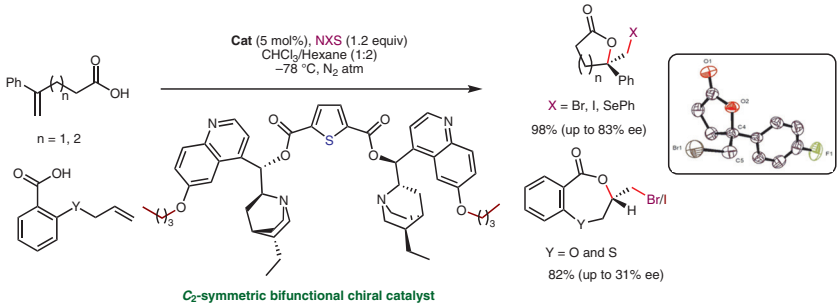
Synlett S. Jana et al. Cluster

Synthesis of Novel C_2-Symmetric Sulfur-Based Catalysts: Asymmetric Formation of Halo- and Seleno-Functionalized Normal- and Medium-Sized Rings

Sadhan Jana
Ajay Verma
Vandana Rathore
Sangit Kumar*

Department of Chemistry, Indian Institute of Science Education and Research (IISER) Bhopal, Bhopal Bypass Road, Bhauri, Bhopal 462066 Madhya Pradesh, India
sangitkumar@iiserb.ac.in

Published as part of the Cluster *Organosulfur and Organoselenium Compounds in Catalysis*



Received: 20.04.2019
Accepted after revision: 25.04.2019
Published online: 29.05.2019
DOI: 10.1055/s-0037-1610715; Art ID: st-2019-w0086-c

Abstract The synthesis of novel, highly functionalized, C_2-symmetric sulfur-based catalysts is developed and their catalytic applications are explored in asymmetric bromo-, iodo- and seleno-functionalizations of alkenoic acids. This protocol provides the corresponding normal- and medium-sized bromo, iodo and selenolactones in up to 98% yield and 83% stereoselectivity.

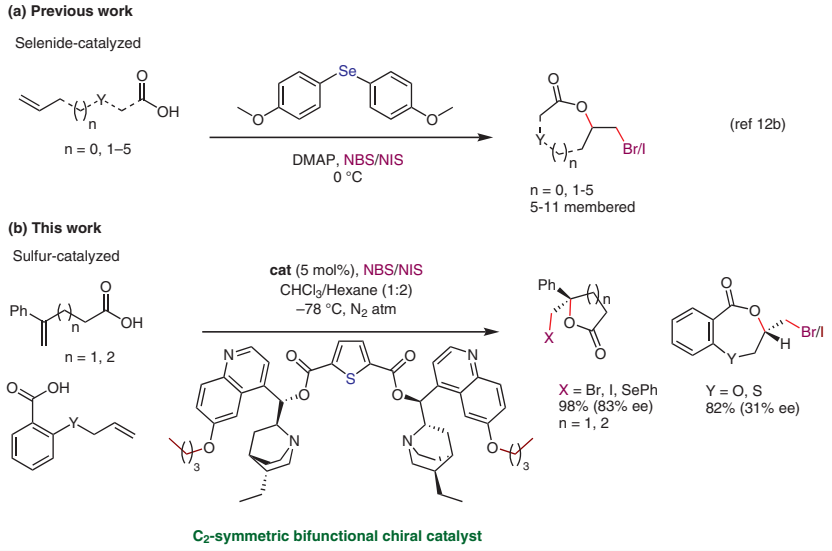
Key words alkenoic acids, organosulfur catalysts, asymmetric catalysis, halolactones, selenolactones

The group 16 donor atoms sulfur (S), selenium (Se) and tellurium (Te) act as Lewis bases. The Lewis base catalyzed halogenation of organic substrates, in which an n–σ* interaction between a Lewis base chalcogenide and a Lewis acidic halogen source leads to an electrophilic halogen species, has been well documented in the literature.[1] Denmark et al. established a variety of chiral and achiral Lewis bases, such as selenides and sulfides, for the activation of halogens.[2] In recent decades, various research groups have been involved in the development of catalytic halocyclization reactions by utilizing chalcogenide-based catalysts.[3,4] In 2012, Yeung and co-workers reported the synthesis of medium-ring-sized seven-membered bromolactones using a sulfur-based organocatalyst.[5] However, catalytic asymmetric halogenation of medium-sized rings has not yet been explored. In contrast to the enantioselective halogenation of five- and six-membered rings,[6] enantioenriched medium-sized halolactones are rare, despite their potential applications in the synthesis of biologically relevant molecules.[7]

