


 Cite this: *RSC Adv.*, 2021, **11**, 13040

 Received 23rd March 2021
 Accepted 23rd March 2021

DOI: 10.1039/d1ra02297k

rsc.li/rsc-advances

Catalytic enantioselective bromohydroxylation of cinnamyl alcohols†

 Jing Li^a and Yian Shi^{*ab}

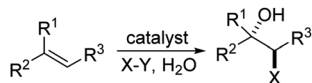
This work describes an effective enantioselective bromohydroxylation of cinnamyl alcohols with (DHQD)₂PHAL as the catalyst and H₂O as the nucleophile, providing a variety of corresponding optically active bromohydrins with up to 95% ee.

Electrophilic halogenation of olefins allows installation of two stereogenic centers onto the C–C double bond and is one of the most important transformations in organic chemistry.¹ Optically active halogen containing products resulting from asymmetric halogenation would serve as versatile chiral building blocks for organic synthesis. As a result, extensive efforts have been devoted to the development of asymmetric halogenation process. In recent years, great progress has been made in both intramolecular^{2,3} and intermolecular^{4,5} reaction processes with various types of olefins and nucleophiles. However, there are still challenges remaining to be addressed. In many cases, the developed catalytic systems often only apply to certain ranges of substrates and the reaction reactivity as well as selectivity can't be rationally adjusted. The substrate scope is also often difficult to be logically extended and requires much experimentation, largely due to the complexity of the reaction systems and the lack of clear understanding of the reaction mechanisms.

Halohydroxylation of olefins simply with H₂O as nucleophile is a classic electrophilic addition reaction in organic chemistry and produces synthetically useful halohydrins (Scheme 1). Asymmetric version of such process has been challenging with

only a few reports.^{6,7} As part of our general interest in asymmetric halogenation,⁸ recently we have been investigating the intermolecular asymmetric reaction processes, particularly with unfunctionalized olefins, which has been a long standing challenging problem. During such studies, we have found that up to 92% ee could be achieved for the bromoesterification of unfunctionalized olefins with (DHQD)₂PHAL (Scheme 2, eqn (a)).⁹ This work represents an early example of asymmetric halogenation for unfunctionalized olefins with high enantioselectivity. To our delight, high enantioselectivity can also be achieved for bromohydroxylation with H₂O upon further investigation, giving optically active bromohydrins with up to 98% ee (Scheme 2, eqn (b)).¹⁰ In our efforts to expand the reaction scope of the asymmetric bromohydroxylation, we have found that cinnamyl alcohols are effective substrates, giving the corresponding bromohydrins with up to 95% ee. Herein, we report our preliminary studies on this subject.

Initial studies were carried out with (*E*)-3-(4-bromophenyl)prop-2-en-1-ol (**1a**) as substrate. Several bromine reagents were examined with 10 mol% (DHQD)₂PHAL (**3a**) (Fig. 1) as the catalyst and 10 mol% (–)-camphorsulfonic acid (CSA) as additive in acetone/H₂O (10 : 1) at –30 °C (Table 1, entries 1–5). *N*-Bromobenzamide gave the highest ee (76%) (Table 1, entry 5). Among the catalysts investigated (Table 1, entries 5–9), (DHQD)₂PHAL (**3a**) was the choice of the catalyst with *N*-bromobenzamide. Solvent studies (Table 1, entries 5 and 10–15) showed that the highest ee (83%) was obtained with

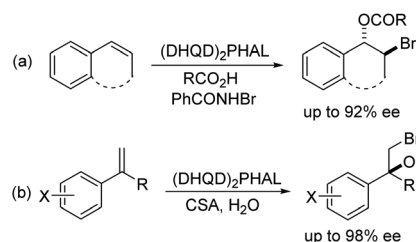


Scheme 1 Asymmetric halohydroxylation of olefins.

^aInstitute of Natural and Synthetic Organic Chemistry, Changzhou University, Changzhou 213164, P. R. China. E-mail: shiyian@cczu.edu.cn

^bDepartment of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA

† Electronic supplementary information (ESI) available: Experimental, characterization data, X-ray structures of **2a**, **2e**, and **12**, HPLC data for determination of enantiomeric excesses, and NMR spectra. CCDC 1941798, 1963482, and 2027431. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra02297k



Scheme 2 Asymmetric oxybromination of olefins.



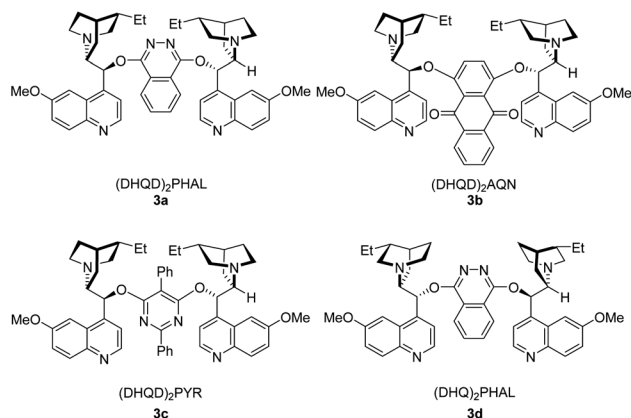


Fig. 1 Selected examples of catalyst examined.

