Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2023, **14**, 12152

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

Parallel kinetic resolution of aziridines *via* chiral phosphoric acid-catalyzed apparent hydrolytic ring-opening†

Juan Liu, Yi-Ying Du, Yu-Shi He, Yan Liang, Shang-Zhong Liu, Yi-Yi Li and Yi-Ming Cao *

Received 27th July 2023
Accepted 10th October 2023

DOI: 10.1039/d3sc03899h

rsc.li/chemical-science

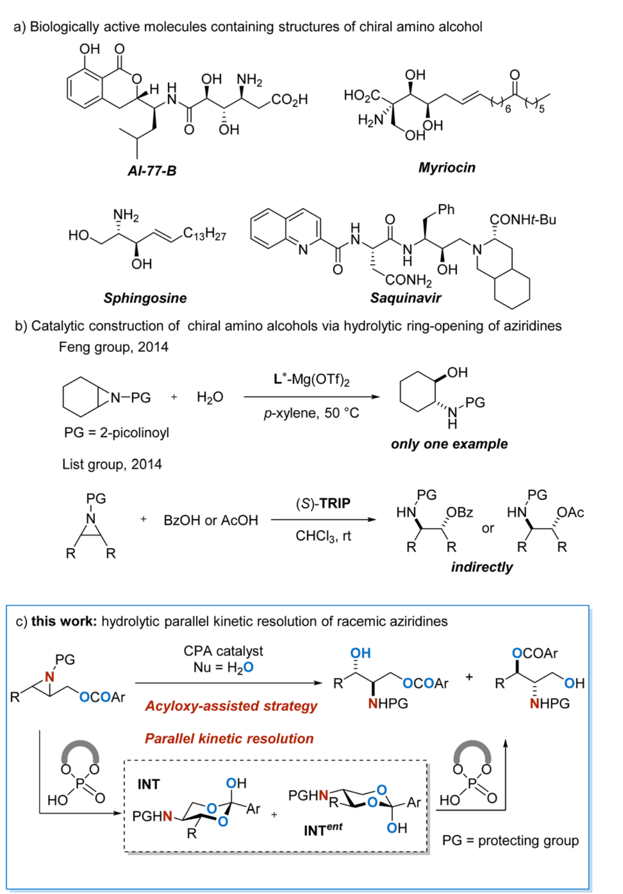
We report a chiral phosphoric acid catalyzed apparent hydrolytic ring-opening reaction of racemic aziridines in a regiodivergent parallel kinetic resolution manner. Harnessing the acyloxy-assisted strategy, the highly stereocontrolled nucleophilic ring-opening of aziridines with water is achieved. Different kinds of aziridines are applicable in the process, giving a variety of enantioenriched aromatic or aliphatic amino alcohols with up to 99% yields and up to >99.5 : 0.5 enantiomeric ratio. Preliminary mechanistic study as well as product elaborations were inducted as well.

Open Access Article. Published on 12 2023. Downloaded on 07-10-2024 3:22:43. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Introduction

Enantiopure β-amino alcohols are frequently encountered in natural products and synthetic molecules[1] which display diverse bioactivities and excellent potential for pharmaceutical use (Scheme 1a).[2] In addition, these units are frequently used as chiral auxiliaries and ligands in asymmetric synthesis.[3] Due to the significant importance of such essential structural motifs, considerable attention has been paid to their enantioselective construction,[4] and a variety of methods have been reported.[5] The catalytic asymmetric hydrolytic ring-opening of aziridines[6] provides an inherently efficient and atom-economical approach for the construction of chiral β-amino alcohols. Nonetheless, water is a rather inert nucleophile that is difficult to activate and control,[7] rendering the method a daunting challenge. In 2014, Feng and co-workers realized a chiral magnesium(II)-catalyzed direct asymmetric ring-opening of *meso*-aziridine with H_2O as the nucleophile (Scheme 1b),[7i] and this is to the best of knowledge, the only work on non-enzymatic catalytic enantioselective hydrolytic ring-opening of aziridines reported so far.[8] In organocatalysis, List and co-workers reported a chiral phosphoric acid catalyzed aziridine ring-opening reaction using carboxylic acid as the nucleophile,[9] which can be considered as an indirect version of asymmetric hydrolysis. In this context, the development of direct asymmetric hydrolytic ring-opening of aziridines (Scheme 1c), especially in organocatalysis, is highly demanded.

Recently, Christmann *et al.* reported a unique catalytic asymmetric halohydroxylation of unactivated alkenes using water as the nucleophile.[10] In their strategy, an intramolecular assisting



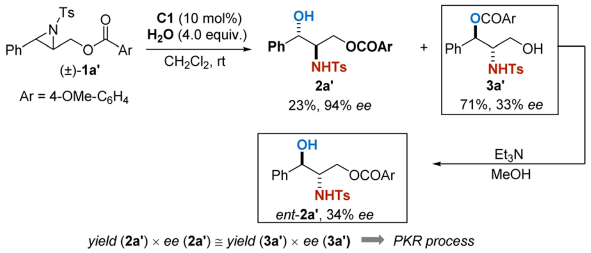
Scheme 1 Enantioselective construction of amino alcohols *via* enantioselective hydrolytic ring-opening of aziridines.

College of Science & China Key Laboratory of National Forestry and Grassland Administration on Pest Chemical Control, China Agricultural University, Beijing 100193, China. E-mail: caoym@cau.edu.cn

† Electronic supplementary information (ESI) available: Experimental procedure, spectral data, NMR-data, and HPLC-data. CCDC 2244430. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3sc03899h

© 2023 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 12 2023. Downloaded on 07-10-2024 3:22:43.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



Scheme 2 Preliminary study on the hydrolytic parallel kinetic resolution.

group is designed to activate H_2O as a nucleophile by forming a temporally covalent interaction. We wondered whether a similar idea would facilitate the hydrolytic ring-opening of aziridines. To our delight, in the preliminary experiment, racemic aziridine (±)-**1a′** successfully transformed into the corresponding products **2a′** and **3a′** in the presence of 4 equivalents of water and 10 mol% of chiral phosphoric acid **C1** (ref. 11*a*) as the catalyst. The relationship between yields and ee is indicative of a parallel kinetic resolution process. When the acyl group was sterically substituted (3,5-di-*tert*-Bu), the enantioselectivity of the reaction was significantly improved, given the approach highly promising to be further optimized (Scheme 2).

