A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201900613
Angew. Chem. 10.1002/ange.201900613

Link to VoR: http://dx.doi.org/10.1002/anie.201900613
http://dx.doi.org/10.1002/ange.201900613

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10.1002/anie.201900613

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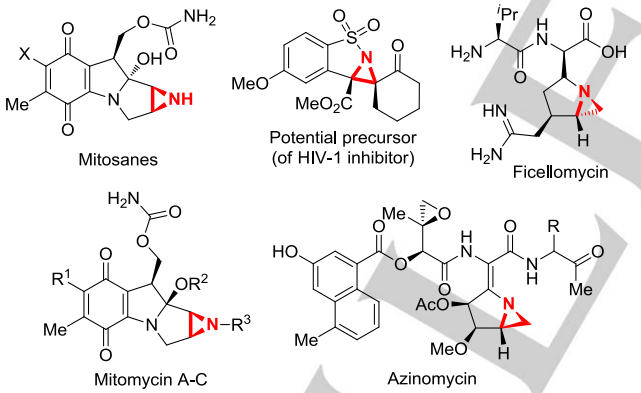
Highly Enantioselective Synthesis of Fused Tri- and Tetra-substituted Aziridines via Bifunctional Phosphonium Salt-Catalyzed Aza-Darzens Reaction **

Jianke Pan[†], Jia-Hong Wu[†], Hongkui Zhang, Xiaoyu Ren, Jian-Ping Tan, Lixiang Zhu, Hong-Su Zhang, Chunhui Jiang, and Tianli Wang*

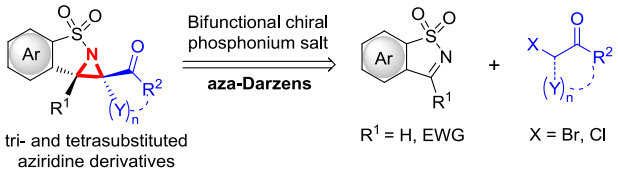
Abstract: *The first enantioselective aza-Darzens reaction of cyclic imines with α-halogenated ketones was realized under mild reaction conditions, by using amino acid-derived bifunctional phosphonium salts as phase-transfer promoters. A variety of structurally dense tri- and tetra-substituted aziridine derivatives, containing benzo-fused heterocycles as well as spiro structures, were readily synthesized in high yields with excellent diastereo- and enantioselectivities (up to >20:1 dr and >99.9% ee). The highly functionalized aziridine products could be easily transformed into different classes of biologically active compounds with significant synthetic challenge.*

Optically pure fused *N*-heterocycles, especially aziridine-containing molecules, are versatile intermediates in chemical synthesis,[1] and they are also prevalent building blocks in many biologically active compounds, including natural alkaloids and pharmaceutical agents (Scheme 1).[2] Accordingly, a number of catalytic methods have been devised for the stereoselective construction of such structural motif over the past two decades.[3-9] In this context, the aza-Darzens reaction becomes one of the most straightforward and efficient approaches for producing such ring systems.[5] Lewis and Brønsted acid-catalyzed aza-Darzens of α-diazoacetates and imines with offering aziridines were first disclosed by Brookhart, Templeton and co-workers, respectively.[6] The asymmetric variants of these acid catalyzed aza-Darzens reactions were pioneeringly reported by Wulff[7] and further developed by Maruoka[8] and others,[9] particularly providing *cis*- or/and *trans*-disubstituted aziridines in high yields with excellent stereoselectivities. However, less success has been achieved in direct construction of trisubstituted chiral aziridine scaffolds via this process; and only two examples were reported.[10] Maruoka and co-workers disclosed a chiral Brønsted acid-catalyzed aziridination between *N*-α-diazoacyl oxazolidinones and *N*-Boc imines, thus creating trisubstituted chiral aziridine skeletons.[10a] Quite recently, Trost developed a Zn-ProPhenol catalyzed aza-Darzens reaction of chlorinated aromatic ketones with *N*-Boc aldimines, providing a novel method for constructing trisubstituted chiral aziridine motifs.[10b] Although these impressive advances have been made, highly enantioselective preparation of trisubstituted aziridine rings is still synthetic challenge, let alone directly asymmetric synthesis of structurally dense tetrasubstituted chiral aziridine molecules. To the best of our knowledge, no general and straightforward catalytic protocol to access optically pure tetrasubstituted aziridines has been reported so far. Therefore, it is highly desirable to explore a utilitarian strategy to fill this void.