CH₃CN/H₂O (10 : 1) (Table 1, entry 10). Addition of 10 mol% (–)-CSA increased both yield and ee (Table 1, entry 10 vs. 16). The best result was obtained with (–)-CSA among the additives examined (Table 1, entry 10 vs. entries 17–21). Slightly higher ee (85%) but lower yield was obtained when the reaction temperature was lowered to –40 °C (Table 1, entry 22 vs. 10).

With the optimized reaction conditions in hand, the substrate scope was subsequently investigated with 10 mol%

(DHQD)₂PHAL (**3a**), *N*-bromobenzamide (1.2 eq.), and 10 mol% (–)-CSA in CH₃CN/H₂O (10 : 1) at –30 °C. As shown in Table 2, the bromohydroxylation can be extended to various cinnamyl alcohols, giving the corresponding bromohydrins in 46–87% yields and 55–95% ee's (Table 2, entries 1–17). The reaction outcome was significantly influenced by the substituent on the phenyl group. In general, the enantioselectivity increased as a substituent was introduced onto the phenyl group. For mono-substituted substrates, it appeared that higher ee was obtained with the *para*-substituent (Table 2, entry 5 vs. 6 vs. 7). Up to 90% ee was achieved with *p*-Ph substituted cinnamyl alcohol (Table 2, entry 4). For 4-substituted substrates, the enantioselectivity remained similar when a second Me group was introduced to the 3 position (Table 2, entries 9–12). However, significantly higher ee's were obtained when the Me group was introduced to the 2-position, giving the corresponding bromohydrins in 90–95% ee (Table 2, entries 13–17). With 2-Me, 4-Br-substituted cinnamyl alcohol (**1m**), MeOH was also found to be effective nucleophile, giving the corresponding bromoether (**2r**) in 75% yield and 90% ee (Table 2, entry 18). A similar ee but lower yield was obtained when the hydroxyl group was replaced with the MeO group, giving the bromohydrin (**2s**) in 31% yield and 80% ee (Table 2, entry 19). The exact reason for this difference is not clear at this moment.

Table 1 Studies on reaction conditions^a

Entry	Cat.	Br source	Additive	Solvent	Yield ^b (ee) ^c %
1	3a	NBS	(–)-CSA	Acetone/H ₂ O (10 : 1)	79 (65)
2	3a	DBDMH	(–)-CSA	Acetone/H ₂ O (10 : 1)	76 (62)
3	3a	TBCO	(–)-CSA	Acetone/H ₂ O (10 : 1)	55 (7)
4	3a	MeCONHBr	(–)-CSA	Acetone/H ₂ O (10 : 1)	48 (67)
5	3a	PhCONHBr	(–)-CSA	Acetone/H ₂ O (10 : 1)	59 (76)
6	3b	PhCONHBr	(–)-CSA	Acetone/H ₂ O (10 : 1)	18 (6)
7	3c	PhCONHBr	(–)-CSA	Acetone/H ₂ O (10 : 1)	9 (0)
8	3d	PhCONHBr	(–)-CSA	Acetone/H ₂ O (10 : 1)	35 (–57)
9	3e (quinidine)	PhCONHBr	(–)-CSA	Acetone/H ₂ O (10 : 1)	31 (0)
10	3a	PhCONHBr	(–)-CSA	CH ₃ CN/H ₂ O (10 : 1)	70 (83)
11	3a	PhCONHBr	(–)-CSA	EtOAc/H ₂ O (10 : 1)	16 (67)
12	3a	PhCONHBr	(–)-CSA	TFE/H ₂ O (10 : 1)	43 (51)
13	3a	PhCONHBr	(–)-CSA	DCM/H ₂ O (10 : 1)	13 (70)
14 ^d	3a	PhCONHBr	(–)-CSA	CH ₃ CN/H ₂ O (5 : 1)	66 (82)
15 ^e	3a	PhCONHBr	(–)-CSA	CH ₃ CN/H ₂ O (20 : 1)	68 (81)
16	3a	PhCONHBr	–	CH ₃ CN/H ₂ O (10 : 1)	36 (77)
17	3a	PhCONHBr	(+)-CSA	CH ₃ CN/H ₂ O (10 : 1)	63 (82)
18	3a	PhCONHBr	PhCO ₂ H	CH ₃ CN/H ₂ O (10 : 1)	34 (77)
19	3a	PhCONHBr	1-NapCO ₂ H	CH ₃ CN/H ₂ O (10 : 1)	32 (77)
20	3a	PhCONHBr	<i>p</i> -TsOH	CH ₃ CN/H ₂ O (10 : 1)	68 (80)
21	3a	PhCONHBr	AlCl ₃	CH ₃ CN/H ₂ O (10 : 1)	39 (57)
22 ^f	3a	PhCONHBr	(–)-CSA	CH ₃ CN/H ₂ O (10 : 1)	49 (85)

^a Reactions were carried out with substrate **1a** (0.30 mmol), catalyst (0.030 mmol), additive (0.030 mmol), and Br source (0.36 mmol) in solvent/H₂O (10 : 1) (3.0 mL + 0.3 mL) at –30 °C for 72 h unless otherwise noted. ^b Isolated yield. ^c Determined by chiral HPLC analysis. ^d CH₃CN/H₂O (5 : 1) (3.0 mL + 0.6 mL). ^e CH₃CN/H₂O (20 : 1) (3.0 mL + 0.15 mL). ^f At –40 °C for 168 h.