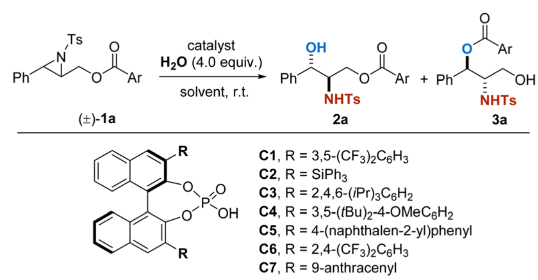
Parallel kinetic resolution (PKR) is a unique type of resolution,[12,13] in which the conversions of both enantiomers of a racemate proceed at similar rates, giving two separable chiral compounds as the products. This relatively uncommon class of reaction has considerable potential compared to traditional kinetic resolution (KR).[14] However, it is a complicated task for one catalyst to accurately discriminate the enantiomers in a racemic mixture, yielding the two products in different directions according to their configurations. Therefore, in sharp contrast to the traditional resolution, much less successful examples have been reported on PKR.[15] Most of the studies developed so far in this field involve metal catalysis,[16] whilst examples of catalytic PKRs in enantioselective organocatalysis are, however, very limited.[10,17]

Chiral phosphoric acids (CPAs),[14k,18] as an important class of organocatalysts, have been widely studied in asymmetric catalysis for their broad spectrum and efficient catalytic characteristics. Though, reports on CPA-catalyzed PKR are scarce. In 2010, List and co-workers reported CPA-catalyzed kinetic resolution of homoaldols *via* intramolecular transacetalization,[19] wherein partial PKR was observed when the substrate was linear aliphatic substituted homoaldol; the group later reported a stereodivergent PKR in racemic diol acetalization[20] and epoxide ring-opening[21] with CPA as a catalyst. In 2011, Ding and co-workers demonstrated the CPA catalyzed Baeyer–Villiger oxidation of racemic cyclobutanones to form regioisomeric lactones in optically enriched forms.[22] In 2019, Zheng and co-workers developed an efficient PKR of acyclic aliphatic *syn*-1,3-diol derived acetals in the presence of CPA.[17e] Very recently, Terada and co-workers reported a unique dynamic parallel kinetic resolution of the α-ferrocenyl cation initiated by the CPA catalyst.[17f] Although handful of examples were reported as mentioned, such a challenging field is still in its infancy, and new strategies as well as systematic development are highly desirable. Herein, we are glad to disclose a CPA-catalyzed asymmetric hydrolytic ring-opening of racemic aziridines *via* regiodivergent PKR, providing a new approach for the synthesis of chiral β-amino alcohols.

We commenced the investigation by using racemic aziridine **1a** as a model substrate (Table 1). A variety of BINOL-derived CPA catalysts were evaluated (entries 2–7), and **C7** (ref. 11*b*) was found to be the superior one, giving **2a** with 99 : 1 enantiomeric ratio (er) and **3a** with >99.5 : 0.5 er (entry 6). Notably, decreasing the catalyst loading from 10 mol% to 5 mol% resulted in almost the same outcomes in an acceptable reaction time (14 h, entry 7). The solvents were further screened and it was found that CH_2Cl_2 remains to be the optimal one. Ultimately, catalyst **C7** in 5 mol% loading, together with CH_2Cl_2 as the solvent showed the best performance, giving **2a** and **3a** in excellent yields and enantioselectivities.

With the optimized conditions in hand, the substrate scope of this parallel kinetic resolution was assessed. Different racemic aryl substituted aziridines were evaluated (Table 2). Aziridines bearing both electron-withdrawing or -donating groups in *para* or *meta* positions on the phenyl ring proceeded smoothly and the corresponding products **2** and **3** were

Table 1 Optimization of the reaction conditions[a]

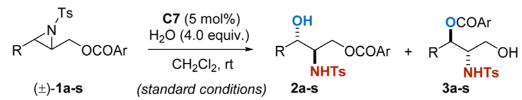


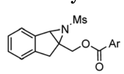
Entry	Cat.	Solv.	Cat. (mol%)	Ratio 3/2	er 2	er 3	Time (h)
1	**C1**	CH_2Cl_2	10	1.12	98 : 2	94 : 6	2
2	**C2**	CH_2Cl_2	10	1.11	90 : 10	87.5 : 12.5	48
3	**C3**	CH_2Cl_2	10	1.07	99 : 1	96 : 4	14
4	**C4**	CH_2Cl_2	10	0.98	72 : 28	72.5 : 27.5	4
5	**C5**	CH_2Cl_2	10	1.09	97 : 3	95 : 5	2
6	**C7**	CH_2Cl_2	10	1.04	99 : 1	>99.5 : 0.5	3
7	**C7**	**CH_2Cl_2**	**5**	**1.03**	**99 : 1**	**>99.5 : 0.5**	**14**
8	**C7**	Toluene	5	0.94	97 : 3	98.5 : 1.5	16
9[b]	**C7**	Et_2O	5	1.01	95 : 5	99 : 1	>72
10[b]	**C7**	EtOAc	5	1.02	95 : 5	97 : 3	>72

[a] Unless otherwise noted, reactions were performed on a 0.05 mmol scale in 1.0 mL solvent at rt; >95% conversion was achieved after the indicated time; ratios were determined by ^1H NMR analysis of the crude mixture; ers were determined by HPLC; Ar = 3,5-(*t*-Bu)$_2$-4-MeO-C_6H_2. [b] The reactions were sluggish and substrates were not fully consumed.

