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Investigating the Enantiodetermining Step of a Chiral Lewis Base Catalyzed Bromocycloetherification of Privileged Alkenes

Dietrich Böse[1]
Scott E. Denmark*

University of Illinois at Urbana-Champaign, Department of Chemistry, 600 S Mathews Ave., Urbana, IL 61801, USA
sdenmark@illinois.edu

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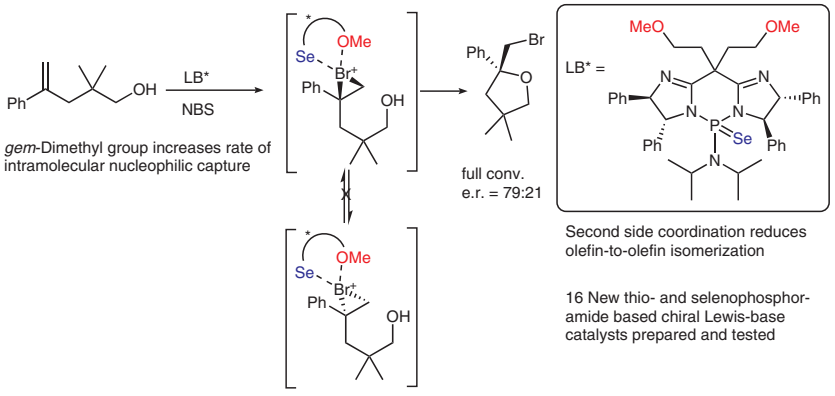

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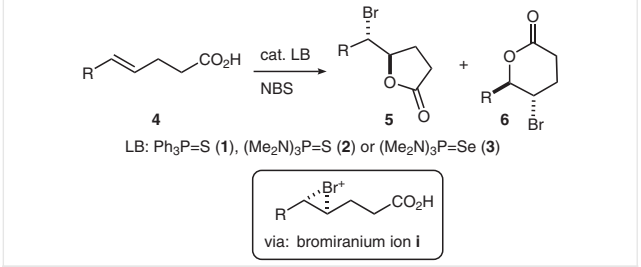
Abstract The development of catalytic, enantioselective halofunctionalizations of unactivated alkenes has made significant progress in recent years. However, the identification of generally applicable catalysts for wide range of substrates has yet to be realized. A detailed understanding of the reaction mechanism is essential to guide the formulation of a truly general catalyst. Herein, we present our investigations on the enantiodetermining step of a Lewis base catalyzed bromocycloetherification that provides important insights and design criteria.

Key words Lewis base, halofunctionalization, alkenes, selenophosphoramides, bromocycloetherification, bromiranium ions

Electrophilic functionalization, in particular halofunctionalization of alkenes, is one of the basic reactions in organic synthesis and has developed over the years from simple dihalogenation reactions to substrate-directed diastereoselective reactions and enantioselective halofunctionalisations.[2] However, catalytic, enantioselective variants emerged only in the past few years and the field has attracted significant attention as illustrated the appearance of several review articles in the last few years.[3]

In this context, these laboratories have focused on the development of the concept of Lewis base activation of Lewis acids to effect catalysis with main-group elements.[4] It has been already demonstrated that this concept can serve as a basis for the development of enantioselective Lewis base catalysis, e.g., for electrophilic seleno- and thiofunctionalizations.[5] Further investigations have demonstrated that Lewis bases such as triphenylphosphine sulfide (**1**), thiophosphoramide **2**, and selenophosphoramide **3** act as efficient catalysts for *racemic* bromo- and iodolactonizations of olefinic acids **4** to stereoselectively form brominated five- and six-membered (**5** and **6**) lactones via the intermediacy of bromiranium ions **i** (Scheme 1).[6] Catalytic, enantioselective bromoetherifications using chiral Brønsted acids have also been achieved.[7]

