HN}_3$  may have an impact to this observation. Furthermore, an obvious correlation of product enantiomeric excess with catalyst loading was observed, which is consistent with the presence of background





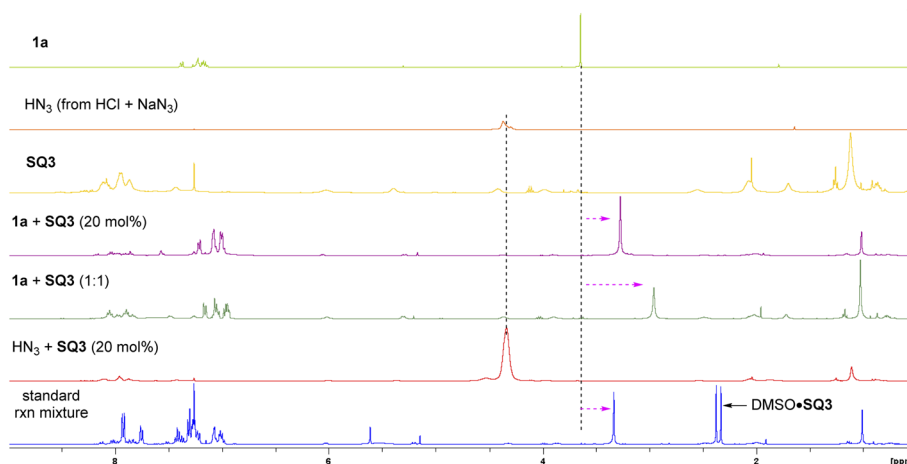


Fig. 1 NMR study of the reaction.

reaction (Scheme 5c). This result may also suggest that the catalyst functions prior to the enantiodetermining substitution step (dynamic interconversion).<sup>27</sup> Finally, the product ee value showed a linear relation to the catalyst ee, suggesting only one catalyst molecule operates in the enantiodetermining transition state (Scheme 5d).<sup>26d</sup>

Based on the above results and the typical HBD activation modes as well as DFT computations (Scheme 5e and Fig. S1 in the ESI† for details†),<sup>16a,20,21,28</sup> we proposed a mechanism for the reaction. The squaramide catalyst initially activates the sulfoxonium ylide with the double N–H motifs. Further reversible protonation of the resulting intermediate **A** by the *in situ* generated HN<sub>3</sub> leads to ion pair **B** as a diastereomeric mixture. The azide anion also has hydrogen bond interactions with the squaramide catalyst (Scheme S1†).<sup>29</sup> The reversible feature of this step allows (*R*)-**B** and (*S*)-**B** to rapidly equilibrate with each other, thus epimerizing the  $\alpha$ -stereogenic center. Next, the azide substitution takes place to deliver the enantioenriched product

through dynamic kinetic resolution. This step is both rate-determining and enantiodetermining. The preference for transition state **S-TS2** can be attributed to the hydrogen-bond interactions between the N–H motifs of **SQ3** and azide (Scheme 5f, N $\cdots$ H1 = 1.91 Å, N $\cdots$ H2 = 1.92 Å), while there is only one N–H $\cdots$ N interaction in **R-TS2** (N $\cdots$ H = 1.89 Å). On the other hand, the steric repulsion between azide and the carbonyl moiety of the substrate in **R-TS2** leads to higher activation energy. Finally, the catalyst is regenerated, which rests in the **DMSO·SQ3** adduct form as indicated by the doublet signal at ~2.4 ppm (Fig. 1 and also the ESI† for details). This mechanistic rationale agrees with all the experimental results.