Open Access Article. Published on 12 2023. Downloaded on 07-10-2024 3:22:43.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Table 2 Scope of the aromatic aziridines[a]



Entry	R		2 Yield (%)	2 er		3 Yield (%)	3 er	Time (h)
1	C_6H_5	**2a**	48	99 : 1	**3a**	50	>99.5 : 0.5	14
2	4-F-C_6H_4	**2b**	49	99.5 : 0.5	**3b**	50	>99.5 : 0.5	14
3	4-Cl-C_6H_4	**2c**	43	99 : 1	**3c**	53	96 : 4	14
4	4-Br-C_6H_4	**2d**	46	98 : 2	**3d**	48	95 : 5	46
5[b]	4-CF_3-C_6H_4	**2e**	46	98 : 2	**3e**	51	97 : 3	48
6[c]	4-Me-C_6H_4	**2f**	43	98 : 2	**3f**	48	90.5 : 9.5	5
7	3-F-C_6H_4	**2g**	49	97.5 : 2.5	**3g**	45	>99.5 : 0.5	48
8	3-Cl-C_6H_4	**2h**	47	97.5 : 2.5	**3h**	48	>99.5 : 0.5	60
9	3-Br-C_6H_4	**2i**	46	98 : 2	**3i**	48	>99.5 : 0.5	72
10	3-MeO-C_6H_4	**2j**	46	97.5 : 2.5	**3j**	45	98 : 2	12
11	3-Me-C_6H_4	**2k**	46	99 : 1	**3k**	45	99.5 : 0.5	12
12	2-F-C_6H_4	**2l**	48	99 : 1	**3l**[d]	48	99 : 1	72
13[b]	2-Cl-C_6H_4	**2m**	46	98.5 : 1.5	**3m**	50	97.5 : 2.5	46
14[b]	2-Br-C_6H_4	**2n**	45	99.5 : 0.5	**3n**	52	95.5 : 4.5	70
15[b]	2-Me-C_6H_4	**2o**[d]	46	99.5 : 0.5	**3o**[d]	47	99 : 1	5
16[c]	1-Naphthyl	**2p**	45	97 : 3	**3p**[e]	46	93.5 : 6.5	14
17[f]	2-Naphthyl	**2q**	46	90 : 10	**3q**	44	91 : 9	12
18[g]	4-Phenyl	**2r**	44	99 : 1	**3r**	46	98 : 2	12
19		**2s**	48	90 : 10	**3s**	47	90 : 10	16

[a] Unless otherwise noted, reactions were performed on a 0.1 mmol scale in 2 mL CH_2Cl_2 at rt for the indicated time; yields are of isolated products; ers were determined by HPLC; Ar = 3,5-(*t*-Bu)$_2$-4-MeO-C_6H_2. [b] *N*-Mesyl aziridine was used as a substrate. [c] **C6** was used as the catalyst. [d] ers are determined after derivatization. [e] Yields and ers are determined after derivatization. [f] 10 mol% catalyst was used. [g] **C3** was used as the catalyst.

© 2023 The Author(s). Published by the Royal Society of Chemistry

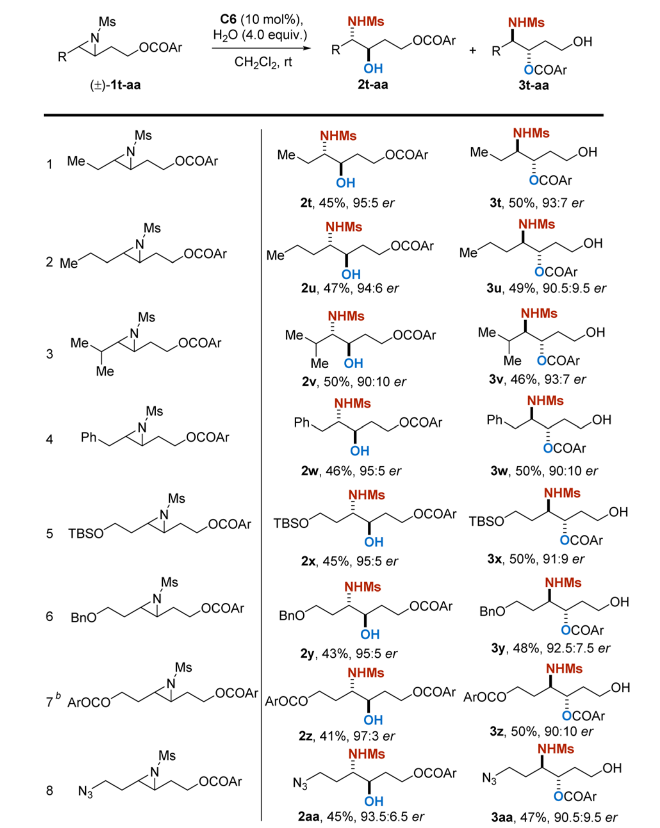
Open Access Article. Published on 12 2023. Downloaded on 07-10-2024 3:22:43. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

obtained in excellent yields and enantioselectivities (entries 2–11). *Ortho*-position-substituted racemic starting materials were also well tolerated under optimal conditions, providing excellent PKR performances, albeit a slower reaction rate was observed possibly due to steric hindrance (entries 12–14). The electronic properties of substituents on the phenyl rings of aziridines have a great impact on their reaction activities, for the electron-deficient substituents require a prolonged reaction time. It is worth noting that a sterically hindered 1-naphthyl derivative was feasible, giving the corresponding **2p** in 45% yield with 97 : 3 er and **3p** in 46% yield with 93.5 : 6.5 er (entry 16). Indene-derived aziridine **1s** was also compatible, although with lower enantioselectivity (90 : 10 er, entry 19). Alcoholysis of **2a** produced its amino alcohol derivative, of which the absolute configuration was unambiguously determined by X-ray crystallography (see Scheme 4a and ESI†).[23]