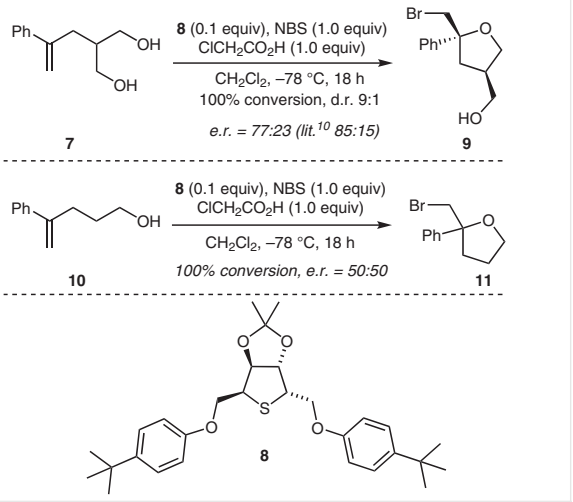


Scheme 1 Lewis base catalyzed bromolactonization via bromiranium ion formation

Successful enantioselective halofunctionalizations therefore depend on chemical and configurational stability of haliranium ions. In 2010, work from these laboratories demonstrated that an inverse relationship exists between chemical and stereochemical stability of such haliranium ions.[8] The experiments involved the generation of enantiomerically enriched haliranium ions (chloriranium and bromiranium) by means of solvolysis followed by a nucleophilic trapping. Whereas chloriranium ions show the lowest chemical stability, their enantioselective formation and nucleophilic opening proceeds without loss of enantiomeric purity. With the more stable bromiranium ions an erosion of enantiomeric purity was observed. This is caused by an alkene-to-alkene exchange mechanism as was first demonstrated by Brown.[9] These observations have an important implication for the catalytic formation and capture of these ions. In the case of chloriranium ions the enantioselectivity can be controlled only during their formation. In contrast, reactions involving bromiranium ions may be controlled by

either a dynamic asymmetric transformation with a chiral catalyst or by catalyst suppression of racemization to achieve high selectivity control over the overall process.[4a]

In 2014 Yeung *et al.* reported an interesting example of a chiral Lewis base catalyzed enantioselective bromocycloetherification of olefinic 1,3-diols **7** using chiral tetrahydrothiophenes **8** as the catalyst.[10] It was striking that only symmetrical 1,3-diols such as **7** are viable substrates to form cyclic ethers **9** enantio- and diastereoselectively (Scheme 2). On the basis of the proposed mechanism, there is no reason to expect that simple alcohols such as **10** should not undergo the same transformation.[11] Therefore, we attempted the enantioselective bromocycloetherification of the simple alcohol **10** using catalyst **8** and were surprised to find that this reaction delivered only *racemic* product **11** (Scheme 2).

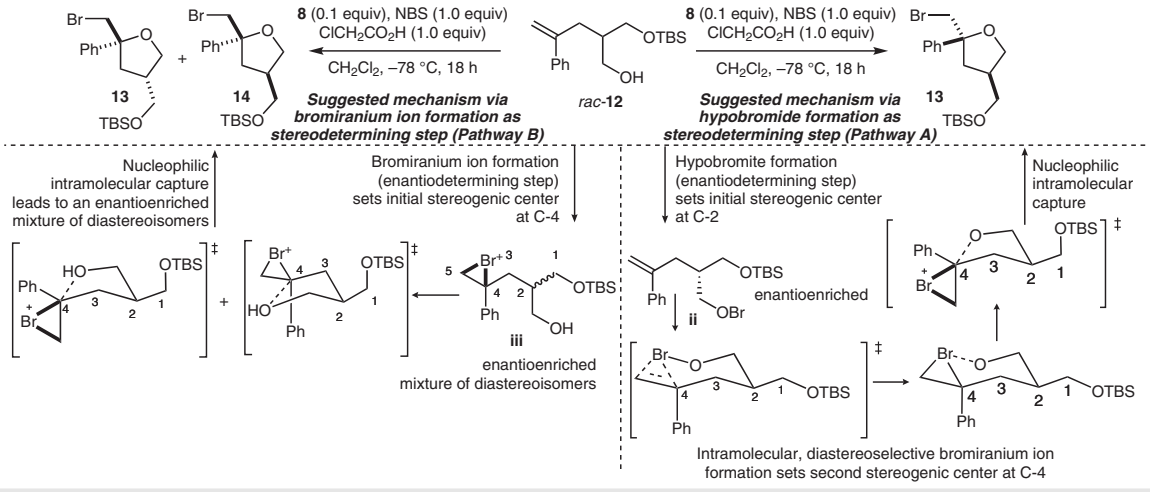


Scheme 2 Chiral tetrahydrothiophene **8** catalyzed enantioselective bromocyclization of 1,3-diols and *racemic* bromocycloetherification of simple olefinic alcohol **10a** using *N*-bromosuccinimide (NBS) and chloroacetic acid

On the basis of these results, it was plausible to argue that the formation of a bromiranium ion might not be the enantiodetermining step of this transformation. Instead, it seems possible that this process might proceed through an enantiotopic group discrimination mechanism, in which the alkoxy hypobromite formation is the stereodetermining first step. This hypobromite then reacts with the olefin intramolecularly, forming a bromiranium ion which is then captured by a nucleophilic attack of one of the alcohol groups. This hypothesis would explain why alcohol **10** cyclizes to the *racemic* product **11** because an achiral alkoxy hypobromite is formed, thus rendering the following reaction steps unselective.