Sulfide-catalyzed electrophilic bromination of various substrates has been achieved. Yeung and co-worker reported the triphenylphosphine sulfide catalyzed bromocyclization of amides to afford oxazolidines and oxazines.[8] Similarly, Mukherjee and Tripathi described selective oxidation of secondary alcohols with NBS using a thiourea derivative as the catalyst.[9] Moreover, Denmark and Burk accomplished the iodolactonization of alkenoic acids with *N*-iodosuccinimide catalyzed by the Lewis base, *n*-Bu_3P=S.[3c]

Numerous methodologies have been reported for the catalytic, enantioselective bromofunctionalization of alkenes.[1d,6c,10] In 2010, Yeung et al. developed a thiocarbamate which acts as a Lewis base for the enantioselective bromofunctionalization of alkenes. This sulfur-based catalyst has been employed in the cyclization of various disubstituted alkenes to obtain enantioenriched halolactones, 3-bromopyrrolidines, and 3,4-dihydroisocoumarins.[10h,11]

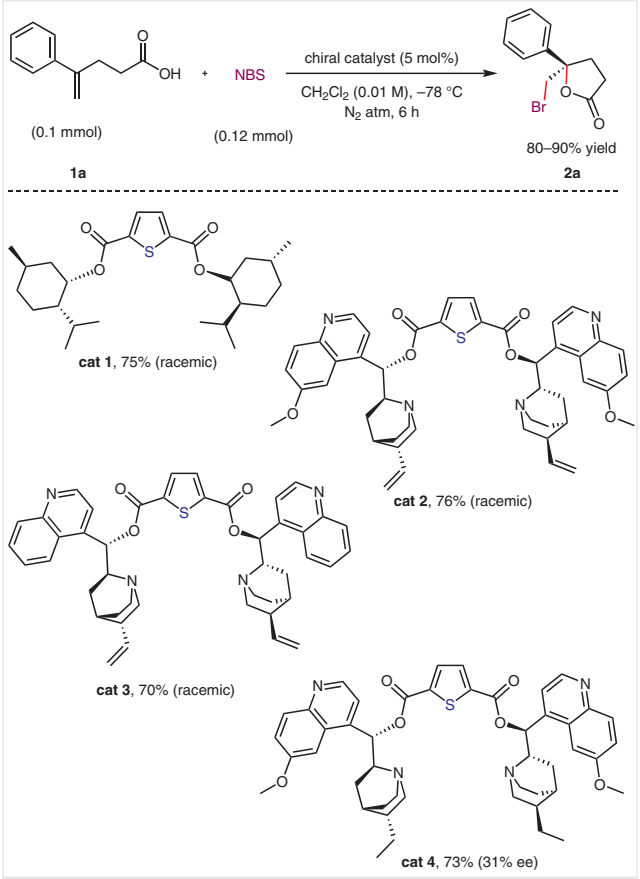
Our group has also been actively involved in selenium-catalyzed halocyclizations of alkenoic acids, where selenium plays a vital role in the transformation.[12] Inspired by our recent development of the regioselective synthesis of medium-sized bromo/iodolactones and bromooxepanes using a catalytic amount of a monoselenide (Scheme 1a),[12b] herein we present our results on the stereoinduction of normal- and medium-size rings (Scheme 1b). Studies on catalytic, enantioselective, chalcogenide-catalyzed medium-sized halogenation reactions are still lacking. Furthermore, the cyclization of linear-chain alkenoic acids is not a favorable process due to enthalpic and entropic factors.[12b] Substrates with an alkyl chain possess a high degree of flexibility that brings a negative entropy change during intramolecular cyclization reactions.[13] Therefore, significant research is still required for the preparation of new chiral Lewis bases and diverse structural analogues.



Scheme 1 Chalcogenide-catalyzed halogenation with formation of medium-sized rings