We were also curious about whether we could mimic the last step using a preformed sulfoxonium chloride salt. Indeed, mixing substrate **1a** with a stoichiometric amount of HCl (aq.) resulted in rapid and clean formation of sulfoxonium salt **C** within 5 min, which was characterized by <sup>1</sup>H and <sup>13</sup>C NMR (Fig. 2a, more details in the ESI†). Further addition of *ent*-**SQ3**

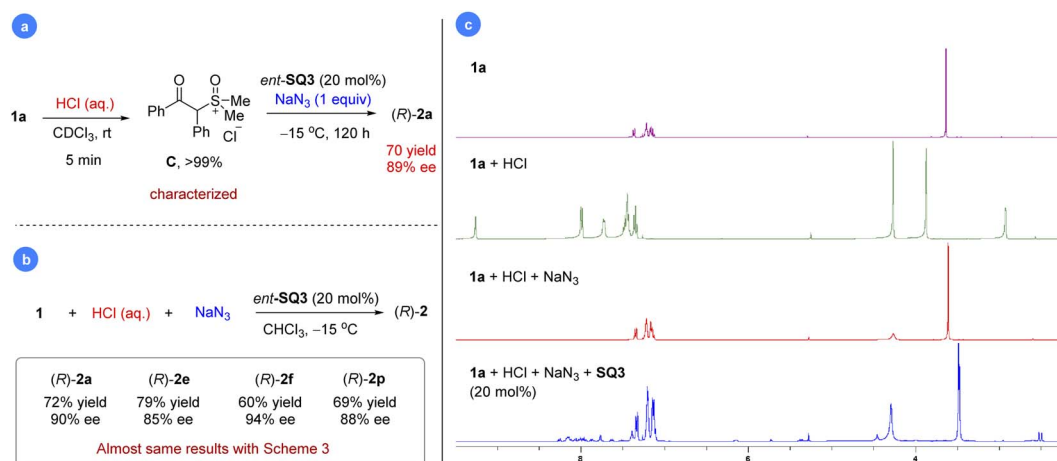


Fig. 2 The use of HCl and NaN<sub>3</sub> for the asymmetric azidation reaction. (a) *In situ* formation of the sulfoxonium chloride salt and their azidation reaction. (b) Selected scope of the azidation protocol with HCl and NaN<sub>3</sub>. (c) NMR monitoring the formation and azidation reaction of the sulfoxonium chloride salt.



and  $\text{NaN}_3$  at  $-15^\circ\text{C}$  led to the desired product **2a** in 70% yield and 89% ee.<sup>29</sup> Indeed, this reaction worked equally well if all the materials ( $\text{HCl}$ ,  $\text{NaN}_3$ , *ent*-**SQ3**, and **1a**) were added in one portion, regardless of the order of addition. Some selected examples were performed for comparison with the standard protocol, which gave almost the same results (Fig. 2b). The high enantioselectivity achieved here was remarkable, considering that the strong acid  $\text{HCl}$  could potentially compete with the catalyst to facilitate the racemic background reaction. This new protocol clearly provided a simplified alternative to the standard reaction with a cheaper azide and proton source. Next, we monitored this reaction progress to check whether it proceeded as expected by direct ion-exchange through phase-transfer. To our surprise, salt **C** immediately reversed to **1a** upon addition of  $\text{NaN}_3$  based on *in situ*  $^1\text{H}$  NMR study (Fig. 2c). Subsequent addition of **SQ3** simply permitted the reaction to proceed slowly to the product, similar to the standard protocol. This result further confirmed that protonation of the sulfoxonium ylide is reversible and salt **C** is just a combined source of the sulfoxonium ylide and proton. The comparable enantioselectivity between these two protocols also suggested that  $\text{PhCO}_2\text{H}$  and  $\text{TMSN}_3$  do not play any additional roles (*e.g.*, substrate activation or catalyst binding for asymmetric induction) other than the  $\text{HN}_3$  source, consistent with the observations during condition optimization where different acids did not influence enantioselectivity.