To gain insight into the reaction mechanism, *racemic*, monoprotected alcohol **12** would be subjected to the bromocycloetherification reaction conditions. The goal of this experiment was to distinguish between the two possible reaction mechanisms. In principle, the non-*racemic* bromocycloetherification can proceed by an enantiotopic group differentiating alkoxy hypobromite formation (pathway A) or by an enantioselective bromiranium ion formation (pathway B) as the stereodetermining step (Scheme 3).

In the case of an enantioselective bromocycloetherification through a stereodetermining hypobromite formation (pathway A) the first step would set the initial stereogenic center at C-2. The following intramolecular bromiranium ion formation, which sets the stereogenic center at C-4, and intramolecular nucleophilic capture should proceed with high diastereoselectivity as it is observed for diol **7**. Thus, an enantioselective formation of alkoxy hypobromite **ii** would not only set the absolute, but also the relative configuration



Scheme 3 Proposed mechanistic pathways for an enantioselective bromocycloetherification desymmetrization of olefinic 1,3-diols with a enantiotopic group differentiating hypobromite **ii** formation as the stereodetermining step (pathway A) and an enantioselective bromiranium ion **iii** formation as the stereodetermining step (pathway B).

of **13**, this pathway should deliver the product as an enantioenriched single diastereomer at 50% conversion. However, at 100% conversion, diastereomerically enriched but *racemic* product **13** would be expected (Scheme 3).

If the bromocycloetherification of alcohol *rac*-**12** is proceeding by an enantioselective bromiranium ion **iii** formation (Scheme 3, pathway B), then the product mixture of **13** and **14** should be composed of two enantioenriched diastereoisomers. In such case the enantioselectivity would be controlled by the catalyst, whereas the diastereoselectivity would be dictated by the substrate. At this point it is assumed that the similarity of the two functional groups (OH vs. OTBS) and their distance to the newly formed bromiranium ion should lead to low diastereoselection.

The bromocycloetherification of *racemic*, monoprotected diol *rac*-**12**, under the conditions shown in Scheme 4, gave after full conversion a 41:59 mixture of two diastereoisomers (**13**/**14**) as determined by ^{1}H NMR analysis.[12] After removal of the TBS group by treatment with TBAF (see Supporting Information for details), the relative and absolute configurations were assigned by comparison of ^{1}H NMR and HPLC data to previous experiments and to previously published results by Yeung *et al.*[10,11] Both diastereoisomers **13** and **14** were formed with an enantiomeric ratio of 60:40, which was also determined after the TBS-group cleavage.

The initial bromiranium ion formation can fundamentally occur with four different rates k_1–k_4, which define the enantiomeric and diastereomeric outcome of the reaction and are represented by the concentrations of isomers **I**–**IV**.

The enantiomeric composition of the diastereoisomers **13** and **14** is then given through: e.r. (**13**) = k_2/k_4, and e.r. (**14**) = k_1/k_3. The diastereomeric ratio is defined through: d.r. (**13**/**14**) = $(k_2 + k_4)/(k_1 + k_3)$ (Scheme 5). Since the starting material is *racemic*, the sum of isomers **I** and **III** should be equal to the sum of isomers **II** and **IV**. The concentration of all isomers can be individually calculated by multiplying the enantiomeric ratios with the diastereomeric ratios, respectively, as shown in Table 1.

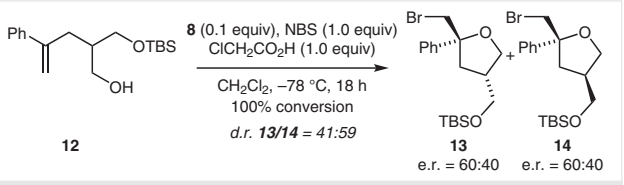
Table 1 Enantiomeric and Diastereomeric Ratios of the Isomers **I**-**IV**

Isomer	e.r.	d.r.	e.r. × d.r.
[**I**]	0.6	0.59	0.354
[**II**]	0.4	0.59	0.236
[**III**]	0.4	0.41	0.164
[**IV**]	0.6	0.41	0.246