Scheme 1. Selected aziridine-containing bioactive molecules.

In this study, we attempted to develop an alternative approach to prepare structurally dense tri- and tetra-substituted aziridines with readily available catalysts and reagents. In the past decades, asymmetric phase-transfer catalysis (PTC) has been recognized as a powerful and versatile tool for the enantioselective synthesis of chiral compounds, and numerous quaternary ammonium salts[11] have been commonly employed in PTC. However, asymmetric PTC involving phosphonium salts as catalysts is still under-developed.[12, 13] The key breakthroughs in this field were recently reported by the groups of Maruoka[14] and Ooi.[15] Later, Ma and co-workers introduced a binol-derived *P*-spiro phosphonium salt and realized its use in asymmetric amination of benzofuranones.[16] More recently, the groups of Zhao[17] and Lu[18] derived several phosphonium salt catalysts from amino acids and initially demonstrated their effectiveness in asymmetric conjugate additions and substitution reactions. Notably, such amino acid-based phosphonium salts possess remarkably high tunability, but its utilization in asymmetric synthesis are rare to date. As part of our



Scheme 2. Construction of densely mutisubstituted aziridines via bifunctional phosphonium salt-catalyzed *aza*-Darzens reaction.

[*] J. Pan,[†] J.-H. Wu,[†] H. Zhang, X. Ren, J.-P. Tan, L. Zhu, H.-S. Zhang, Dr. C. Jiang, Prof. Dr. T. Wang
Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University
29 Wangjiang Road, Chengdu 610064 (P. R. China)
E-mail: wangtl@scu.edu.cn
Dr. C. Jiang
School of Environmental and Chemical Engineering, Jiangsu University of Science and Technology, 2 Mengxi Road, Zhenjiang 212003 (P. R. China)
[†] These authors contributed equally to this work.
Supporting information for this article can be found under: https://doi.org/10.1002/anie.2019xxxxx.

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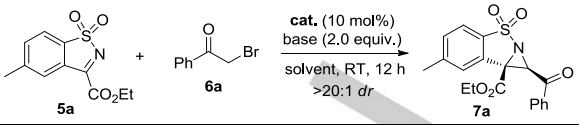
research interest in the development of asymmetric synthetic methods catalyzed by amino-acid-based organocatalysts,[19] we envisioned that employment of highly tunable bifunctional phosphonium salts may result in a practical asymmetric aza-Darzens cyclization protocol to construct densely tri- and tetra-substituted aziridine cores (Scheme 2). Herein, we describe our successful development of amino acid-derived bifunctional phosphonium salt-catalyzed enantioselective aza-Darzens reaction between cyclic imines and α-halogenated ketones. It provides facile access to structurally dense tri- and tetra-substituted chiral aziridines under mild conditions.

For our initial investigations, the aza-Darzens reaction between cyclic *N*-sulfonyl α-ketimino ester **5a** and α-bromoacetophenone **6a** was chosen as a model reaction to evaluate catalytic effects of the candidated bifunctional phosphonium salts (Table 1), which were prepared in our laboratory via a P-alkylation reaction of our previous organophosphines[19] with the appropriate alkyl halides. Pleasingly, all the phosphonium salts examined were effective in promoting this reaction, leading the desired aziridine products in moderate to excellent isolated yields with high diastereoselectivities. Generally, L-Valine-derived bifunctional phosphonium salts with a sulfonamide, amide, thiourea or dipeptide were found to be ineffective in asymmetric induction, affording the cyclization products with low ee values (entries 1−5). L-Threonine-derived dipeptide-based phosphonium salts were discovered favorable in stereochemical controls, furnishing the desired products with good diastereo- and enantioselectivities (entries 6−9). The O-TBDPS-L-Thr-D-*tert*-Leu-based phosphonium salt **4b** turned out to be the best, affording the Darzens reaction product in 93% yield and with 72% ee (entry 9). Subsequently, we further optimized the reaction condition of base (entries 10−14). Among all the bases tested, it was found that 4.0 equivalent of K_3PO_4 $7H_2O$ proved to be the best, and the ee value could be improved to 78% (entry 14). At last, a quick solvent screening (entries 15−17)[20] identified that the mixture of hexane/toluene (4/1, v/v) was the solvent of choice (entry 17). Indeed, only 5 mol% catalyst was also sufficient to promote this reaction, and the corresponding product was isolated in 93% yield with >99% ee (entry 18).