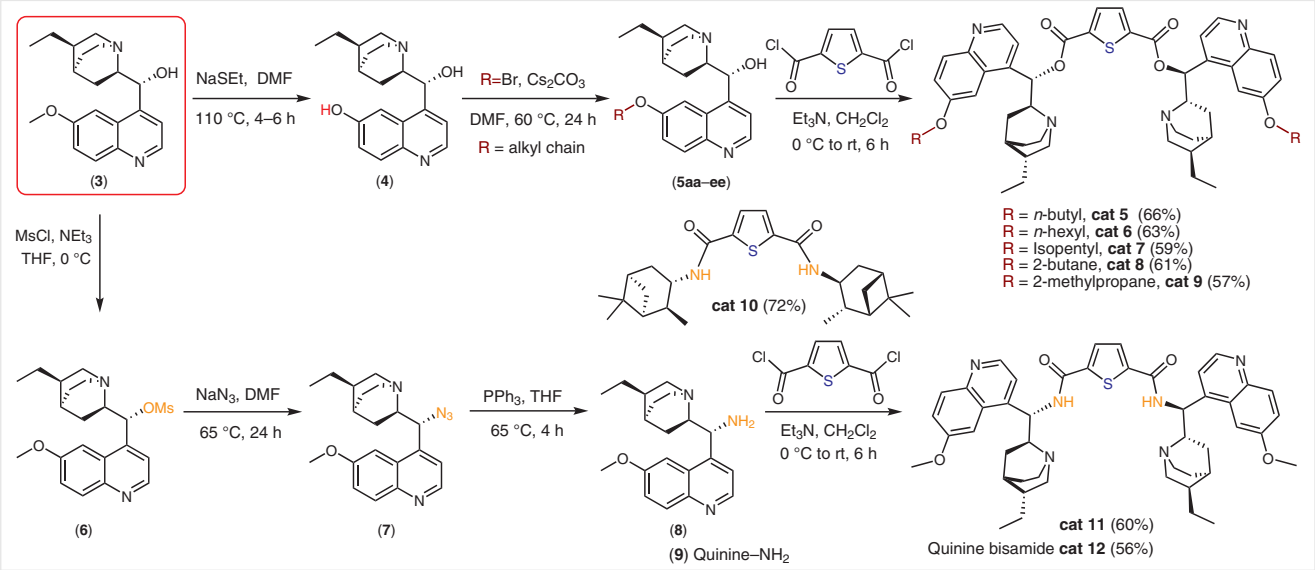
In continuation of our studies on organochalcogen chemistry,[12,14] we rationalized that the Lewis base sulfur would be able to activate a halogen for the synthesis of highly strained, medium-sized rings. Thus, we have designed a range of novel C_2-symmetric sulfur-based chiral catalysts for the synthesis of enantioenriched bromolactones. Initially, the bromolactonization of 4-phenyl-4-pentenoic acid (**1a**) was carried out using 1.2 equivalents of NBS and 5 mol% of the chiral catalyst in dichloromethane at –78 °C. We screened thiophene dicarboxylates such as (–)-menthol-based **cat 1** and found that it catalyzed the bromolactonization reaction, however, no enantioselectivity was observed (Scheme 2).

Further, we attempted to incorporate a nitrogen-based chiral scaffold to make an effective chiral catalyst and chose various cinchona alkaloid as skeletons. However, the resulting catalysts, quinine **cat 2** and cinchonine **cat 3** (Scheme 2), had no effect on the enantioselectivity and only racemic mixtures were obtained. Surprisingly, changing the skeleton to dihydroquinine (DHQN) **cat 4** (Scheme 2) resulted in an enantioselectivity (ee) of 31%. To further improve the enantioselectivity, we explored the impact of the ligand on the structure of the catalyst. Two sites in the catalyst were tuned: (i) the ester and amide units, and (ii) the *O*-alkoxy substituents on the hydroquinine unit, which was accomplished by demethylation followed by alkylation. The C_2-symmetry of the scaffold also simplified the catalyst design and modification. Moreover, different substituents have been introduced to tune the steric hindrance. The catalyst was modified by demethylation using sodium ethylthiolate followed by incorporation of different alkyl chains such as *n*-butyl, *n*-hexyl, *tert*-butyl, *iso*-butyl, 2-butane and 2-methylpropane[15] (Scheme 3). Similarly, the azide formed from the *O*-mesylated derivative of DHQN followed by azide



Scheme 2 Catalyst screening

reduction and hydrolysis provided 9-amino-(9-deoxy)-*epi*-cinchona alkaloids (DHQN-NH_2).[16] Thus, the alkoxy or amine derivative of the cinchona alkaloid was treated with

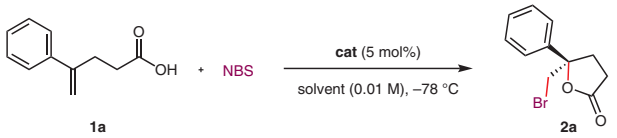


Scheme 3 Synthesis of modified catalysts

2,5-thiophenedicarbonyl dichloride under basic conditions to afford catalysts **cat 5–9** and **cat 10–12**, respectively. These bifunctional sulfur-based catalysts were then subjected to the asymmetric bromocyclization reaction.