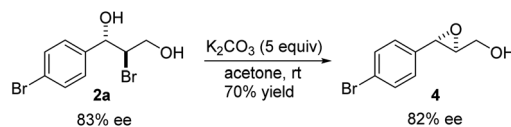


Table 2 Asymmetric bromohydroxylation of cinnamyl alcohols^a

Entry	Substrate	Product	Yield ^b (%)	ee ^c (%)
1	X = <i>p</i> -Br, 1a	2a (X-ray)	70	83
2	X = <i>p</i> -Cl, 1b	2b	64	80
3	X = <i>p</i> -F, 1c	2c	75	76
4 ^d	X = <i>p</i> -Ph, 1d	2d	87	90
5	X = <i>p</i> -Me, 1e	2e (X-ray)	76	82
6	X = <i>m</i> -Me, 1f	2f	71	62
7	X = <i>o</i> -Me, 1g	2g	77	70
8	X = H, 1h	2h	46	55
9	X = Br, 1i	2i	70	80
10	X = Cl, 1j	2j	71	80
11	X = F, 1k	2k	84	80
12	X = Me, 1l	2l	73	82
13	X = Br, 1m	2m	72	95
14	X = Cl, 1n	2n	78	94
15	X = F, 1o	2o	83	91
16	X = Ph, 1p	2p	84	94
17	X = Me, 1q	2q	87	90
18 ^e	1m	2r	75	90
19	1r	2s	31	80

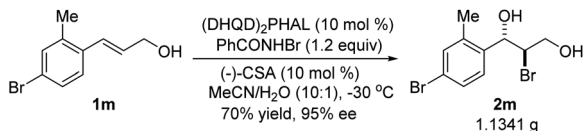
^a Reactions were carried out with substrate **1** (0.50 mmol), (DHQD)₂PHAL (0.050 mmol), (–)-CSA (0.050 mmol), and PhCONHBr (0.60 mmol) in CH₃CN (5.0 mL) and water (0.50 mL) at –30 °C for 72 h unless otherwise noted. ^b Isolated yield. ^c Determined by chiral HPLC analysis. For entry **1**, the absolute configuration was determined by comparing the optical rotation of the corresponding epoxide with the reported one¹¹ upon treatment with K₂CO₃ in acetone (Scheme 3). For others, the absolute configurations were tentatively assigned by analogy. ^d The reaction was carried out at –40 °C for 168 h. ^e MeOH was used as nucleophile.

The absolute configuration of bromohydrin **2a** was determined by converting it to the corresponding epoxide **4** with K₂CO₃ (Scheme 3) and comparing the optical rotation of the epoxide with the reported one.¹¹ The bromohydroxylation reaction can also be carried out on a relatively large scale. For example, 1.1341 g of bromohydrin **2m** was obtained in 70% yield with 95% ee (Scheme 4). As shown in Scheme 5, bromohydrin **2m** can be converted to bromoacetal **5** in 86% yield

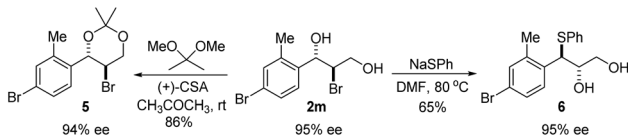


Scheme 3 Determination of absolute configuration of bromohydrin **2a**.





Scheme 4 Bromohydroxylation on gram scale.

Scheme 5 Synthetic transformations of bromohydrin **2m**.

without loss of the ee. Sulfide **6** was obtained in 65% yield and 95% ee when **2m** was reacted with sodium thiophenolate.

Optically active bromoether like **2r** could also serve as useful intermediates for further transformations (Scheme 6). Treating **2r** with NaN_3 in DMF at 80 °C gave azide **7** in 50% yield and 90% ee with inversion of configuration. The bromide of **2r** could also be converted to chloride **8** in 90% ee while the yield was somewhat low. Epoxide **9** was obtained in 87% yield and 90% ee by treatment of **2r** with NaOH in dioxane and water. When **2r** was reacted with PhSNa in DMF at 80 °C, sulfide **10** was isolated in 73% yield and 90% ee. The reaction likely proceeded *via* epoxide **9**. The synthetic application is further illustrated in Scheme 7. Azide **11** and chloride **12** were obtained from **9** in 80% and 78% yield, respectively, without erosion of the optical activity.¹²

A precise understanding of the reaction mechanism awaits further study. As previously described,¹⁰ two possible transition state models are outlined in Fig. 2. The substrate is likely docked in the chiral pocket through π,π -stacking with quinoline of the catalyst. Such π,π -interaction appeared to be enhanced by the substituents on the phenyl groups, consequently leading to the significant increase of the enantioselectivity. In model A, *N*-bromobenzamide was activated by both the tertiary amine of the catalyst and additive (–)-CSA to increase its electrophilicity toward the double bond of the reacting substrate. In model B, the tertiary amine of the catalyst could first be protonated by additive (–)-CSA, and *N*-