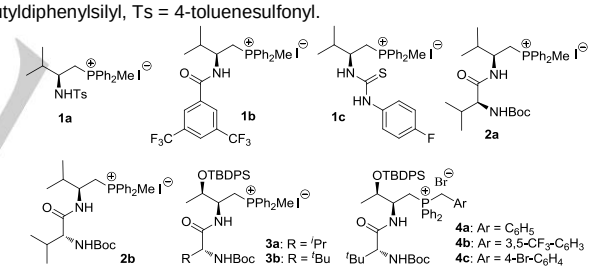
Having established the optimal reaction conditions, the substrate scope for aza-Darzens cyclization between cyclic imines and α-halogenated acetophenones was investigated for preparing tri- and di-substituted chiral aziridines (Table 2). In general, various cyclic ketimines bearing electron-neutral, -donating, or -withdrawing groups on the phenyl ring could be well employed, furnishing the corresponding products **7a**–**h** in high yields (86–96%) with excellent both diastereo- and enantioselectivities (>20:1 *dr*, 83–>99% ee). Additionally, when 1-naphthyl and 2-naphthyl-containing substrates were used, enantiomerically enriched products were also isolated in high yields with excellent stereoselectivities (**7g** and **7h**). The substrate bearing 2-Cl substitutent on the phenyl ring slightly lowered the enantioselectivity of the reaction (**7f**), mainly due to the steric hindrance. Subsequently, we further explored the substrate scope of α-bromo acetophenones under the optimal conditions. A wide range of α-bromoacetophenones **6** with substituents in the *ortho*-, *meta*-, or *para*-position of the phenyl ring proceeded very well to furnish the desired products **7i**–**o** in high yields (92–98%) with excellent ee values (87–>99% ee). Notably, thienyl and naphthyl substituted α-bromoketones also proved to be excellent substrates and afforded the products **7p** and **7q** with exceptionally high ee values as >99.9% and 98%, respectively. Moreover, the catalytic reactions worked well for cyclic aldimines **5'** when employing the α-chloro acetophenones **6'** as nucleophilic reaction partners,[19] giving the products (**8a**–**f**) with excellent stereoselectivities in high

Table 1: Optimization for the asymmetric *aza*-Darzens reaction of cyclic ketimine **5a** with α-bromoacetophenone **6a**.[a]



Entry	Cat.	Sol.	Base	Yield [%][b]	*ee* [%][c]
1	**1a**	toluene	Cs_2CO_3	63	31
2	**1b**	toluene	Cs_2CO_3	68	16
3	**1c**	toluene	Cs_2CO_3	57	37
4	**2a**	toluene	Cs_2CO_3	88	16
5	**2b**	toluene	Cs_2CO_3	96	34
6	**3a**	toluene	Cs_2CO_3	94	38
7	**3b**	toluene	Cs_2CO_3	93	48
8	**4a**	toluene	Cs_2CO_3	95	59
9	**4b**	toluene	Cs_2CO_3	93	72
10	**4b**	toluene	Na_2CO_3	75	70
11	**4b**	toluene	K_2CO_3	74	74
12	**4b**	toluene	K_3PO_4	78	68
13	**4b**	toluene	$K_3PO_4·7H_2O$	92	73
14[d]	**4b**	toluene	$K_3PO_4·7H_2O$	93	78
15[d]	**4b**	hexane	$K_3PO_4·7H_2O$	21	92
16[d]	**4b**	hexane/toluene (9/1, v/v)	$K_3PO_4·7H_2O$	61	99
17[d]	**4b**	hexane/toluene (4/1, v/v)	$K_3PO_4·7H_2O$	93	>99
18[d,e]	**4b**	hexane/toluene (4/1, v/v)	$K_3PO_4·7H_2O$	93	>99

[a] Reactions were performed with **5a** (0.05 mmol), **6a** (0.06 mmol), catalyst (0.005 mmol) and the base (2.0 equiv.) in solvent (0.5 mL) at room temperature for 12 h. All *dr* values were determined by ^{1}H NMR of crude product. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] 4.0 equivalent of base was used. [e] The catalyst loading was 5 mol% and the reaction time was 24 h. TBDPS = *tert*-butyldiphenylsilyl, Ts = 4-toluenesulfonyl.