Encouraged by the satisfactory results obtained, we further broaden the substrate scope for PKR to alkyl-substituted aziridines, for their products, aliphatic amino alcohols, were found to be more common units in bioactive molecules. However, as the aliphatic aziridines are not electronically biased as aromatic ones, such substrates are relatively inert and hard to be activated for the transformation. As expected, aliphatic aziridine *rac*-**1t** as a substrate under the standard conditions resulted in a sluggish reaction. Therefore, several kinds of catalysts that are more electron-deficient were further screened (see the ESI†).[24] Gratifyingly, **C6** (R = 2,4-$(CF_3)_2C_6H_3$)[24c] as a catalyst was found to be satisfactory, resulting in **2t** and **3t** in excellent yield and high enantioselectivity (see the ESI†). Various kinds of alkyl-substituted aziridines reacted smoothly under the modified catalytic system, and a range of aliphatic chiral amino alcohols were synthesized (Table 3). Et, *n*-Pr, *i*-Pr and Bn substituted aziridines were well tolerated, providing the secondary alcohol products **2t–2w** with 90 : 10 er to 95 : 5 er and the primary alcohol products **3t–3w** with 90 : 10 er to 93 : 7 er (entries 1–4). Aziridines with terminal hydroxyl groups protected by silyl, benzyl and acyl-groups were amendable as well, and corresponding products were obtained in excellent yield and good to excellent enantioselectivity (entries 5–7). In addition, aziridine with an azide substitution was also applicable, which provided a convenient site for further derivatization (entry 8). It is noteworthy that the hydrolyses are all highly regioselective, although there is no electron effect provided by the aromatic ring as before in the examples in Table 2.

To further understand the mechanism of this developed reaction, control experiments were conducted (Scheme 3). Reaction employing Bn- instead of acyl-protected 2,3-aziridinyl alcohol was performed under the standard conditions, and no reaction took place, implying that the presence of an acyloxy moiety as an assisting group is crucial for the reaction to occur (Scheme 3a). When racemic constitutional isomers *rac*-**2a** or *rac*-**3a** were subjected to the standard conditions, no resolution was observed, which rules out the mechanisms involving interconversion between products (Scheme 3b). An isotopic labeling experiment was performed by using $H_2{}^{18}O$ instead of H_2O

Table 3 Scope of the aliphatic aziridines[a]

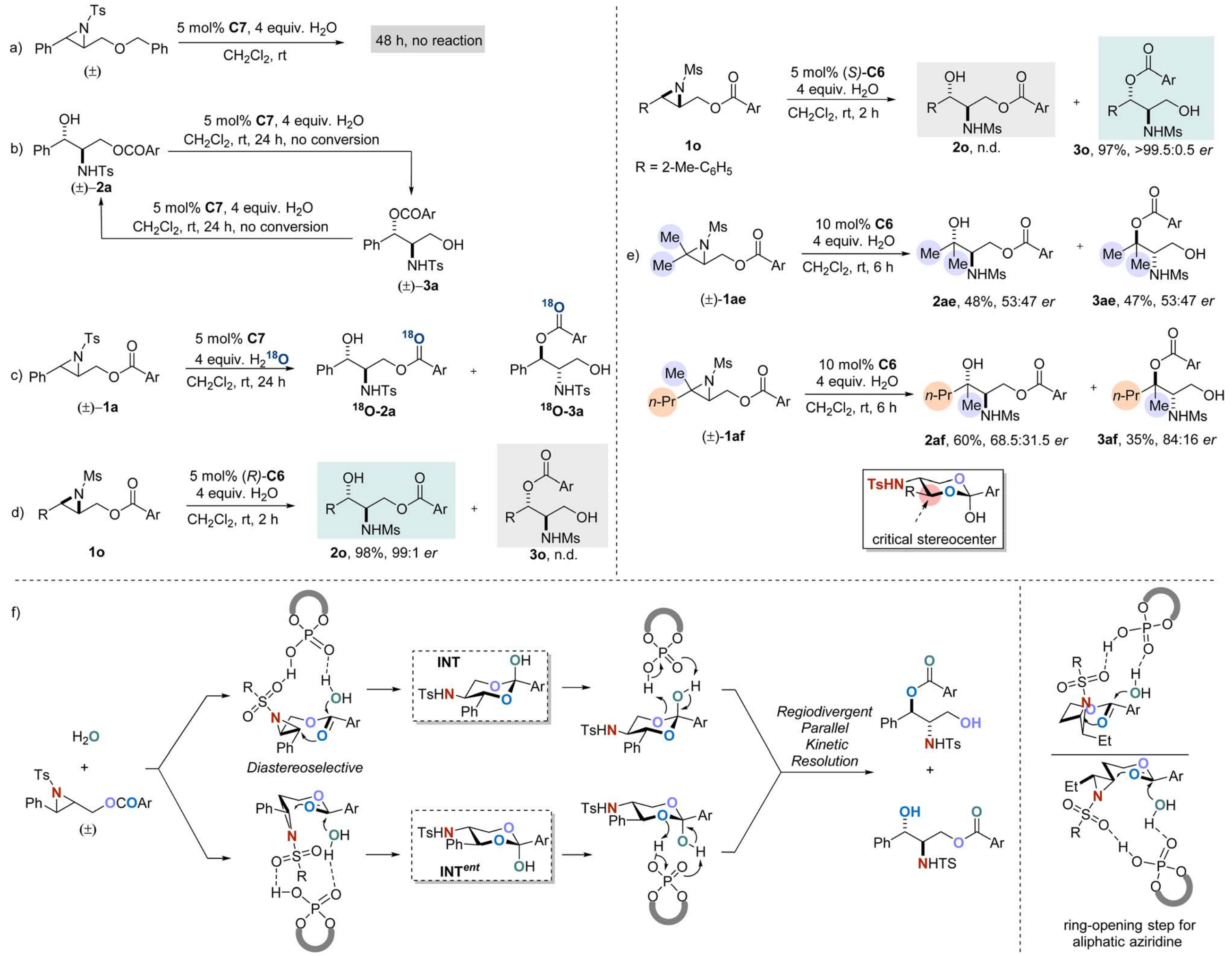


[a] Unless otherwise noted, reactions were performed on a 0.1 mmol scale in 2 mL CH_2Cl_2 at rt for the indicated time; yields are of isolated products; ers were determined by HPLC; Ar = 3,5-(*t*-Bu)$_2$-4-MeO-C_6H_2. [b] **C7** was used as the catalyst.