## Conclusions

In summary, catalytic asymmetric azidation provides efficient access to enantioenriched  $\alpha$ -azido carbonyl compounds. However, known approaches are limitedly available and developed with drawbacks (*e.g.*, all limited to quaternary stereocenters, mostly for 1,3-dicarbonyls). Here we have developed the first catalytic asymmetric azidation for the efficient synthesis of  $\alpha$ -azido ketones bearing a labile tertiary stereocenter by formal asymmetric  $\text{H}-\text{N}_3$  insertion of the versatile  $\alpha$ -carbonyl sulfoxonium ylides. This mild, base- and metal-free organocatalytic approach represents an extraordinary complement to the powerful metal-catalyzed asymmetric  $\text{H}-\text{X}$  insertion of diazo-carbonyl compounds, which remains incapable of  $\text{H}-\text{N}_3$  insertion. The proper choice of a superb chiral squaramide catalyst, together with careful optimization of other parameters, overcame many disfavored factors (*e.g.*, background reaction, product labile chirality) and resulted in excellent efficiency and enantiocontrol. Control experiments and *in situ* NMR studies suggested that the reaction proceeds *via* reversible activation and protonation of the sulfoxonium ylide followed by rate- and enantiodetermining azide substitution *via* dynamic kinetic resolution. Our mechanistic curiosity related to the use of a preformed sulfoxonium salt also led to the discovery of a simplified protocol with a cheaper  $\text{HN}_3$  source.

## Data availability

All experimental data is available within the article and the ESI.†

## Author contributions

W. Guo: conceptualization, methodology, investigation, data curation, and writing-original draft. S. Li: methodology, investigation, data curation, and writing-original draft. F. Jiang: resources. J. Sun: conceptualization, supervision, writing-review & editing.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support was provided by National Natural Science Foundation of China (91956114), Hong Kong Research Grants Council (16303420, 6309321), Innovation and Technology Commission (ITC-CNERC14SC01), Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110), Jiangsu specially appointed professors program, Shenzhen Science and Technology Innovation Committee (JCYJ20200109141408054), and the start-up funding to W. G. by Changzhou University (ZMF21020030). We thank Prof. Lijuan Song for helpful discussion on DFT results. We also thank the Analysis and Testing Center, NERC Biomass of Changzhou University for the assistance in NMR analysis.

## Notes and references

- Reviews on the utility of organic azides: (a) S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188–5240; (b) S. Bräse and K. Banert, *Organic Azides: Synthesis and Applications*, Wiley-VCH, Weinheim, 2009.
- Application in chemical biology, drug discovery, and material science: (a) H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128–1137; (b) X. Jiang, X. Hao, L. Jing, G. Wu, D. Kang, X. Liu and P. Zhan, *Expert Opin. Drug Discovery*, 2019, **14**, 779–789; (c) A. Qin, J. W. Y. Lam and B. Z. Tang, *Chem. Soc. Rev.*, 2010, **39**, 2522–2544; (d) R. K. Iha, K. L. Wooley, A. M. Nyström, D. J. Burke, M. J. Kade and C. J. Hawker, *Chem. Rev.*, 2009, **109**, 5620–5686; (e) J. C. Jewett and C. R. Bertozzi, *Chem. Soc. Rev.*, 2010, **39**, 1272–1279; (f) P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905–4979.
- Application in organic synthesis: (a) F. Palacios, C. Alonso, D. Aparicio, G. Rubiales and J. M. de los Santos, *Tetrahedron*, 2007, **63**, 523–575; (b) T. Uchida and T. Katsuki, *Chem. Rec.*, 2014, **14**, 117–129; (c) C. Bednarek, I. Wehl, N. Jung, U. Schepers and S. Bräse, *Chem. Rev.*, 2020, **120**, 4301–4354.
- Reviews on  $\alpha$ -azido carbonyls: (a) T. Patonay, K. Kónya and É. Juhász-Tóth, *Chem. Soc. Rev.*, 2011, **40**, 2797–2847; (b) S. Faiz, A. F. Zahoor, N. Rasool, M. Yousaf, A. Mansha, M. Zia-Ul-Haq and H. Z. E. Jaafar, *Molecules*, 2015, **20**, 14699–14745.