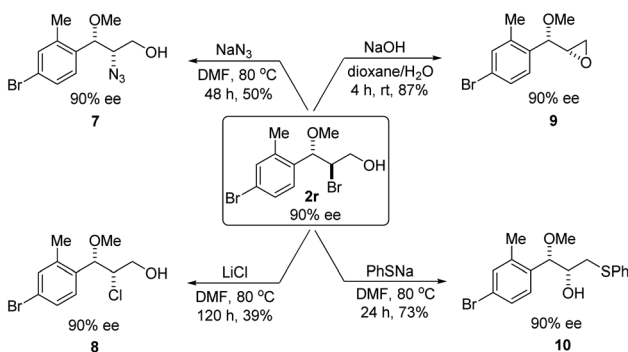
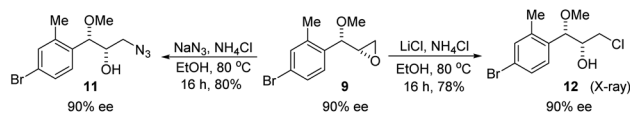
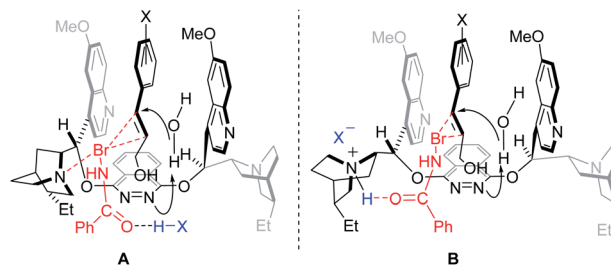
Scheme 6 Synthetic transformations of bromoether **2r**.Scheme 7 Synthetic transformations of epoxide **9**.

Fig. 2 Two possible transition state models.

bromobenzamide would subsequently be activated by the resulting quaternary ammonium salt *via* hydrogen bonding.

Conclusions

In summary, bromohydroxylation of olefins is a classic and important electrophilic addition reaction in organic chemistry. Asymmetric version of this reaction process has been challenging. In this work, we have found that cinnamyl alcohols are effective substrates for asymmetric bromohydroxylation with (DHQD)₂PHAL as catalyst, (–)-CSA additive, PhCONHBr as bromine source, and H₂O as nucleophile, providing the corresponding optically active bromohydrins with up to 95% ee. The resulting bromohydrin and related bromoether can be transformed into various highly functionalized molecules with maintained ee's. The current reaction process represents a significant progress in asymmetric bromohydroxylation. Further understanding reaction mechanism, developing more effective catalyst system, and expanding the substrate scope are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (21632005) and Changzhou University for the financial support. We also thank Miao Zhao at Changzhou University for some experimental contributions.

Notes and references

- For leading reviews on halogenations of olefins, see: (a) M. D. Dowle and D. I. Davies, Synthesis and synthetic utility of halolactones, *Chem. Soc. Rev.*, 1979, **8**, 171; (b) G. Li, S. R. S. S. Kotti and C. Timmons, Recent development of regio- and stereoselective