When the reaction of **1a** and NBS was conducted with C_2-symmetric sulfur-based **cat 5** (5 mol%) in dichloromethane (CH_2Cl_2), the desired bromolactone **2a** was obtained in 88% yield with poor enantioselectivity (36% ee) within 16 hours (Table 1, entry 1). Next, various solvent systems were explored to improve the selectivity of the reaction. We observed that among several solvents, including dichloromethane, chloroform and toluene, the reaction in the less polar solvent hexane proceeded with modest enantioselectivity (45% ee) (entries 2–4). On varying the polarity with mixed solvent systems, $CHCl_3$/hexane (1:2) showed the highest efficiency with an optimum 83% ee being obtained (entries 5–9). The nonpolar solvent mixture reduced the noncatalyzed reaction and strengthened the polar interaction among the alkenoic acid, NBS, and the catalyst, resulting in enhancement of the enantioselectivity. The hexyl substitution on the quinolone moiety of thiophene dicarboxylate **cat 6**, under the same conditions, gave a lower enantioselectivity (entry 10). Similarly, reactions with **cat 7**, **cat 8** and **cat 9** occurred with low enantioselectivity (entries 11–13). Furthermore, screening the efficient isopinocampheylamine/cinchonine framework, endeavoring to increase the acidity of the carboxylate in **cat 10–12** by replacement with an amide functional group, however, resulted in a racemic mixture for **cat 10**, moderate 52% ee for **cat 11** (entry 14), and 43% ee for **cat 12**, respectively. Also, the use of additives failed to improve the stereoselectivity.

Table 1 Optimization of the Reaction Conditions[a]



Entry	Cat.	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**cat 5**	CH_2Cl_2	16	88	36
2	**cat 5**	toluene	20	75	15
3	**cat 5**	$CHCl_3$	28	85	34
4	**cat 5**	hexane	30	80	45
5	**cat 5**	toluene/CH_2Cl_2 (1:1)	35	87	38
6	**cat 5**	$CHCl_3$/toluene (1:1)	32	85	62
7	**cat 5**	$CHCl_3$/toluene (1:2)	10	81	44
8	**cat 5**	$CHCl_3$/hexane (1:1)	24	90	60
9	**cat 5**	**$CHCl_3$/hexane (1:2)**	**31**	**97**	**83**
10	**cat 6**	$CHCl_3$/hexane (1:2)	88	92	60
11	**cat 7**	$CHCl_3$/hexane (1:2)	68	87	55
12	**cat 8**	$CHCl_3$/hexane (1:2)	80	89	66
13	**cat 9**	$CHCl_3$/hexane (1:2)	50	92	45
14	**cat 11**	$CHCl_3$/hexane (1:2)	40	85	52

[a] All reactions were carried out with **1a** (0.1 mmol), NBS (0.12 mmol) and the chiral catalyst (5 mol%) in 2 mL of solvent at –78 °C in a 10 mL Schlenk tube under nitrogen. The reaction progress was monitored by TLC.
[b] Yield of isolated **2a**.
[c] Enantiopurity was determined by HPLC analysis using a ChiralPak IC-3 column.

Having optimized the catalyst and reaction conditions, we next investigated the substrate scope. A broad range of 4-phenyl-4-pentenoic acids containing aromatic substituents on the olefin was converted into the corresponding bromolactones with high yields and good to moderate enantioselectivities (Figure 1). In particular, better results were obtained with the substrates **1b** and **1c** having electron-rich methyl and methoxy groups at the *para* positions of the aromatic rings, with the lactones **2b** and **2c** being obtained with 82% and 66% ee, respectively. Electron-deficient fluoro-, chloro-, and difluoro-substituted substrates **1d–f** provided bromolactones **2d–f** with good enantioselectivities (43–66%). The X-ray crystal structure of 4-fluorophenyl γ-lactone **2d** is shown in Figure 1. Biphenyl-substituted alkenoic acid **1g** provided bromolactone **2g** with moderate selectivity (27% ee).

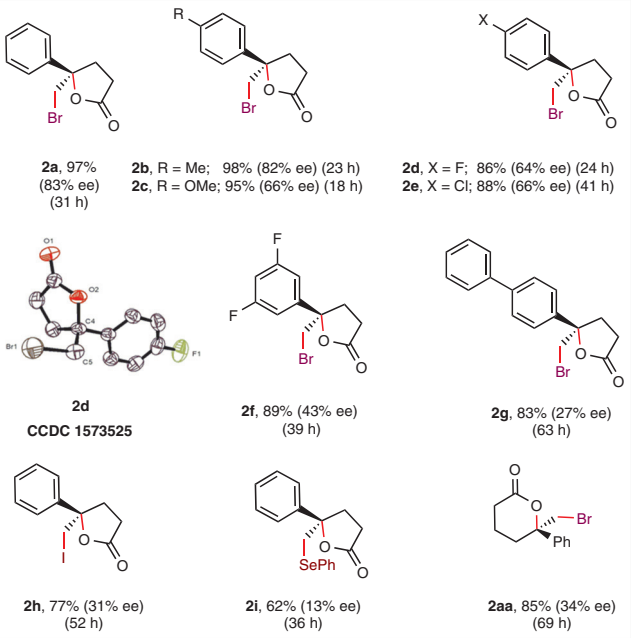


Figure 1 Scope of catalytic enantioselective halo/seleno lactonization

When *N*-iodosuccinimide (NIS) was used as the halogen source, γ-iodolactone **2h** was formed with 31% enantiomeric excess. By utilizing this protocol, five-membered selenolactone **2i**[17] was also prepared with 13% enantioselectivity and 62% yield. Furthermore, when 5-phenyl-5-hexanoic acid was subjected to the bromocyclization with NBS in the presence of 5 mol% of chiral catalyst **5** in $CHCl_3$/hexane (1:1) at –60 °C, the desired product **2aa** was obtained with 34% ee.