isolated yields. The X-ray crystal of *rac*-**7a** was obtained[21], and the absolute configuration of the aza-Darzens products listed in Table 2 were assigned by comparing both the optical rotation and HPLC analysis of product **7a'** with previously reported results.[4j,20]

Encouraged by these results, we set our goal to extend this novel strategy to synthesize intimidating tetrasubstituted aziridine derivatives. This seems to be a formidable challenge as rarely that the constructed aziridines possess all-carbon quaternary stereogenic centers which were extremely sterically hindered; and we reasoned we may be able to tackle this task by using this highly tunable bifunctional phosphonium salt. To our delight, the aza-Darzens reaction between cyclic ketimines **5** and cyclic α-bromoketones **9** proceeded smoothly with affording the desirable tetrasubstituted aziridine products in the presence of dipeptide-based phosphonium **4b** under the above optimal conditions. As shown in Table 3, the reaction was applicable to various cyclic ketimines bearing different aromatic rings, regardless of the positions and electronic properties of the substituents on the aromatic moiety, producing the expected tetrasubstituted aziridines **10a**–**l** in high yields (87–98%) with excellent stereoselectivities

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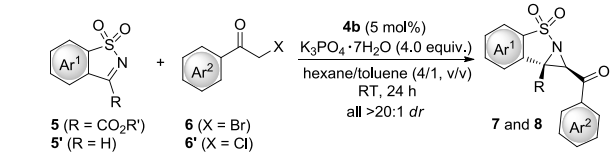
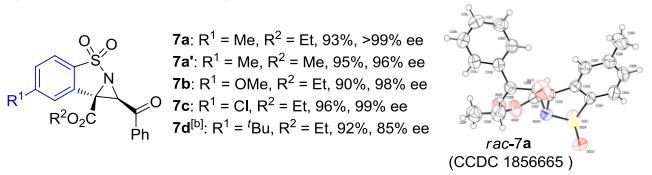
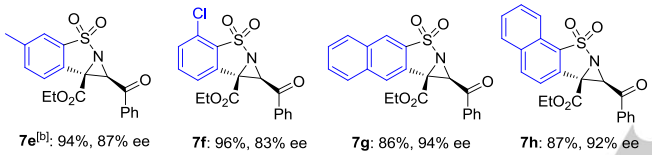
(up to >20:1 *dr*, 91–>99.9% ee). As well, a broad range of cyclic α-bromo benzopyrones with different substituents in the *ortho*-, *meta*-, or *para*-position of the phenyl ring were found to be variable substrates, delivering the desired products **11a**–**n** in high yields (86–99%) with high ee values (91–>99.9%). Furthermore, the seven-membered (hetero)-cyclic α-bromoketones also proved to be suitable substrates (**11o** and **11p**). The absolute configurations of these fused spiro aziridine products were assigned based on X-ray crystal structural analysis of **10a**.[20, 21]

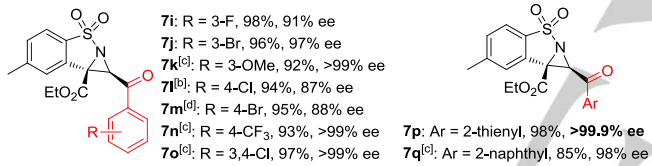
Table 2: Scope for *aza*-Darzens reaction of cyclic imines **5**/**5'** with α-halogenated acetophenones **6**/**6'**.[a]



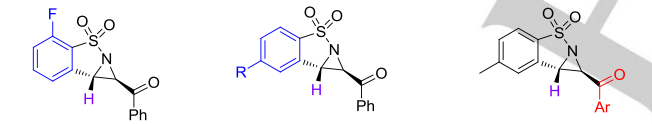
a) *aza*-Darzens between cyclic ketimines and α-bromo acetophenones







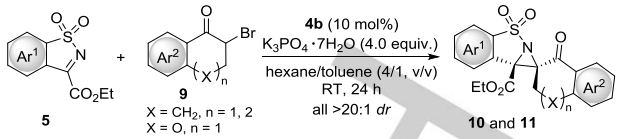
b) *aza*-Darzens between cyclic aldimines and α-chloro acetophenones[e]