- 5 Selected utility of  $\alpha$ -azido ketones: (a) J. Vantikommu, S. Palle, P. S. Reddy, V. Ramanatham, M. Khagga and V. R. Pallapothula, *Eur. J. Med. Chem.*, 2010, **45**, 5044–5050; (b) Z. Kádár, É. Frank, G. Schneider, J. Molnár, I. Zupkó, J. Kóti, B. Schönecker and J. Wölfling, *ARKIVOC*, 2012, 279–296; (c) M. R. Morales, K. T. Mellem and A. G. Myers, *Angew. Chem., Int. Ed.*, 2012, **51**, 4568–4571.
- 6 Recent reviews on the synthesis of azides: (a) P.-G. Ding, X.-S. Hu, F. Zhou and J. Zhou, *Org. Chem. Front.*, 2018, **5**, 1542–1559; (b) P. Sivaguru, Y. Ning and X. Bi, *Chem. Rev.*, 2021, **121**, 4253–4307, For selected examples about azidation of olefins with sulfonium salt under metal free conditions;; (c) D. S. Rao, T. R. Reddy, A. Gurawa, M. Kumar and S. Kashyap, *Org. Lett.*, 2019, **21**, 9990–9994; (d) T. R. Reddy, D. S. Rao and S. Kashyap, *Chem. Commun.*, 2019, **55**, 2833–2836.
- 7 Asymmetric electrophilic azidations: (a) Q.-H. Deng, T. Bleith, H. Wadepohl and L. H. Gade, *J. Am. Chem. Soc.*, 2013, **135**, 5356–5359; (b) M. V. Vita and J. Waser, *Org. Lett.*, 2013, **15**, 3246–3249; (c) C.-J. Wang, J. Sun, W. Zhou, J. Xue, B.-T. Ren, G.-Y. Zhang, Y.-L. Mei and Q.-H. Deng, *Org. Lett.*, 2019, **21**, 7315–7319.
- 8 Asymmetric oxidative nucleophilic azidations: (a) M. Tiffner, L. Stockhammer, J. Schörghenheimer, K. Röser and M. Waser, *Molecules*, 2018, **23**, 1142–1150; (b) M. Uyanik, N. Sahara, M. Tsukahara, Y. Hattori and K. Ishihara, *Angew. Chem., Int. Ed.*, 2020, **59**, 17110–17117.
- 9 Asymmetric  $S_N2X$  approaches: (a) X. Zhang, J. Ren, S. M. Tan, D. Tan, R. Lee and C.-H. Tan, *Science*, 2019, **363**, 400–404; (b) J. Ren, X. Ban, X. Zhang, S. M. Tan, R. Lee and C.-H. Tan, *Angew. Chem., Int. Ed.*, 2020, **59**, 9055–9058.
- 10 Asymmetric radical approaches: (a) L. Wu, Z. Zhang, D. Wu, F. Wang, P. Chen, Z. Lin and G. Liu, *Angew. Chem., Int. Ed.*, 2021, **60**, 6997–7001; (b) W. Liu, M. Pu, J. He, T. Zhang, S. Dong, X. Liu, Y.-D. Wu and X. Feng, *J. Am. Chem. Soc.*, 2021, **143**, 11856–11863, For a recent approach for diastereoselective electro-oxidative tandem azidation-radical cyclization to access quinolinones;; (c) D. Maiti, K. Mahanty and S. D. Sarkar, *Chem.-Asian J.*, 2021, **16**, 748–752.
- 11 For selected examples of non-azidation approaches (without carbon-azide bond formation in the enantiodetermining step): (a) N. S. Chowdari, M. Ahmad, K. Albertshofer, F. Tanaka and C. F. Barbas, *Org. Lett.*, 2006, **8**, 2839–2842; (b) J. McNulty and C. Zepeda-Velázquez, *Angew. Chem., Int. Ed.*, 2014, **53**, 8450–8454; (c) Á. Martínez-Castañeda, K. Kędziora, I. Lavandera, H. Rodríguez-Solla, C. Concellón and V. del Amo, *Chem. Commun.*, 2014, **50**, 2598–2600; (d) M. V. Vita, P. Caramenti and J. Waser, *Org. Lett.*, 2015, **17**, 5832–5835; (e) K. Weidner, Z. Sun, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2015, **54**, 6236–6240; (f) X. Ye, Y. Pan and X. Yang, *Chem. Commun.*, 2020, **56**, 98–101; (g) P.-G. Ding, F. Zhou, X. Wang, Q.-H. Zhao, J.-S. Yu and J. Zhou, *Chem. Sci.*, 2020, **11**, 3852–3861.
- 12 For selected examples from enantioenriched precursors, see: (a) K. Shibatomi, Y. Soga, A. Narayama, I. Fujisawa and S. Iwasa, *J. Am. Chem. Soc.*, 2012, **134**, 9836–9839; (b) R. da S. Gomes and E. J. Corey, *J. Am. Chem. Soc.*, 2019, **141**, 20058–20061.