(Scheme 3c), and the transformation resulted in an installation of both isomers with the ^{18}O atom exclusively on the carbonyl group (see the ESI†). The outcome demonstrated that the addition of water proceeds *via* the assistance of acyloxyl but not a direct nucleophilic addition. Furthermore, enantiopure aziridine substrate **1o** was subjected to the standard conditions. As anticipated, the reaction with (*R*)-**C6** exclusively generated **2o**, while the catalyst (*S*)-**C6** with opposite configuration selectively afforded the corresponding product **3o** (Scheme 3d). The performance of aziridine *rac*-**1ae** with two identical methyl substituents was evaluated, and this resulted in products **2ae** and **3ae** in almost racemic form. In contrast, when we subjected the disubstituted aziridine *rac*-**1af** with different substituents (methyl and *n*-propyl groups) to the reaction, the products **2af** and **3af** were both obtained with significantly increased er values (Scheme 3e). These results suggested that the steric difference at the carbon in the small ring distal to the acyloxy group is essential for the catalyst to discriminate substrates.

On the basis of these results from the control experiments, a plausible reaction mechanism for the parallel kinetic resolution process is proposed (Scheme 3f). First, aziridine and H_2O

Open Access Article. Published on 12 2023. Downloaded on 07-10-2024 3:22:43.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



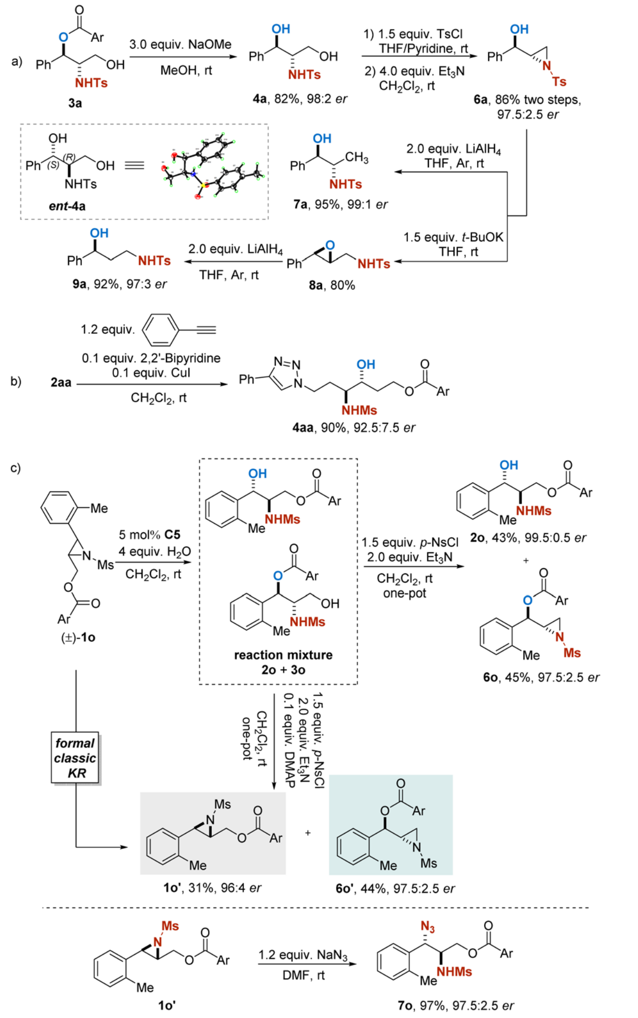
Scheme 3 Preliminary study of the mechanism: (a) reaction of substrate without assisting group. (b) Products interconversion experiment. (c) Isotopic labeling experiment. (d) Reactions with enantiopure substrate. (e) Steric effect studies. (f) Proposed mechanism.

are both activated by CPA, and the two ends are connected by a double nucleophilic attack sequence throughout the carbonyl group in the substrate. During the course, the critical intermediates, racemic cyclic hemi-orthoesters (**INT** and *ent*-**INT**) containing three stereocenters are formed with excellent diastereoselectivity. Afterwards, the resulting two enantiomers of hemi-orthoester are regiodivergently protonated by CPA, leading to the corresponding final products.

Furthermore, transformations of the obtained products from this approach were presented for the elaboration of its synthetic utility (Scheme 4). Alcoholysis of isomer **3a** readily provided 1,3-dihydroxy-2-amino compound **4a**. Selective tosylation of **4a** followed by treatment with Et_3N regenerated a terminal aziridine **6a** in 86% yield and 97.5 : 2.5 er. Reduction of **6a** with $LiAlH_4$ successfully afforded β-*N*-tosylaminoalcohol **7a** in 95% yield and 99 : 1 er. In addition, treatment of **6a** with *t*-BuOK gave aza-Payne rearrangement product **8a.** The γ-*N*-tosylated amino alcohol **9a** could be obtained by further transformation of **8a** with $LiAlH_4$ in 92% yield with maintained enantiopurity (Scheme 4a). Compound **9a** is of interest as an intermediate in the synthesis of fluoxetine, which is a drug for treating depression and other disorders.[25] Through the azide–alkyne cycloaddition, **2aa** was transformed into a triazole (**4aa**) with almost complete retention of the stereochemical integrity (Scheme 4b).

As shown in Scheme 4c, treatment of the reaction mixture containing products **2o** and **3o** after the PKR with *p*-NsCl and Et_3N resulted in a selective transformation, in which the primary alcohol **3o** could be readily converted into terminal aziridine **6o** with high efficiency, while the secondary alcohol **2o** remained. However, when DMAP was additionally employed, the secondary alcohol **2o** could be transformed into enantioenriched aziridine **1o**′ as well. The obtained internal aziridine appeared to be one of the enantiomers of the starting materials in the PKR reaction, and this one-pot procedure resulted in a formal traditional KR of racemic aziridine **1o.** Enantioenriched aziridines provided by the transformations mentioned above are synthetically useful for their propensity to

Open Access Article. Published on 12 2023. Downloaded on 07-10-2024 3:22:43.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



Scheme 4 Transformations of the product: (a) derivatizations of **3a**. (b) Azide–alkyne reaction of **2aa**. (c) Reactions of **1o**.

undergo ring-opening reactions to give a series of functionalized molecules. For instance, by treatment of NaN_3, chiral azido amide **7o** could be regioselectively obtained in 97% yield with 97.5 : 2.5 er.