Next, the synthesis of various seven-membered bromo- and iodolactones was explored starting from the corresponding alkenoic acids (Figure 2). Bromolactone **3a** with a phenyl ring attached was obtained as a racemic mixture using the developed protocol. Lactones **3b–i** having an additional heteroatom in the chain were obtained in good to excellent yields (22–82%) and moderate to low enantiomeric excesses, which can be attributed to the reduction of transannular strain in the presence of the heteroatom. Electron-withdrawing Cl and NO_2 substituents on the aromatic rings yielded products **3d**,**e** with low enantioselectivities (<20%). Interestingly, electron-donating Me and OMe substituents induced slightly higher enantioselectivities (>30%) in products **3f**,**g**. Polyaromatic bromolactone **3h** containing a naphthyl ring was obtained with 14% ee.

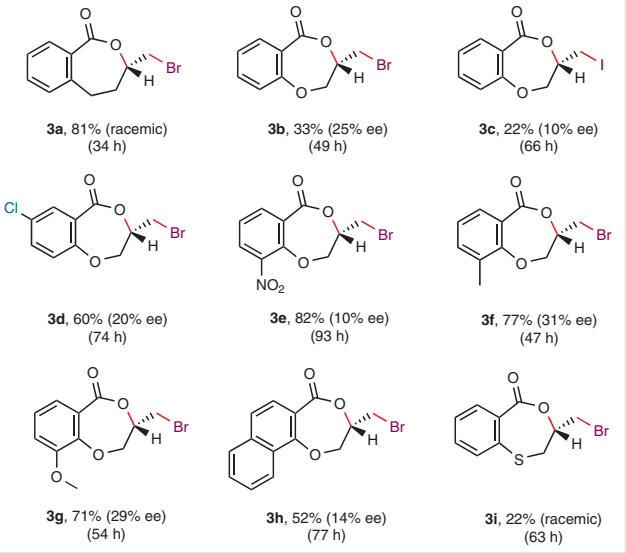
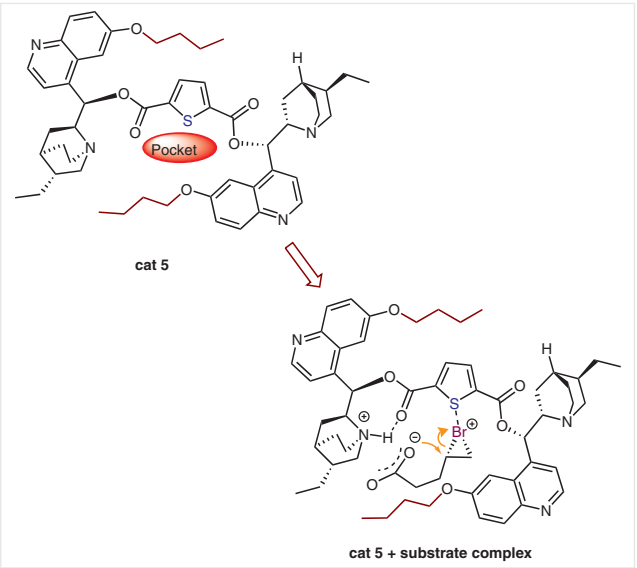


Figure 2 Scope of the enantioselective formation of seven-membered bromo/iodolactones

We speculate that the halocyclization reaction proceeds through a rigid transition state model, in which the olefin–olefin halogen exchange[18] and the transannular strain in the ring[13] could be suppressed through Lewis basic sulfur[1] or via hydrogen bond activation. The *n*-butyl moiety on the quinine scaffold leads to a pocket in which the carboxylic acid of the substrate was deprotonated by the quinine nitrogen of **cat 5** to form an ion pair (Scheme 4). **Cat 5** serves as a bifunctional catalyst by interacting with both the carboxylate nucleophile and the NBS electrophile, facilitating 5-*exo* cyclization to form desired five- to seven-membered halolactones.

In conclusion, we have developed a novel C_2-symmetric sulfur-based chiral catalyst for the enantioselective bromolactonization of alkenoic acids.[19] This protocol allows for the asymmetric synthesis of γ-, δ- and ω-lactones and selenolactones. Further mechanistic studies and investigations of this class of catalysts in another asymmetric electrophilic cyclization reactions are underway.