- aminohalogenation reaction of alkenes, *Eur. J. Org. Chem.*, 2007, 2745; (c) A. J. Cresswell, S. T.-C. Eey and S. E. Denmark, Catalytic, stereoselective dihalogenation of alkenes: challenges and opportunities, *Angew. Chem., Int. Ed.*, 2015, **54**, 15642.
- 2 For leading reviews on intramolecular asymmetric halogenation of olefins, see: (a) G. Chen and S. Ma, Enantioselective halocyclization reactions for the synthesis of chiral cyclic compounds, *Angew. Chem., Int. Ed.*, 2010, **49**, 8306; (b) A. Castellanos and S. P. Fletcher, Current methods for asymmetric halogenation of olefins, *Chem.-Eur. J.*, 2011, **17**, 5766; (c) C. K. Tan, L. Zhou and Y.-Y. Yeung, Organocatalytic enantioselective halolactonizations: strategies of halogen activation, *Synlett*, 2011, 1335; (d) U. Hennecke, New catalytic approaches towards the enantioselective halogenation of alkenes, *Chem.-Asian J.*, 2012, **7**, 456; (e) S. E. Denmark, W. E. Kuester and M. T. Burk, Catalytic, asymmetric halofunctionalization of alkenes—a critical perspective, *Angew. Chem., Int. Ed.*, 2012, **51**, 10938; (f) K. Murai and H. Fujioka, Recent progress in organocatalytic asymmetric halocyclization, *Heterocycles*, 2013, **87**, 763; (g) S. R. Chemler and M. T. Bovino, Catalytic aminohalogenation of alkenes and alkynes, *ACS Catal.*, 2013, **3**, 1076; (h) C. K. Tan and Y.-Y. Yeung, Recent advances in stereoselective bromofunctionalization of alkenes using *N*-bromoamide reagents, *Chem. Commun.*, 2013, **49**, 7985; (i) C. B. Tripathi and S. Mukherjee, Catalytic enantioselective halocyclizations beyond lactones: emerging routes to enantioenriched nitrogenous heterocycles, *Synlett*, 2014, **25**, 163; (j) Y. A. Cheng, W. Z. Yu and Y.-Y. Yeung, Recent advances in asymmetric intra- and intermolecular halofunctionalizations of alkenes, *Org. Biomol. Chem.*, 2014, **12**, 2333; (k) S. Zheng, C. M. Schienebeck, W. Zhang, H.-Y. Wang and W. Tang, Cinchona alkaloids as organocatalysts in enantioselective halofunctionalization of alkenes and alkynes, *Asian J. Org. Chem.*, 2014, **3**, 366.
- 3 For leading references on intramolecular asymmetric halogenation of olefins, see: (a) T. Inoue, O. Kitagawa, O. Ochiai, M. Shiro and T. Taguchi, Catalytic asymmetric iodocarbocyclization reaction, *Tetrahedron Lett.*, 1995, **36**, 9333; (b) R. B. Grossman and R. J. Trupp, The first reagent-controlled asymmetric halolactonizations. Dihydroquinidine–halogen complexes as chiral sources of positive halogen ion, *Can. J. Chem.*, 1998, **76**, 1233; (c) S. H. Kang, S. B. Lee and C. M. Park, Catalytic enantioselective iodocyclization of γ -hydroxy-*cis*-alkenes, *J. Am. Chem. Soc.*, 2003, **125**, 15748; (d) M. Wang, L. X. Gao, W. P. Mai, A. X. Xia, F. Wang and S. B. Zhang, Enantioselective iodolactonization catalyzed by chiral quaternary ammonium salts derived from cinchonidine, *J. Org. Chem.*, 2004, **69**, 2874; (e) A. Sakakura, A. Ukai and K. Ishihara, Enantioselective halocyclization of polyprenoids induced by nucleophilic phosphoramidites, *Nature*, 2007, **445**, 900; (f) D. C. Whitehead, R. Yousefi, A. Jaganathan and B. Borhan, An organocatalytic asymmetric chlorolactonization, *J. Am. Chem. Soc.*, 2010, **132**, 3298; (g) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei and W. Tang, Enantioselective bromolactonization of conjugated (*Z*)-enynes, *J. Am. Chem. Soc.*, 2010, **132**, 3664; (h) L. Zhou, C. K. Tan, X. Jiang, F. Chen and Y.-Y. Yeung, Asymmetric bromolactonization Using amino-thiocarbamate catalyst, *J. Am. Chem. Soc.*, 2010, **132**, 15474; (i) G. E. Veitch and E. N. Jacobsen, Tertiary aminourea-catalyzed enantioselective iodolactonization, *Angew. Chem., Int. Ed.*, 2010, **49**, 7332; (j) K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura and H. Fujioka, Asymmetric bromolactonization catalyzed by a C_3 -symmetric chiral trisimidazoline, *Angew. Chem., Int. Ed.*, 2010, **49**, 9174; (k) U. Hennecke, C. H. Müller and R. Fröhlich, Enantioselective haloetherification by asymmetric opening of meso-halonium ions, *Org. Lett.*, 2011, **13**, 860; (l) Z.-M. Chen, Q.-W. Zhang, Z.-H. Chen, H. Li, Y.-Q. Tu, F.-M. Zhang and J.-M. Tian, Organocatalytic asymmetric halogenation/semipinacol rearrangement: highly efficient synthesis of chiral α -oxa-quaternary β -haloketones, *J. Am. Chem. Soc.*, 2011, **133**, 8818; (m) O. Lozano, G. Blessley, T. M. D. Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman and V. Gouverneur, Organocatalyzed enantioselective fluorocyclizations, *Angew. Chem., Int. Ed.*, 2011, **50**, 8105; (n) V. Rauniyar, A. D. Lackner, G. L. Hamilton and F. D. Toste, Asymmetric electrophilic fluorination using an anionic chiral phase-transfer catalyst, *Science*, 2011, **334**, 1681; (o) S. E. Denmark and M. T. Burk, Enantioselective bromocycloetherification by Lewis base/chiral Brønsted acid cooperative catalysis, *Org. Lett.*, 2012, **14**, 256; (p) M. C. Dobish and J. N. Johnston, Achiral counterion control of enantioselectivity in a Brønsted acid catalyzed iodolactonization, *J. Am. Chem. Soc.*, 2012, **134**, 6068; (q) M. T. Bovino and S. R. Chemler, Catalytic enantioselective alkene aminohalogenation/cyclization involving atom transfer, *Angew. Chem., Int. Ed.*, 2012, **51**, 3923; (r) D. H. Paull, C. Fang, J. R. Donald, A. D. Pansick and S. F. Martin, Bifunctional catalyst promotes highly enantioselective bromolactonizations to generate stereogenic C-Br Bonds, *J. Am. Chem. Soc.*, 2012, **134**, 11128; (s) H. J. Lee and D. Y. Kim, Catalytic enantioselective bromolactonization of alkenoic acids in the presence of palladium complexes, *Tetrahedron Lett.*, 2012, **53**, 6984; (t) J. E. Tungen, J. M. J. Nolsøe and T. V. Hansen, Asymmetric iodolactonization utilizing chiral squaramides, *Org. Lett.*, 2012, **14**, 5884; (u) K. Ikeuchi, S. Ido, S. Yoshimura, T. Asakawa, M. Inai, Y. Hamashima and T. Kan, Catalytic desymmetrization of cyclohexadienes by asymmetric bromolactonization, *Org. Lett.*, 2012, **14**, 6016; (v) X. Zeng, C. Miao, S. Wang, C. Xia and W. Sun, Asymmetric 5-*endo* chloroetherification of homoallylic alcohols toward the synthesis of chiral β -chlorotetrahydrofurans, *Chem. Commun.*, 2013, **49**, 2418; (w) F. Romanov-Michailidis, L. Guénee and A. Alexakis, Enantioselective organocatalytic fluorination-induced