- 13 Potential instability and over-azidation issues: (a) J. H. Boyer and F. C. Canter, *Chem. Rev.*, 1954, **54**, 1–57; (b) T. Patonay and R. V. Hoffman, *J. Org. Chem.*, 1995, **60**, 2368–2377; (c) K. Holzschneider, F. Mohr and S. F. Kirsch, *Org. Lett.*, 2018, **20**, 7066–7070; (d) T.-Y. Yu, Z.-J. Zheng, T.-T. Dang, F.-X. Zhang and H. Wei, *J. Org. Chem.*, 2018, **83**, 10589–10594.
- 14 (a) S.-F. Zhu and Q.-L. Zhou, *Acc. Chem. Res.*, 2012, **45**, 1365–1377; (b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKerverey, *Chem. Rev.*, 2015, **115**, 9981–10080.
- 15 Reviews of sulfur ylides: (a) A. C. B. Burtoloso, R. M. P. Dias and I. A. Leonarczyk, *Eur. J. Org. Chem.*, 2013, **2013**, 5005–5016; (b) D. Kaiser, I. Klose, R. Oost, J. Neuhaus and N. Maulide, *Chem. Rev.*, 2019, **119**, 8701–8780; (c) C. A. D. Caiuby, L. G. Furniel and A. C. Burtoloso, *Chem. Sci.*, 2022, **13**, 1192–1209.
- 16 Pioneering studies: (a) P. B. Momo, A. N. Leveille, E. H. E. Farrar, M. N. Grayson, A. E. Mattson and A. C. B. Burtoloso, *Angew. Chem., Int. Ed.*, 2020, **59**, 15554–15559; (b) L. G. Furniel, R. Echemendía and A. C. B. Burtoloso, *Chem. Sci.*, 2021, **12**, 7453–7459; (c) A. N. Leveille, R. Echemendía, A. E. Mattson and A. C. B. Burtoloso, *Org. Lett.*, 2021, **23**, 9446–9450.
- 17 For our efforts, see:(a) W. Guo, Y. Luo, H. H. Y. Sung, I. D. Williams, P. Li and J. Sun, *J. Am. Chem. Soc.*, 2020, **142**, 14384–14390; (b) W. Guo, M. Wang, Z. Han, H. Huang and J. Sun, *Chem. Sci.*, 2021, **12**, 11191–11196.
- 18 For synthesis of racemic  $\alpha$ -carbonyl azides through a one pot fluorination/azidation sequence of ketosulfoxonium ylide: D. P. Day, J. A. M. Vargas and A. C. B. Burtoloso, *J. Org. Chem.*, 2021, **86**, 12427–12435.
- 19 For *In situ* generation of  $\text{HN}_3$ : D. J. Guerin and S. J. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 2134–2136.
- 20 Selected reviews of hydrogen bonding catalysis: (a) Y. Takemoto, *Org. Biomol. Chem.*, 2005, **3**, 4299–4306; (b) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713–5743; (c) Z. Zhang and P. R. Schreiner, *Chem. Soc. Rev.*, 2009, **38**, 1187–1198; (d) J. Alemán, A. Parra, H. Jiang and K. A. Jørgensen, *Chem.-Eur. J.*, 2011, **17**, 6890–6899; (e) T. Akiyama and K. Mori, *Chem. Rev.*, 2015, **115**, 9277–9306; (f) T. James, M. van Gemmeren and B. List, *Chem. Rev.*, 2015, **115**, 9388–9409; (g) J. Kikuchi and M. Terada, *Chem.-Eur. J.*, 2021, **27**, 10215–10225.
- 21 (a) L. G. Mancheño, *Anion-Binding Catalysis*, Wiley-VCH, 5<sup>th</sup> edn, 2022; (b) K. Brak and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2013, **52**, 534–561.
- 22 For a selected review and leading examples of enhancing Brønsted acid reactivity by hydrogen bond donors: (a) H. Yamamoto and K. Futatsugi, *Angew. Chem., Int. Ed.*, 2005, **44**, 1924–1942; (b) T. Weil, M. Kotke, C. M. Kleiner and P. R. Schreiner, *Org. Lett.*, 2008, **10**, 1513–1516; (c) R. S. Klausen and E. N. Jacobsen, *Org. Lett.*, 2009, **11**, 887–890; (d) D. A. Strassfeld, R. F. Algera, Z. K. Wickens and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2021, **143**, 9585–9594.