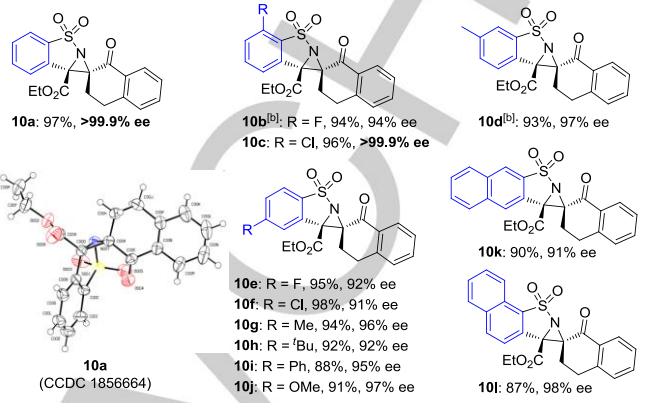


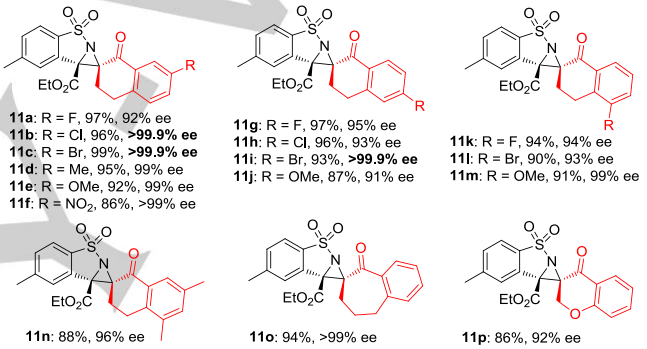
[a] Reactions were performed with **5** or **5'** (0.1 mmol), **6** or **6'** (0.12 mmol), **4b** (0.005mmol, 5 mol%) and K_3PO_4 $7H_2O$ (0.4 mmol) in hexane/toluene (1.0 mL, v/v = 4/1) at room temperature for 24 h. The *dr* values were determined by ^{1}H NMR of crude products. The ee value was determined by HPLC analysis on a chiral stationary phase. [b] The solvent was *p*-xylene. [c] The solvent was hexane/chlorobenzene (1.0 mL, v/v = 4/1). [d] The reaction was stirred at -10 °C for 48 hours. [e] The solvent was hexane/fluorobenzene (1.0 mL, v/v = 4/1).

To evaluate the scalability and the practicality of the process, one gram of cyclic ketimine **5a** was used to perform the aza-Darzens reaction with α-bromoacetophenone **6a**, and the product **7a** was obtained in 88% yield with >20:1 *dr* and >99% ee (Scheme 3). These highly functionalized aziridine products are not only biologically interesting,[2] but also synthetically valuable. As illustrated in Scheme 3, product **7a** could be readily converted to cyclic *N*-sulfonylamine **12** in high yield via a ring-opening reaction without any loss of enantioselectivity (99% ee). Direct reduction of product **7a** using $NaBH_4$ furnished hydroxyl-functionalized compound **13** in excellent yield. Alternatively, treatment of **7a** with benzoic acid under strong basic condition led to simultaneous ring-opening of the aziridine framework and substitution of the α-

Table 3: Enantioselective synthesis of tetrasubstituted aziridines through *aza*-Darzens reaction of cyclic ketimines **5** with cyclic α-bromoketones **9**.[a]







[a] Reactions were performed with **5** (0.1 mmol), **9** (0.12 mmol), **4b** (0.01 mmol) and K_3PO_4 $7H_2O$ (0.4 mmol) in hexane/toluene (1 mL, v/v = 4/1) at room temperature for 24 h. The *dr* values were determined by ^{1}H NMR of crude product and the ee value was determined by HPLC analysis on a chiral stationary phase. [b] The solvent was hexane/chlorobenzene (1 mL, v/v = 4/1).

position of the ketone moiety, affording compound **14** in high isolated yield. Moreover, a biologically active compound **18**, which has potential activity as an HIV-1 inhibitor,[2e-h] was prepared in high yield with good stereoselectivities by using this aza-Darzens protocol (Scheme 4).[20]