Scheme 4 Proposed working model

Funding Information

We are grateful for the financial support from the Science and Engineering Research Board (SERB), Department of Science & Technology (DST), New Delhi (EMR/2015/000061). S.J., A.V. and V.R. acknowledge the Indian Institute of Science Education and Research (IISER) Bhopal and UGC, New Delhi for fellowships.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610715.

References and Notes

(1) (a) Mellegaard-Waetzig, S. R.; Wang, C.; Tunge, J. A. *Tetrahedron* **2006**, *62*, 7191. (b) Ahmad, S. M.; Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Tetrahedron Lett.* **2007**, *48*, 915. (c) Castellote, I.; Morón, M.; Burgos, C.; Alvarez-Builla, J.; Martin, A.; Gómez-Sal, P.; Vaquero, J. J. *Chem. Commun.* **2007**, 1281. (d) Zhang, W.; Xu, H.; Xu, H.; Tang, W. *J. Am. Chem. Soc.* **2009**, *131*, 3832. (e) Cao, L.; Ding, J.; Yin, G.; Gao, M.; Li, Y.; Wu, A. *Synlett* **2009**, 1445. (f) *Lewis Base Catalysis in Organic Synthesis, 1st ed*; Vedejs, E.; Denmark, S. E., Ed.; Wiley-VCH: Weinheim, **2016**. (g) Perin, G.; Barcellos, A. M.; Peglow, T. J.; Nobre, P. C.; Cargnelutti, R.; Lenardão, E. J.; Marini, F.; Santi, C. *RSC Adv.* **2016**, *6*, 103657. (h) Sancineto, L.; Mangiavacchi, F.; Tidei, C.; Bagnoli, L.; Marini, F.; Gioiello, A.; Scianowski, J.; Santi, C. *Asian J. Org. Chem.* **2017**, *6*, 988.

(2) (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560. (b) Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752. (c) Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256.

(3) Electrophilic halogenation catalyzed by Lewis basic chalcogens: (a) Mellegaard, S. R.; Tunge, J. A. *J. Org. Chem.* **2004**, *69*, 8979. (b) Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899. (c) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655. (d) Snyder, S.; Treitler, A. D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303. (e) Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232. (f) Sawamura, Y.; Nakatsuji, H.; Sakakura, A.; Ishihara, K. *Chem. Sci.* **2013**, *4*, 4181. (g) Ke, Z.; Tan, C. K.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2014**, *136*, 5627. (h) Kawato, Y.; Kubota, A.; Ono, H.; Egami, H.; Hamashima, Y. *Org. Lett.* **2015**, *17*, 1244. (i) Ke, Z.; Tan, C. K.; Liu, Y.; Lee, K. G. Z.; Yeung, Y.-Y. *Tetrahedron* **2016**, *72*, 2683. (j) See, J. Y.; Yang, H.; Zhao, Y.; Wong, M. W.; Ke, Z.; Yeung, Y.-Y. *ACS Catal.* **2018**, *8*, 850.

(4) Catalytic halocyclization reactions by sulfur-based catalysts: (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171. (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (c) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354. (d) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273. (e) Laya, M. S.; Banerjee, A. K.; Cabrera, E. V. *Curr. Org. Chem.* **2009**, *13*, 720. (f) Montana, A. M.; Batalla, C.; Barcia, J. A.; Montana, A. M.; Batalla, C. *Curr. Org. Chem.* **2009**, *13*, 919. (g) Chung, W.-j.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2016**, *55*, 4396.

(5) Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 16492.

(6) For reviews on enantioselective halofunctionalization, see: (a) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10938. (b) Tan, C. K.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 7985. (c) Cheng, Y. A.; Yu, W. Z.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2014**, *12*, 2333.

(7) (a) Boye, A. C.; Meyer, D.; Ingison, C. K.; French, A. N.; Wirth, T. *Org. Lett.* **2003**, *5*, 2157. (b) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602. (c) Kambe, N.; Iwasaki, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937. (d) Shiina, I. *Chem. Rev.* **2007**, *107*, 239. (e) Gao, W.-C.; Xiong, Z.-Y.; Pirhaghani, S.; Wirth, T. *Synthesis* **2019**, *51*, 276.

(8) (a) Wong, Y.-C.; Ke, Z.; Yeung, Y.-Y. *Org. Lett.* **2015**, *17*, 4944. (b) Ke, Z.; Wong, Y.-C.; See, J. Y.; Yeung, Y.-Y. *Adv. Synth. Catal.* **2016**, *358*, 1719.

(9) (a) Tripathi, C. B.; Mukherjee, S. *J. Org. Chem.* **2012**, *77*, 1592. (b) Tripathi, C. B.; Mukherjee, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 8450. (c) Tripathi, C. B.; Mukherjee, S. *Synlett* **2014**, *25*, 163.