Conclusions

In summary, we reported an intriguing CPA-catalyzed asymmetric hydrolytic ring-opening of racemic aziridines *via* regiodivergent PKR. A wide array of aromatic and aliphatic aziridines were well compatible, providing amino alcohol derivatives in generally excellent yield and enantioselectivities. Preliminary mechanistic studies indicate that such a PKR process may have proceeded *via* the formation of cyclic hemi-orthoester intermediates and a subsequent regiodivergent resolution. In addition, facile and versatile transformations of the enantioenriched products demonstrated the utilities of the method in asymmetric synthesis. Further study on the mechanism as well as the applications of this methodology are underway.

Data availability

All experimental data and detailed procedures are available in the ESI.†

Author contributions

J. L. performed the main part of the experiments, and prepared the ESI† and manuscript. Y.-Y. D. participated in the synthesis of substrates, compound characterization, and ESI† preparation. Y.-S. H. and Y. L. participated in the synthesis of substrates and discussion. S.-Z. L. and Y.-Y. L. participated in the discussion and helped with the optimization of the manuscript. Y.-M. C. conceived and directed the project. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the financial support from the National Key R&D Program (2022YFD1700403) and the 2115 Talent Development Program of China Agricultural University.

Notes and references

1 (*a*) I. Gallou and C. H. Senanayake, *Chem. Rev.*, 2006, **106**, 2843; (*b*) P. Zhang, D. J. Dairaghi, J. C. Jaen and J. P. Powers, in *Annual Reports in Medicinal Chemistry*, ed. M. C. Desai, Academic Press, New York, 2013, vol. 48, p. 133.
2 (*a*) H. Umezawa, T. Aoyagi, H. Suda, M. Hamada and T. Takeuchi, *J. Antibiot.*, 1976, **29**, 97; (*b*) J. Kobayashi, J.-F. Cheng, M. Ishibashi, M. R. Wälchli, S. Yamamura and Y. Ohizumi, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1135; (*c*) Y. A. Hannun and C. M. Linardic, *Biochim. Biophys. Acta, Biomembr.*, 1993, **1154**, 223; (*d*) Y. Ohta and I. Shinkai, *Bioorg. Med. Chem.*, 1997, **5**, 465.
3 (*a*) D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835; (*b*) J. L. Vicario, D. Badia, L. Carrillo, E. Reyes and J. Etxebarria, *Curr. Org. Chem.*, 2005, **9**, 219; (*c*) G. Della Sala, A. Russo and A. Lattanzi, *Curr. Org. Chem.*, 2011, **15**, 2147; (*d*) U. V. S. Reddy, M. Chennapuram, C. Seki, E. Kwon, Y. Okuyama and H. Nakano, *Eur. J. Org Chem.*, 2016, **2016**, 4124.
4 For selected reviews, see: (*a*) S. C. Bergmeier, *Tetrahedron*, 2000, **56**, 2561; (*b*) F. D. Klingler, *Acc. Chem. Res.*, 2007, **40**, 1367; (*c*) O. N. Burchak and S. Py, *Tetrahedron*, 2009, **65**, 7333; (*d*) T. J. Donohoe, C. K. A. Callens, A. Flores, A. R. Lacy and A. H. Rathi, *Chem. – Eur. J.*, 2011, **17**, 58; (*e*) C. Weng, H. Zhang, X. Xiong, X. Lu and Y. Zhou, *Asian J. Chem.*, 2014, **26**, 3761; (*f*) H. Sasai, in *Comprehensive Organic Synthesis II*, ed. P. Knochel, and G. A. Molander, Elsevier, Amsterdam, 2014, vol. 2, p. 543.
5 For selected examples, see: (*a*) S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai and M. Shibasaki, *J. Am. Chem.*

Open Access Article. Published on 12 2023. Downloaded on 07-10-2024 3:22:43.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Soc., 2004, **126**, 8777; (*b*) B. M. Trost, J. Jaratjaroonphong and V. Reutrakul, *J. Am. Chem. Soc.*, 2006, **128**, 2778; (*c*) J.-H. Xie, S. Liu, W.-L. Kong, W.-J. Bai, X.-C. Wang, L.-X. Wang and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2009, **131**, 4222; (*d*) K. S. Williamson and T. P. Yoon, *J. Am. Chem. Soc.*, 2012, **134**, 12370; (*e*) H.-C. Shen, Y.-F. Wu, Y. Zhang, L.-F. Fan, Z.-Y. Han and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2018, **57**, 2372; (*f*) M. Tang, H. Gu, S. He, S. Rajkumar and X. Yang, *Angew. Chem., Int. Ed.*, 2021, **60**, 21334.

6 For selected reviews on ring-opening reaction of racemic aziridines: (*a*) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701; (*b*) S. Stanković, M. D'Hooghe, S. Catak, H. Eum, M. Waroquier, V. V. Speybroeck, N. D. Kimpe and H.-J. Ha, *Chem. Soc. Rev.*, 2012, **41**, 643; (*c*) R. Akhtar, S. A. R. Naqvi, A. F. Zahoor and S. Saleem, *Mol. Diversity*, 2018, **22**, 447; (*d*) Z. Chai, *Synthesis*, 2020, **52**, 1738. For selected reviews on ring-opening reaction of meso-aziridines:; (*e*) M. Pineschi, *Eur. J. Org Chem.*, 2006, **2006**, 4979; (*f*) C. Schneider, *Angew. Chem., Int. Ed.*, 2009, **48**, 2082; (*g*) P.-A. Wang, *Beilstein J. Org. Chem.*, 2013, **9**, 1677; (*h*) P.-J. Yang and Z. Chai, *Org. Biomol. Chem.*, 2023, **21**, 465.