Based on the obtained results and our previous studies,[19c-f] the plausible stereocontrol models are presented in Table 4. We propose that amide and carbamate portions of the catalyst interact with cyclic imines via hydrogen bonding interactions, which contribute significantly to the key transition state models leading to the formation of the observed major stereoisomer. To provide experimental support, we prepared methylated catalysts **4b-1** and **4b-2**. When methylated phosphonium salts were used as the catalyst, respectively; the reaction became much slower, and the enantioselectivities decreased dramatically. When the reaction was performed in the solvent of methanol, only racemic product was obtained. These results clearly support the importance of the hydrogen bonding interactions in our catalytic system. Moreover, preliminary DFT calculations were performed to gain a better understanding of our reaction.[22] Although the (*Z*)-enolate generated from **6a** is more thermodynamically stable than the (*E*)-enolate, **TS1** shows that irrespective of the enolate configuration, the *S* configuration of the new quaternary carbon at the 7b-position in final product will be generated. This is determined by the

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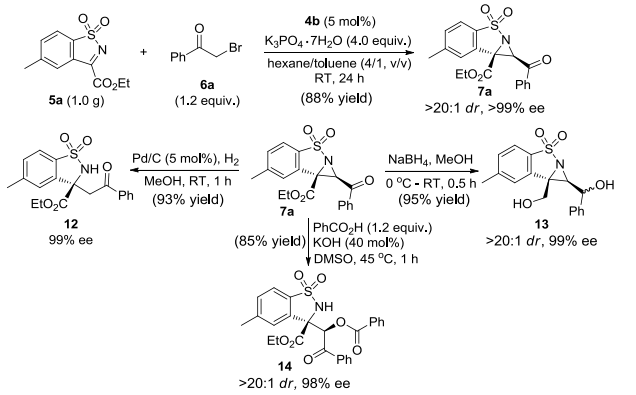
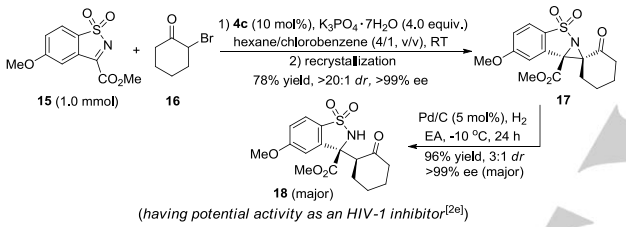
approaching direction of the enolate, which preferentially attacks the imine substrate from its *Si* face. Subsequently, rapid ring closure by the intramolecular nucleophilic substitution of the bromide will afford product with either 1*R* (from (*Z*)-enolate, as shown in **TS2-(*R*,*S*)**) or 1*S* (from (*E*)-enolate, as shown in **TS2-(*S*,*S*)** in SI)[20] configuration. Thermodynamic equilibrium will lead to the observed 1*R*-epimer which is more stable than (1*S*,7b*S*)-**7a** by 4.1 kcal/mol. [20]

In conclusion, we have disclosed a highly efficient aza-Darzens cyclization between cyclic imines and α-halogenated ketones by employing dipeptide-based chiral phosphonium salt as phase-transfer catalyst. A wide range of optically pure trisubstituted aziridines were obtained in high yields with excellent diastereo- and enantioselectivities under mild reaction conditions. In addition, plenty of structurally dense and stereodefined tetrasubstituted aziridines possessing complex spiro-fused scaffolds, which had never been accessible directly by any kind of catalytic asymmetric transformation, were readily synthesized in a highly stereoselective manner according to this methodology. The practicality and the utility of this protocol were demonstrated by the scale-up synthetic reaction and facile elaborations. Detailed mechanistic investigations and applications of this novel phosphonium salt catalysis to other challenging organic synthesis are currently ongoing in our laboratory.

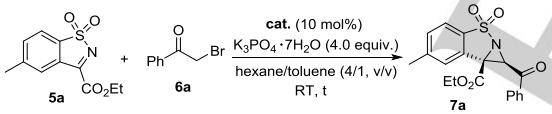


Scheme 3. Gram-scale synthesis and synthetic manipulations of **7a**.



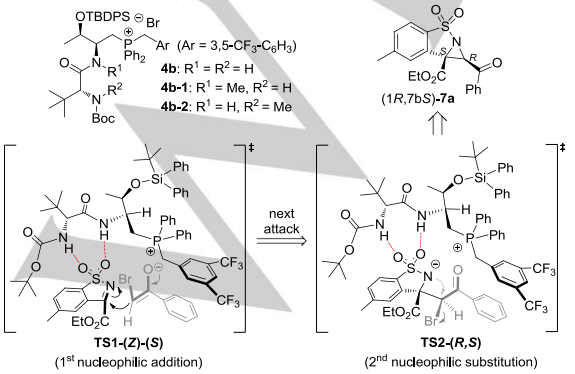
Scheme 4. Synthesis of a biologically active compound **18**.