Wagner–Meerwein rearrangement, *Angew. Chem., Int. Ed.*, 2013, **52**, 9266; (x) C. B. Tripathi and S. Mukherjee, Catalytic enantioselective iodoetherification of oximes, *Angew. Chem., Int. Ed.*, 2013, **52**, 8450; (y) Q. Yin and S.-L. You, Enantioselective chlorocyclization of indole derived benzamides for the synthesis of spiro-indolines, *Org. Lett.*, 2013, **15**, 4266; (z) A. Armstrong, D. C. Braddock, A. X. Jones and S. Clark, Catalytic asymmetric bromolactonization reactions using (DHQD)₂PHAL-benzoic acid combinations, *Tetrahedron Lett.*, 2013, **54**, 7004; (aa) W. Xie, G. Jiang, H. Liu, J. Hu, X. Pan, H. Zhang, X. Wan, Y. Lai and D. Ma, Highly enantioselective bromocyclization of tryptamines and its application in the synthesis of (-)-chimonanthine, *Angew. Chem., Int. Ed.*, 2013, **52**, 12924; (ab) X. Han, C. Dong and H.-B. Zhou, C₃-Symmetric cinchonine-squaramide-catalyzed asymmetric chlorolactonization of styrene-type carboxylic acids with 1,3-dichloro-5,5-dimethylhydantoin: an efficient method to chiral isochroman-1-ones, *Adv. Synth. Catal.*, 2014, **356**, 1275; (ac) C.-L. Zhu, J.-S. Tian, Z.-Y. Gu, G.-W. Xing and H. Xu, Iron(II)-catalyzed asymmetric intramolecular olefin aminochlorination using chloride ion, *Chem. Sci.*, 2015, **6**, 3044; (ad) Y. Cai, P. Zhou, X. Liu, J. Zhao, L. Lin and X. Feng, Diastereoselectively switchable asymmetric haloaminocyclization for the synthesis of cyclic sulfamates, *Chem.–Eur. J.*, 2015, **21**, 6386; (ae) Y.-M. Yu, Y.-N. Huang and J. Deng, Catalytic asymmetric chlorocyclization of 2-vinylphenylcarbamates for Synthesis of 1,4-Dihydro-2H-3,1-benzoxazin-2-one Derivatives, *Org. Lett.*, 2017, **19**, 1224; (af) R. Nishiyori, A. Tsuchihashi, A. Mochizuki, K. Kaneko, M. Yamanaka and S. Shirakawa, Design of chiral bifunctional dialkyl sulfide catalysts for regio-, diastereo-, and enantioselective bromolactonization, *Chem.–Eur. J.*, 2018, **24**, 16747; (ag) Y. Nishikawa, Y. Hamamoto, R. Satoh, N. Akada, S. Kajita, M. Nomoto, M. Miyata, M. Nakamura, C. Matsubara and O. Hara, Enantioselective bromolactonization of trisubstituted olefinic acids catalyzed by chiral pyridyl phosphoramides, *Chem.–Eur. J.*, 2018, **24**, 18880; (ah) W. Wang, H. He, M. Gan, H. Wang, Y. Wang and X. Jiang, Enantioselective syntheses of α -exo-methylene-lactones via organocatalytic halolactonization, *Adv. Synth. Catal.*, 2019, **361**, 4797; (ai) Q. Cao, J. Luo and X. Zhao, Chiral sulfide catalysis for desymmetrizing enantioselective chlorination, *Angew. Chem., Int. Ed.*, 2019, **58**, 1315.

4 For leading reviews on intermolecular asymmetric halogenation of olefins, see: (a) J. Chen and L. Zhou, Recent progress in the asymmetric intermolecular halogenation of alkenes, *Synthesis*, 2014, 586; (b) M. L. Landry and N. Z. Burns, Catalytic enantioselective dihalogenation in total synthesis, *Acc. Chem. Res.*, 2018, **51**, 1260; (c) Y. Cai, X. Liu, P. Zhou and X. Feng, Asymmetric catalytic halofunctionalization of α,β -unsaturated carbonyl compounds, *J. Org. Chem.*, 2019, **84**, 1.