- 23 **SQ3** was first developed by Jacobsen and co-workers: H. Zhang, S. Lin and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2014, **136**, 16485–16488.
- 24 For unsuccessful examples in scope study, see ESI† for details.
- 25 (a) D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835–875; (b) R. D. Santo, R. Costi, A. Roux, M. Artico, O. Befani, T. Meninno, E. Agostinelli, P. Palmegiani, P. Turini, R. Cirilli, R. Ferretti, B. Gallinella and F. L. Torre, *J. Med. Chem.*, 2005, **48**, 4220–4223.
- 26 (a) We also attempted to examine aliphatic keto sulfoxonium ylides, but these sulfoxonium ylides were either unreactive or difficult to prepare; (b) We also tried the direct click reaction, but it led to erosion in enantiopurity.; (c) The enantiopurity of **2a** was stable in the presence of PhCO<sub>2</sub>H, indicating H/D exchange after product formation was not responsible for this result.; (d) Notably, the product enantiopurity decreased in the presence of some acids and bases, such as **CPA1**, **SQ1** (cinchona alkaloid) and Et<sub>3</sub>N. This also explained the difficulty in search for a suitable catalyst for this process.
- 27 N. M. Rezayee, V. J. Enemærke, S. T. Linde, J. N. Lamhauge, G. J. Reyes-Rodríguez, K. A. Jørgensen, C. Lu and K. N. Houk, *J. Am. Chem. Soc.*, 2021, **143**, 7509–7520.
- 28 In order to reduce the computational effort, a simplified **SQ3** was employed in which a phenyl group was used in place of 1-pyrenyl group.
- 29 For a recent elegant example about catalytic asymmetric azidation under hydrogen bonding phase-transfer catalysis: J. Wang, M. A. Horwitz, A. B. Dürr, F. Ibba, G. Pupo, Y. Gao, P. Ricci, K. E. Christensen, T. P. Pathak, T. D. W. Claridge, G. C. Lloyd-Jones, R. S. Paton and V. Gouverneur, *J. Am. Chem. Soc.*, 2022, **144**, 4572–4584.