(10) (a) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (b) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9174. (c) Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y. Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164. (d) Castellanos, A.; Fletcher, S. P. *Chem. Eur. J.* **2011**, *17*, 5766. (e) Jiang, X.; Tan, C. K.; Zhou, L.; Yeung, Y. Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 7771. (f) Hennecke, U. *Chem. Asian J.* **2012**, *7*, 456. (g) Zhang, W.; Liu, N.; Schienebeck, C. M.; Decloux, K.; Zheng, S.; Werness, J. B.; Tang, W. *Chem. Eur. J.* **2012**, *18*, 7296. (h) Tan, C. K.; Le, C.; Yeung, Y. Y. *Chem. Commun.* **2012**, *48*, 5793. (i) Zhou, L.; Tay, D. W.; Chen, J.; Leung, G. Y.; Yeung, Y. Y. *Chem. Commun.* **2013**, *49*, 4412. (j) Fujioka, H.; Murai, K. *Heterocycles* **2013**, *87*, 763. (k) Armstrong, A.; Braddock, D. C.; Jones, A. X.; Clark, S. *Tetrahedron Lett.* **2013**, *54*, 7004. (l) Tan, C. K.; Yu, W. Z.; Yeung, Y.-Y. *Chirality* **2014**, *26*, 328. (m) Zheng, S.; Schienebeck, C. M.; Zhang, W.; Wang, H.-Y.; Tang, W. *Asian J. Org. Chem.* **2014**, *3*, 366. (n) Tay, D. W.; Leung, G. Y.; Yeung, Y. Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 5161. (o) Tan, C. K.; Er, J. C.; Yeung, Y.-Y. *Tetrahedron Lett.* **2014**, *55*, 1243. (p) Denmark, S. E.; Burk, M. T. *Chirality* **2014**, *26*, 344. (q) Chen, T.; Foo, T. J. Y.; Yeung, Y.-Y. *ACS Catal.* **2015**, *5*, 4751. (r) Samanta, R. C.; Yamamoto, H. *J. Am. Chem. Soc.* **2017**, *139*, 1460. (s) Gieuw, M. H.; Ke, Z.; Yeung, Y. Y. *Chem. Rec.* **2017**, *17*, 287.

(11) Catalytic asymmetric bromolactonization: (a) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474. (b) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 2738. (c) Chen, J.; Zhou, L.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2012**, *10*, 3808. (d) Chen, J.; Zhou, L.; Tan, C. K.; Yeung, Y.-Y. *J. Org. Chem.* **2012**, *77*, 999.

(12) (a) Balkrishna, S. J.; Prasad, C. D.; Panini, P.; Detty, M. R.; Chopra, D.; Kumar, S. *J. Org. Chem.* **2012**, *77*, 9541. (b) Verma, A.; Jana, S.; Durga Prasad, C.; Yadav, A.; Kumar, S. *Chem. Commun.* **2016**, *52*, 4179. (c) Balkrishna, S. J.; Kumar, S.; Kumar, A.; Panini, P.; Kumar, S. *Proc. Natl. Acad. Sci., India Sect. A: Phys. Sci.* **2016**, *86*, 589.

(13) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(14) (a) Kumar, S.; Yan, J.; Poon, J.-F.; Singh, V. P.; Lu, X.; Ott, M. K.; Engman, L.; Kumar, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 3729. (b) Prasad, Ch. D.; Sattar, M.; Kumar, S. *Org. Lett.* **2017**, *19*, 774. (c) Rathore, V.; Upadhyay, A.; Kumar, S. *Org. Lett.* **2018**, *20*, 6274.

(15) (a) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (b) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167. (c) Choudhury, A. R.; Mukherjee, S. *Org. Biomol. Chem.* **2012**, *10*, 7313.

(16) Cassani, C.; Martín-Rapún, R.; Arceo, E.; Bravo, F.; Melchiorre, P. *Nat. Protoc.* **2013**, *8*, 325.

(17) (a) Khokhar, S. S.; Wirth, T. *Eur. J. Org. Chem.* **2004**, 4567. (b) Khokhar, S. S.; Wirth, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 631. (c) Niu, W.; Yeung, Y.-Y. *Org. Lett.* **2015**, *17*, 1660.

(18) (a) Brown, R. S.; Nagorski, R. W.; Bennet, A. J.; McClung, R. E. D.; Aarts, G. H. M.; Klobukowski, M.; McDonald, R.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 2448. (b) Neverov, A.; Brown, R. S. *J. Org. Chem.* **1996**, *61*, 962. (c) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131. (d) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232.