5 For leading references on intermolecular asymmetric halogenation of olefins, see: (a) Y. Cai, X. Liu, Y. Hui, J. Jiang, W. Wang, W. Chen, L. Lin and X. Feng, Catalytic

asymmetric bromoamination of chalcones: highly efficient synthesis of chiral α -Bromo- β -Amino ketone derivatives, *Angew. Chem., Int. Ed.*, 2010, **49**, 6160; (b) Y. Cai, X. Liu, J. Jiang, W. Chen, L. Lin and X. Feng, Catalytic asymmetric chloroamination reaction of α,β -unsaturated γ -keto esters and chalcones, *J. Am. Chem. Soc.*, 2011, **133**, 5636; (c) Y. Cai, X. Liu, J. Li, W. Chen, W. Wang, L. Lin and X. Feng, Asymmetric iodoamination of chalcones and 4-aryl-4-oxobutenoates catalyzed by a complex based on scandium(III) and a N,N'-dioxide ligand, *Chem.–Eur. J.*, 2011, **17**, 14916; (d) K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch and J. S. Chen, Enantioselective dichlorination of allylic alcohols, *J. Am. Chem. Soc.*, 2011, **133**, 813; (e) G.-X. Li, Q.-Q. Fu, X.-M. Zhang, J. Jiang and Z. Tang, First asymmetric intermolecular bromoesterification catalyzed by chiral Brønsted acid, *Tetrahedron: Asymmetry*, 2012, **23**, 245; (f) A. Alix, C. Lalli, P. Retailleau and G. Masson, Highly enantioselective electrophilic α -bromination of enecarbamates: chiral phosphoric acid and calcium phosphate salt catalysts, *J. Am. Chem. Soc.*, 2012, **134**, 10389; (g) W. Zhang, N. Liu, C. M. Schienebeck, X. Zhou, I. I. Izhar, I. A. Guzei and W. Tang, Enantioselective intermolecular bromoesterification of allylic sulfonamides, *Chem. Sci.*, 2013, **4**, 2652; (h) Y. Cai, X. Liu, P. Zhou, Y. Kuang, L. Lin and X. Feng, Iron-catalyzed asymmetric haloamination reactions, *Chem. Commun.*, 2013, **49**, 8054; (i) D. X. Hu, G. M. Shibuya and N. Z. Burns, Catalytic enantioselective dibromination of allylic alcohols, *J. Am. Chem. Soc.*, 2013, **135**, 12960; (j) J. Qi, G.-T. Fan, J. Chen, M.-H. Sun, Y.-T. Dong and L. Zhou, Catalytic enantioselective bromoamination of allylic alcohols, *Chem. Commun.*, 2014, **50**, 13841; (k) D. X. Hu, F. J. Seidl, C. Bucher and N. Z. Burns, Catalytic chemo-, regio-, and enantioselective bromochlorination of allylic alcohols, *J. Am. Chem. Soc.*, 2015, **137**, 3795; (l) M. L. Landry, D. X. Hu, G. M. Mckenna and N. Z. Burns, Catalytic enantioselective dihalogenation and the selective synthesis of (-)-deschloromytilipin A and (-)-danicalipin A, *J. Am. Chem. Soc.*, 2016, **138**, 5150; (m) W.-S. Huang, L. Chen, Z.-J. Zheng, K.-F. Yang, Z. Xu, Y.-M. Cui and L.-W. Xu, Catalytic asymmetric bromochlorination of aromatic allylic alcohols promoted by multifunctional Schiff base ligands, *Org. Biomol. Chem.*, 2016, **14**, 7927; (n) C. Lebé, F. Blanchard and G. Masson, Highly enantioselective intermolecular iodo- and chloroamination of enecarbamates catalyzed by chiral phosphoric acids or calcium phosphate salts, *Synlett*, 2016, 27, 559; (o) S. Guo, F. Cong, R. Guo, L. wang and P. Tang, Asymmetric silver-catalysed intermolecular bromotrifluoromethoxylation of alkenes with a new trifluoromethoxylation reagent, *Nat. Chem.*, 2017, **9**, 546; (p) B. Soltanzadeh, A. Jaganathan, Y. Yi, H. Yi, R. J. Staples and B. Borhan, Highly regio- and enantioselective vicinal dihalogenation of allyl amides, *J. Am. Chem. Soc.*, 2017, **139**, 2132; (q) P. Zhou, L. Lin, L. Chen, X. Zhong, X. Liu and X. Feng, Iron-catalyzed asymmetric haloazidation of α,β -unsaturated ketones: construction of organic azides