7 For selected examples using water as a nucleophile: (*a*) M. Tokunaga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936; (*b*) J. M. Ready and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2001, **123**, 2687; (*c*) S.-F. Zhu, C. Chen, Y. Cai and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2008, **47**, 932; (*d*) S.-F. Zhu, Y. Cai, H.-X. Mao, J.-H. Xie and Q.-L. Zhou, *Nat. Chem.*, 2010, **2**, 546; (*e*) G. Dong, P. Teo, Z. K. Wickens and R. H. Grubbs, *Science*, 2011, **333**, 1609; (*f*) M. Gärtner, S. Mader, K. Seehafer and G. Helmchen, *J. Am. Chem. Soc.*, 2011, **133**, 2072; (*g*) N. Kanbayashi and K. Onitsuka, *Angew. Chem., Int. Ed.*, 2011, **50**, 5197; (*h*) D. D. Ford, L. P. C. Nielsen, S. J. Zuend, C. B. Musgrave and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2013, **135**, 15595; (*i*) J. Li, Y. Liao, Y. Zhang, X. Liu, L. Lin and X. Feng, *Chem. Commun.*, 2014, **50**, 6672; (*j*) Q.-K. Kang, L. Wang, Q.-J. Liu, J.-F. Li and Y. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 14594; (*k*) X. Zhang, J. Li, H. Tian and Y. Shi, *Chem. – Eur. J.*, 2015, **21**, 11658; (*l*) W. Guo, L. Martínez-Rodríguez, E. Martin, E. C. Escudero-Adán and A. W. Kleij, *Angew. Chem., Int. Ed.*, 2016, **55**, 11037; (*m*) W. Li, P. Zhou, G. Li, L. Lin and X. Feng, *Adv. Synth. Catal.*, 2020, **362**, 1982; (*n*) Z. Xi, X.-J. Liu, Z. Guo, Z. Gao, Z.-X. Yu and H. Gao, *Nat. Synth.*, 2023, **2**, 778; (*o*) J. Li, Z. Wang, X. Wang and Y. Shi, *Tetrahedron Chem*, 2023, **6**, 100039.

8 For enzyme-catalyzed reactions, see: (*a*) T. Watabe and S. Suzuki, *Biochem. Biophys. Res. Commun.*, 1972, **46**, 1120; (*b*) G. M. Lacourciere, V. N. Vakharia, C. P. Tan, D. I. Morris, G. H. Edwards, M. Moos and R. N. Armstrong, *Biochemistry*, 1993, **32**, 2610.

9 M. R. Monaco, B. Poladura, M. D. de Los Bernardos, M. Leutzsch, R. Goddard and B. List, *Angew. Chem., Int. Ed.*, 2014, **53**, 7063.

10 Y.-M. Cao, D. Lentz and M. Christmann, *J. Am. Chem. Soc.*, 2018, **140**, 10677.

11 (*a*) T. Akiyama, H. Morita, J. Itoh and K. Fuchibe, *Org. Lett.*, 2005, **7**, 2583; (*b*) D. Uraguchi, K. Sorimachi and M. Terada, *J. Am. Chem. Soc.*, 2005, **127**, 9360.

12 (*a*) E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1997, **119**, 2584; (*b*) H. B. Kagan, *Tetrahedron*, 2001, **57**, 2449.

13 After the concept of PKR was introduced, it is also used to describe the process in which only one catalyst is involved. Such a reaction is similar to the concept of divergent reaction on a racemic mixture (divergent RRM). In this article, PKR and divergent RRM are equal.

14 For selected reviews of KR, see: (*a*) H. B. Kagan and J. C. Fiaud, in *Topics in Stereochemistry*, ed. E. L. Eliel and S. H. Wilen, Wiley-VCH, Weinheim, 1988, vol. 18, p. 249; (*b*) G. R. Cook, *Curr. Org. Chem.*, 2000, **4**, 869; (*c*) J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5; (*d*) D. E. J. E. Robinson and S. D. Bull, *Tetrahedron: Asymmetry*, 2003, **14**, 1407; (*e*) E. Vedejs and M. Jure, *Angew. Chem., Int. Ed.*, 2005, **44**, 3974; (*f*) C. E. Müller and P. R. Schreiner, *Angew. Chem., Int. Ed.*, 2011, **50**, 6012; (*g*) H. Pellissier, *Adv. Synth. Catal.*, 2011, **353**, 1613; (*h*) G. Ma and M. P. Sibi, *Chem. – Eur. J.*, 2015, **21**, 11644; (*i*) R. Gurubrahamam, Y.-S. Cheng, W.-Y. Huang and K. Chen, *ChemCatChem*, 2016, **8**, 86; (*j*) I. Kreituss and J. W. Bode, *Acc. Chem. Res.*, 2016, **49**, 2807; (*k*) K. S. Petersen, *Asian J. Org. Chem.*, 2016, **5**, 308; (*l*) W. Liu and X. Yang, *Asian J. Org. Chem.*, 2021, **10**, 692.

15 For selected reviews of PKR, see: (*a*) H. B. Kagan, *Tetrahedron*, 2001, **57**, 2449; (*b*) J. R. Dehli and V. Gotor, *Chem. Soc. Rev.*, 2002, **31**, 365; (*c*) E. Vedejs and M. Jure, *Angew. Chem., Int. Ed.*, 2005, **44**, 3974; (*d*) R. R. Kumar and H. B. Kagan, *Adv. Synth. Catal.*, 2010, **352**, 231; (*e*) L. C. Miller and R. Sarpong, *Chem. Soc. Rev.*, 2011, **40**, 4550; (*f*) N. Funken, Y.-Q. Zhang and A. Gansäuer, *Chem. – Eur. J.*, 2017, **23**, 19.