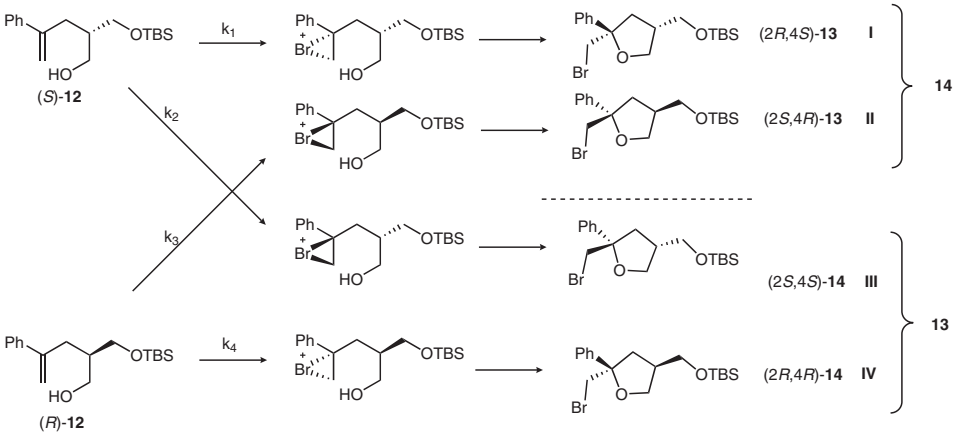
[**I**] + [**III**] = 0.354 + 0.164 = 0.518
[**II**] + [**IV**] = 0.236 + 0.246 = 0.482

This result shows that the observed ratios are in good agreement (0.52 ≈ 0.48) with a bromocycloetherification mechanism based on an enantioselective bromiranium ion formation (pathway B) as depicted in Scheme 3. A possible racemization by an olefin-to-olefin interchange of bromiranium ions does not interfere with the drawn conclusions.

Therefore, the hypobromite formation can be ruled out as the productive mechanism for an enantioselective bromocycloetherification via an enantiotopic group discrimination process (pathway A). At the same time, the data provided in Table 1 is in good agreement with an enantioselective bromiranium ion formation (pathway B) as the enantiodetermining step. However, this conclusion still does not provide an explanation for why the simple alcohol

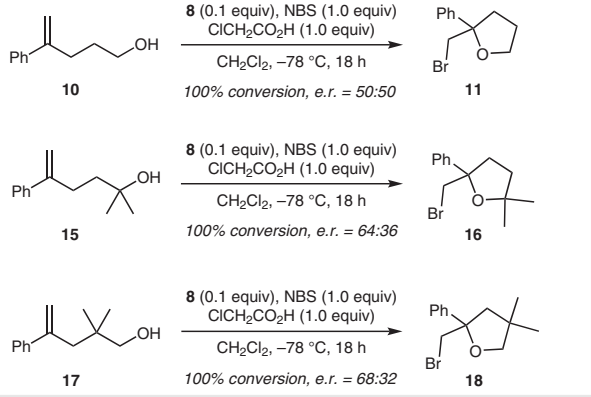


Scheme 4 Mechanistic probe reaction set up to investigate the enantiodetermining step of the Lewis base catalyzed bromocycloetherification



Scheme 5 Mechanistic analysis for an enantioselective bromocycloetherification with stereodetermining bromiranium ion formation (pathway B)

10 does not undergo an enantioselective bromocycloetherification. A possible explanation could be connected to the rate with which the intramolecular nucleophilic attack on the bromiranium ion takes place. If the attack is slower than the racemization of the bromiranium ion by olefin-to-olefin interchange, the product would be a *racemic*. Therefore, the reason for the observed enantioselectivity for substrate **7**, or the lack of thereof in substrate **10**, might arise from in the increased rate of cyclization owing to the Thorpe–Ingold effect in substrate **7a**.[13] To test this hypothesis, a short substrate survey was conducted with three different simple alcohols **10**, **15**, and **17** (Scheme 6).



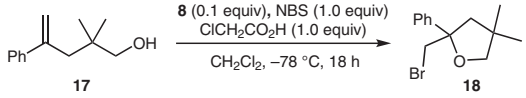
Scheme 6 Enantioselective bromocycloetherification of *gem*-dimethyl-containing olefinic alcohols

In contrast to the primary alcohol **10** which cyclized to form *racemic* product **1**, tertiary alcohol **15** cyclized to form product **16** with an enantiomeric ratio of 64:36. This result further supports pathway B (chiral bromiranium ion formation as the enantiodetermining step) as the primary mechanism. Finally, neopentyl alcohol **17** (containing two methyl groups in the β-position) afforded cyclization product **18** with an enantiomeric ratio of 68:32. These observations clearly underline the fact that the Thorpe–Ingold effect plays a major role for the enantioselectivity of this type of reaction.[13]