(19) **Catalyst Preparation**

To a stirred solution of 2,5-thiophenedicarbonyl dichloride (1.0 equiv, 1.0 mmol, 209 mg) in CH_2Cl_2 (20 mL) at 0 °C were added dropwise the alkyl derivative of the cinchona alkaloid (2.1 equiv, 2.1 mmol) and Et_3N (4.0 equiv, 4.0 mmol) in CH_2Cl_2 (15 mL) using a dropping funnel. After the addition was complete, the mixture was stirred for 6 h at 0 °C to room temperature. After completion of the reaction, saturated $NaHCO_3$ solution (20 mL) was added to the mixture. The resulting solution was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layer washed with brine (20 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator under vacuum. The resulting solid was purified by column chromatography with CH_2Cl_2/MeOH (10:1).

2-{(1*S*)-(6-Butoxyquinolin-4-yl)[(2*S*)-5-ethylquinuclidin-2-yl]methyl} 5-{(1*S*)-(6-Butoxyquinolin-4-yl)[(2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl]methyl} Thiophene-2,5-dicarboxylate (Cat 5)

White solid; yield: 576 mg (66%); mp 147–150 °C; $[\alpha]_D^{19.4}$ +24.9 (*c* 0.33, $CHCl_3$). IR (plate): 1722, 1715, 1620, 1596, 1530, 1507, 1462, 1448, 1362, 1320, 1241 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 4.49 Hz, 2 H), 8.00 (d, *J* = 9.15 Hz, 2 H), 7.79 (s, 2 H), 7.41–7.35 (m, 6 H), 6.67 (d, *J* = 1.48 Hz, 2 H), 4.17–4.08 (m, 4 H), 3.43–3.38 (m, 2 H), 3.06 (q, *J* = 12.64 Hz, 2 H), 2.69–2.64 (m, 2 H), 2.36 (d, *J* = 12.96 Hz, 2 H), 1.87–1.71 (m, 12 H), 1.66–1.62 (m, 2 H), 1.58–1.49 (m, 6 H), 1.45–1.40 (m, 2 H), 1.37–1.25 (m, 4 H), 0.98 (t, *J* = 7.35 Hz, 6 H), 0.83 (t, *J* = 7.25 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 157.7, 147.2, 144.6, 142.8, 138.8, 133.7, 131.8, 126.7, 122.4, 118.3, 101.8, 75.7, 68.1, 59.0, 58.5, 42.8, 37.3, 31.2, 28.5, 27.7, 25.3, 23.6, 19.3, 13.8, 12.0. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{52}H_{64}N_4O_6S$: 873.4618; found: 873.4619.

Halolactones 2 and 3

To a solution of alkenoic acid (1.0 equiv, 0.1 mmol) and catalyst **cat 5** (0.05 equiv, 0.005 mmol, 4.6 mg) in a mixture of $CHCl_3$ (2 mL) and hexane (4 mL) at –78 °C in the dark under N_2 was added *N*-bromosuccinimide (NBS) (1.2 equiv, 0.12 mmol, 21 mg) or *N*-iodosuccinimide (NIS). The resulting mixture was stirred at –78 °C and the reaction progress monitored by TLC. After completion, the reaction was quenched with saturated Na_2SO_3 (2 mL) at –78 °C and then warmed to room temperature. The solution was diluted with H_2O (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography using hexane/EtOAc to yield the corresponding halolactone.

(*R*)-5-(Bromomethyl)-5-phenyldihydrofuran-2(3*H*)-one (2a)

Colorless oil; yield: 24.7 mg (97%); $[\alpha]_D^{20.5}$ –13.95 (*c* 0.66, $CHCl_3$); 83% ee. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.32 (m, 5 H), 3.72 (d, *J* = 11.31 Hz, 1 H), 3.67 (d, *J* = 11.31 Hz, 1 H), 2.85–2.74 (m, 2 H), 2.58–2.47 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 140.7, 128.8, 128.6, 124.9, 86.4, 41.0, 32.3, 29.0. HPLC (Daicel ChiralPak IC-3, *i*-PrOH/hexane = 25:75, 0.6 mL/min, 214 nm): t_1 = 21.8 (minor), t_2 = 25.0 (major).

3-(Bromomethyl)-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (3a)

White semi-solid; yield: 20.7 mg (81%); $[\alpha]_D^{26.1}$ –3.5 (*c* 0.2, $CHCl_3$); racemic. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 7.5, 0.7 Hz, 1 H), 7.47 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 1 H), 7.20 (d, *J* = 7.5 Hz, 1 H), 4.30–4.17 (m, 1 H), 3.55 (dd, *J* = 10.8, 6.1 Hz, 1 H), 3.47 (dd, *J* = 10.8, 5.4 Hz, 1 H), 3.05–2.95 (m, 1 H), 2.83–2.75 (m, 1 H), 2.20–2.10 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 137.7, 133.0, 131.2, 130.3, 128.8, 127.6, 77.1, 32.8, 32.6, 29.4. HPLC (Daicel ChiralPak IC-3, *i*-PrOH/hexane = 25:85, 0.6 mL/min, 214 nm): t_1 = 25.0 (minor), t_2 = 29.1 (major).