Table 4. Asymmetric *aza*-Darzens reaction promoted by different phosphonium salts and the proposed transition state models.[a]



Entry	Cat.	t (h)	Yield [%][b]	*dr*[c]	ee [%][d]
1	**4b**	10	92	>20:1	>99
2	**4b-1**	24	85	>20:1	3
3	**4b-2**	24	80	>20:1	72
4[e]	**4b**	1	96	>20:1	0

[a] Reaction conditions: **5a** (0.10 mmol), **6a** (0.12 mmol), $K_3PO_4·7H_2O$ (0.4 mmol) and catalyst (0.01 mmol) in hexane/toluene (1.0 mL, v/v = 4/1). [b] Isolated yield. [c] Determined by ^{1}H NMR of crude product. [d] Determined by HPLC analysis on a chiral stationary phase. [e] The solvent was methanol (1.0 mL).



Acknowledgements

Financial support was provided by the National Natural Science Foundation of China (21702139), the "1000-Youth Talents Program" (YJ201702), and the Fundamental Research Funds for the Central Universities. We thank Prof. Yixin Lu (Department of Chemistry, National University of Singapore), Prof. Xiaoming Feng (Sichuan University), Prof. Qing-Hua Fan (Institute of Chemistry, Chinese Academy of Sciences), and Dr. Peiyuan Yu (Lawrence Berkeley National Laboratory) for invaluable help. We also acknowledge the comprehensive training platform of the Specialized Laboratory in the College of Chemistry at Sichuan University and the Analytical & Testing Center of Sichuan University for compound testing.

Conflict of interest

The authors declare no conflict of interest.

Keywords: bifunctional phosphonium salts · *aza*-Darzens reaction · tetrasubstituted aziridines · α-halogenated ketones · cyclic imines·

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[20] See Supporting Information (SI) for details.

[21] CCDC 1856665 (**7a**) and CCDC 1856664 (**10a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Date Centre.

[22] See section 10B (S111−S113) of the SI for DFT studies.

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10.1002/anie.201900613

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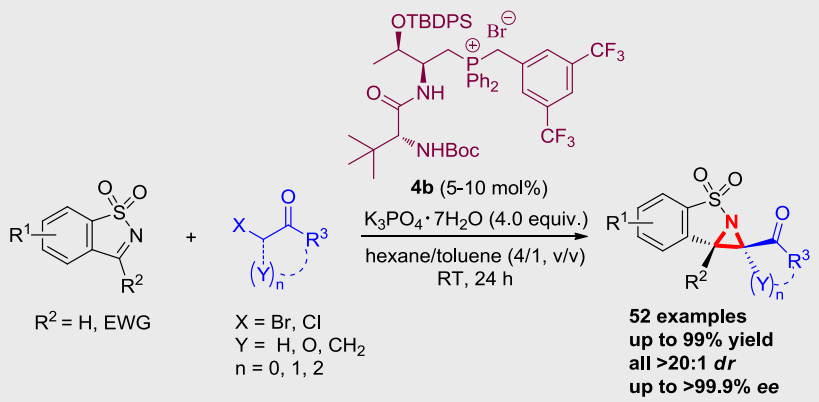

A highly enantioselective aza-Darzens cyclization between cyclic imines and α-halogenated ketones catalysed by amino acid-derived bifunctional phosphonium salts has been developed. In the presence of 5–10 mol% catalyst **4b**, the aza-Darzens reaction could be completed within 24 hours, and a wide range of enantioenriched fused tri- and tetra-substituted aziridines were isolated in high yields with excellent diastereo- and enantioselectivities (up to >20:1 *dr* and >99.9% ee). Scale-up synthesis and valuable transformations were also demonstrated.

Jianke Pan, [†] *Jia-Hong Wu,* [†] *Hongkui Zhang, Xiaoyu Ren, Jian-Ping Tan, Lixiang Zhu, Hong-Su Zhang, Chuihui Jiang, and Tianli Wang**

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Highly Enantioselective Synthesis of Fused Tri- and Tetra-substituted Aziridines via Bifunctional Phosphonium Salt-Catalyzed Aza-Darzens Reaction of Cyclic Imines with α-Halogenated Ketones

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