- with two vicinal stereocenters, *J. Am. Chem. Soc.*, 2017, **139**, 13414; (r) A. J. Burckle, B. Gàl, F. J. Seidl, V. H. Vasilev and N. Z. Burns, Enantiospecific solvolytic functionalization of bromochlorides, *J. Am. Chem. Soc.*, 2017, **139**, 13562; (s) F. J. Seidl, C. Min, J. A. Lopez and N. Z. Burns, Catalytic regio- and enantioselective haloazidation of allylic alcohols, *J. Am. Chem. Soc.*, 2018, **140**, 15646; (t) N. Li, H. Yu, R. Wang, J. Shen, W.-Q. Wu, K. Liu, T.-T. Sun, Z.-Z. Zhang, C.-Z. Yao and J. Yu, Enantioselective intermolecular iodoacetalization of enol ethers catalyzed by chiral Co(III)-complex-templated Brønsted acids, *Tetrahedron Lett.*, 2018, **59**, 3605; (u) V. Wedek, R. V. Lommel, C. G. Daniliuc, F. D. Proft and U. Hennecke, Organocatalytic, enantioselective dichlorination of unfunctionalized alkenes, *Angew. Chem., Int. Ed.*, 2019, **58**, 9239; (v) T. Arai, K. Horigane, T. K. Suzuki, R. Itoh and M. Yamanaka, Catalytic asymmetric iodoesterification of simple alkenes, *Angew. Chem., Int. Ed.*, 2020, **59**, 12680; (w) D. C. Steigerwald, B. Soltanzadeh, A. Sarkar, C. C. Morgenstern, R. J. Staples and B. Borhan, Ritter-enabled catalytic asymmetric chloroamidation of olefins, *Chem. Sci.*, 2021, **12**, 1834.
- 6 For oxyfluorination of enamides, see: T. Honjo, R. J. Phipps, V. Rauniyar and F. D. Toste, A doubly axially chiral phosphoric acid catalyst for the asymmetric tandem oxyfluorination of enamides, *Angew. Chem., Int. Ed.*, 2012, **51**, 9684.
- 7 For halohydroxylation, see: (a) B. Soltanzadeh, A. Jaganathan, R. J. Staples and B. Borhan, Highly stereoselective intermolecular haloetherification and haloesterification of allyl amides, *Angew. Chem., Int. Ed.*, 2015, **54**, 9517; (b) Y.-M. Cao, D. Lentz and M. Christmann, Synthesis of enantioenriched bromohydrins *via* divergent reactions of racemic intermediates from anchimeric oxygen borrowing, *J. Am. Chem. Soc.*, 2018, **140**, 10677; (c) W. Li, P. Zhou, G. Li, L. Lin and X. Feng, Catalytic asymmetric halohydroxylation of α,β -unsaturated ketones with water as the nucleophile, *Adv. Synth. Catal.*, 2020, **362**, 1982.
- 8 (a) D. Huang, H. Wang, F. Xue, H. Guan, L. Li, X. Peng and Y. Shi, Enantioselective bromocyclization of olefins catalyzed by chiral phosphoric acid, *Org. Lett.*, 2011, **13**, 6350; (b) D. Huang, X. Liu, L. Li, Y. Cai, W. Liu and Y. Shi, Enantioselective bromoaminocyclization of allyl *N*-tosylcarbamates catalyzed by a chiral phosphine-Sc(OTf)₃ complex, *J. Am. Chem. Soc.*, 2013, **135**, 8101; (c) H. Huang, H. Pan, Y. Cai, M. Liu, H. Tian and Y. Shi, Enantioselective 6-*endo* bromoaminocyclization of 2,4-dienyl *N*-tosylcarbamates catalyzed by a chiral phosphine oxide-Sc(OTf)₃ complex. A dramatic additive effect, *Org. Biomol. Chem.*, 2015, **13**, 3566; (d) W. Liu, H. Pan, H. Tian and Y. Shi, Enantioselective 6-*exo*-bromoaminocyclization of homoallylic *N*-tosylcarbamates catalyzed by a novel monophosphine-Sc(OTf)₃ complex, *Org. Lett.*, 2015, **17**, 3956; (e) Z. Li and Y. Shi, Chiral phosphine oxide-Sc(OTf)₃ complex catalyzed enantioselective bromoaminocyclization of 2-benzofuranylmethyl *N*-tosylcarbamates. Approach to a novel class of optically active spiro compounds, *Org. Lett.*, 2015, **17**, 5752; (f) H. Pan, H. Huang, W. Liu, H. Tian and Y. Shi, Phosphine oxide-Sc(OTf)₃ catalyzed highly regio- and enantioselective bromoaminocyclization of (*E*)-cinnamyl tosylcarbamates. An approach to a class of synthetically versatile functionalized molecules, *Org. Lett.*, 2016, **18**, 896; (g) X. Tan, H. Pan, H. Tian and Y. Shi, Phosphine oxide-Sc(OTf)₃ catalyzed enantioselective bromoaminocyclization of *tri*-substituted allyl *N*-tosylcarbamates, *Sci. China: Chem.*, 2018, **61**, 656.
- 9 L. Li, C. Su, X. Liu, H. Tian and Y. Shi, Catalytic asymmetric intermolecular bromoesterification of unfunctionalized olefins, *Org. Lett.*, 2014, **16**, 3728.
- 10 (a) X. Zhang, J. Li, H. Tian and Y. Shi, Catalytic asymmetric bromination of unfunctionalized olefins with H₂O as a nucleophile, *Chem.-Eur. J.*, 2015, **21**, 11658; (b) J. Li, Z. Li, X. Zhang, B. Xu and Y. Shi, Catalytic enantioselective bromohydroxylation of aryl olefins with flexible functionalities, *Org. Chem. Front.*, 2017, **4**, 1084.
- 11 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, Hi. Masamune and K. B. Sharpless, Catalytic asymmetric epoxidation and kinetic resolution modified procedures including *in situ* derivatization, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
- 12 The stereochemistry of 5–11 was tentatively assigned based on mechanistic considerations.