16 For selected related examples in metal catalysis, see: (*a*) F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2001, **40**, 930; (*b*) K. Tanaka and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 8078; (*c*) K. Tanaka, Y. Hagiwara and M. Hirano, *Angew. Chem., Int. Ed.*, 2006, **45**, 2734; (*d*) A. Gansäuer, C.-A. Fan, F. Keller and J. Keil, *J. Am. Chem. Soc.*, 2007, **129**, 3484; (*e*) C. K. Jana and A. Studer, *Angew. Chem., Int. Ed.*, 2007, **46**, 6542; (*f*) D. Minato, Y. Nagasue, Y. Demizu and O. Onomura, *Angew. Chem., Int. Ed.*, 2008, **47**, 9458; (*g*) R. Webster, C. Böing and M. Lautens, *J. Am. Chem. Soc.*, 2009, **131**, 444; (*h*) B. Wu, J. R. Parquette and T. V. RajanBabu, *Science*, 2009, **326**, 1662; (*i*) A. Gansäuer, L. Shi and M. Otte, *J. Am. Chem. Soc.*, 2010, **132**, 11858; (*j*) D. Katayev, M. Nakanishi, T. Bürgi and E. P. Kündig, *Chem. Sci.*, 2012, **3**, 1422; (*k*) M. Mulzer, W. C. Ellis, E. B. Lobkovsky and G. W. Coates, *Chem. Sci.*, 2014, **5**, 1928; (*l*) B. Wu, J. C. Gallucci, J. R. Parquette and T. V. RajanBabu, *Chem. Sci.*, 2014, **5**, 1102; (*m*) Y. Xu, K. Kaneko, M. Kanai, M. Shibasaki and S. Matsunaga, *J. Am. Chem. Soc.*, 2014, **136**, 9190; (*n*) D. Grosheva and N. Cramer, *ACS Catal.*, 2017, **7**, 7417; (*o*) Y. Yuan, Z.-J. Zheng, L. Li, X.-F. Bai, Z. Xu, Y.-M. Cui, J. Cao,

 © 2023 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 12 2023. Downloaded on 07-10-2024 3:22:43.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

K.-F. Yang and L.-W. Xu, *Adv. Synth. Catal.*, 2018, **360**, 3002; (*p*) X. Wang, Y. Luo, J. Li, C. Wang, Q. Liu, Y. He, S. Luo and Q. Zhu, *ACS Catal.*, 2022, **12**, 14918.

17 For selected related examples in organocatalysis, see: (*a*) J. M. Rodrigo, Y. Zhao, A. H. Hoveyda and M. L. Snapper, *Org. Lett.*, 2011, **13**, 3778; (*b*) A. D. Worthy, X. Sun and K. L. Tan, *J. Am. Chem. Soc.*, 2012, **134**, 7321; (*c*) F. Romanov-Michailidis, M. Pupier, L. Guénée and A. Alexakis, *Chem. Commun.*, 2014, **50**, 13461; (*d*) C. R. Shugrue, A. L. Featherston, R. M. Lackner, A. Lin and S. J. Miller, *J. Org. Chem.*, 2018, **83**, 4491; (*e*) H. Yang and W.-H. Zheng, *Org. Lett.*, 2019, **21**, 5197; (*f*) Y. Toda, T. Korenaga, R. Obayashi, J. Kikuchi and M. Terada, *Chem. Sci.*, 2021, **12**, 10306; (*g*) K. Yamashita, R. Hirokawa, M. Ichikawa, T. Hisanaga, Y. Nagao, R. Takita, K. Watanabe, Y. Kawato and Y. Hamashima, *J. Am. Chem. Soc.*, 2022, **144**, 3913; (*h*) A. Adili, J.-P. Webster, C. Zhao, S. C. Mallojjala, M. A. Romero-Reyes, I. Ghiviriga, K. A. Abboud, M. J. Vetticatt and D. Seidel, *ACS Catal.*, 2023, **13**, 2240.

18 For selected reviews, see: (*a*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744; (*b*) M. Terada, *Chem. Commun.*, 2008, 4097; (*c*) D. Kampen, C. M. Reisinger and B. List, in *Asymmetric Organocatalysis*, ed. B. List, Topics in Current Chemistry, Springer, Berlin, 2010, vol. 291, p. 201; (*d*) M. Rueping, R. M. Koenigs and I. Atodiresei, *Chem. – Eur. J.*, 2010, **16**, 9350; (*e*) M. Terada, *Synthesis*, 2010, **2010**, 1929; (*f*) M. Rueping, A. Kuenkel and I. Atodiresei, *Chem. Soc. Rev.*, 2011, **40**, 4539; (*g*) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047; (*h*) R. Maji, S. C. Mallojjala and S. E. Wheeler, *Chem. Soc. Rev.*, 2018, **47**, 1142; (*i*) B. P. Neupane and G. K. Friestad, *Curr. Org. Chem.*, 2022, **26**, 991.

19 I. Čorić, S. Müller and B. List, *J. Am. Chem. Soc.*, 2010, **132**, 17370.

20 J. H. Kim, I. Čorić, C. Palumbo and B. List, *J. Am. Chem. Soc.*, 2015, **137**, 1778.

21 M. R. Monaco, D. Fazzi, N. Tsuji, M. Leutzsch, S. Liao, W. Thiel and B. List, *J. Am. Chem. Soc.*, 2016, **138**, 14740.

22 S. Xu, Z. Wang, X. Zhang and K. Ding, *Eur. J. Org Chem.*, 2011, **2011**, 110.

23 Deposition Number 2244430 (for ent-**4a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

24 (*a*) N. Momiyama, H. Okamoto, J. Kikuchi, T. Korenaga and M. Terada, *ACS Catal.*, 2016, **6**, 1198; (*b*) N. Momiyama, H. Nishimoto and M. Terada, *Org. Lett.*, 2011, **13**, 2126; (*c*) T. Sakamoto, J. Itoh, K. Mori and T. Akiyama, *Org. Biomol. Chem.*, 2010, **8**, 5448.

25 X.-M. Kan, J. Zhu, P.-H. Li, Z.-C. Wu and P.-J. Yang, *Tetrahedron*, 2023, **132**, 133263.