Because substrate **17** is clearly viable, an additional optimization of reaction conditions was conducted (see Supporting Information for details). These investigations showed that the reaction conditions employed were indeed suitable for achieving high conversion. In a recent study, Yeung and his group investigated the influence of catalyst structure, temperature, addition sequence of components, catalyst loading, and MsOH additive on the outcome of the bromocycloetherification of olefinic 1,3-diols.[11] However, we also found that the enantioselectivities observed in the bromocycloetherification are strongly dependent on the water content of the solvent used. All experiments described in this study were conducted in dichloromethane freshly taken from a solvent-drying system. However, rigorously dried dichloromethane (using highly activated molecular sieves) led to reduced enantioselectivities. This surprising observation implied an unexpected role for water as the reaction medium, something not accounted for in any mechanistic rationalization.

Therefore, dichloromethane with varying water content was prepared and tested in the enantioselective bromocycloetherification (Table 2). It was very surprising to find that the highest enantioselectivity was observed with dichloromethane saturated with water. An explanation for this behavior is obscure at this time.

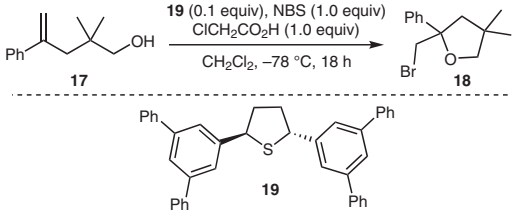
Table 2 Influence of Water Content on the Enantioselectivity of the Lewis Base Catalyzed Bromocycloetherification of **17**



Entry	Water content (μg/mL)[a]	Source	Conversion (%)[b]	e.r.[c]
1	0	dried with 4Å MS	100	53:47
2	8	fresh from SDS	100	68:32
3	48	water added	100	68:32
4	112	water added	100	70:30
5	416[a]	commercial bottle	100	74:26
6	1985[a]	saturated with water	100	74:26

[a]Determined by Karl-Fischer titration.
[b] Determined by ^{1}H-NMR analysis of the crude reaction mixture.
[c] Determined by CSP-HPLC.

Table 3 Bromocycloetherification of **17** Catalyzed by Chiral Tetrahydrothiophenes



Entry	Catalyst	Conversion (%)[a]	e.r.[b]
1	**8**	100	74:26
2	**19**	100	49:51

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture.
[b] Determined by CSP-HPLC.

With the optimal substrate and the optimized reaction conditions in hand a second catalyst survey was conducted (Table 3).[14] For all further experiments dichloromethane with a water content >500 μg/mL was used.

For these experiments, two different C_2-symmetric tetrahydrothiophenes were tested. These results, together with similar results published by Yeung *et al.*,[11] clearly indi-

cate that a tetrahydrothiophene core structure alone in the catalyst is not sufficient for an enantioselective reaction. The primary difference between these catalyst structures is the presence of the phenolic ethers in catalyst **8** which is absent in catalyst **19**. Thus, it is possible that a second Lewis basic coordinating side in the catalyst's structure is necessary for observable enantioselectivities.

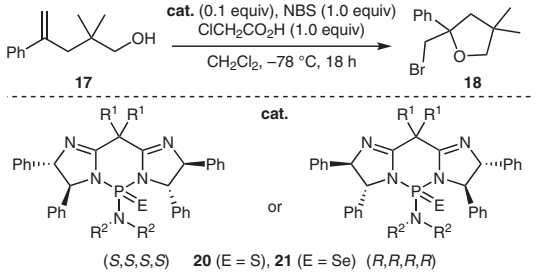
To test this hypothesis, a new family of catalysts was envisioned that could incorporate the additional coordinating group into the structure. Chiral thiophosphoramides and selenophosphoramides were identified as these functional groups proved to be effective catalysts for these types of transformations.[6] To enable introduction of the second coordinating site, a number of bisimidazoline-based catalysts **20** and **21** was prepared in which the bridging carbon could be functionalized with different substituents.

The evaluation of the enantioselective bromocycloetherification of **17** began with thiophosphoramides **20a–f** which were ineffective as Lewis base catalysts for the reaction (Table 4, entries 1–6). All thiophosphoramides **20** gave very low conversions (less than 28%) and none provided any enantioselection.

Next, chiral selenophosphoramides **21a–l** were investigated. The selenophosphoramides were considerably more effective catalysts than the thiophosphoramides and led to a clean and full conversion in almost all cases. Additionally, several catalysts showed moderate to good enantioselectivities. The results obtained with catalysts **21a** vs. **21c** and **21b** vs. **21d** (Table 4, entries 7–10) clearly show that the steric effect of the groups attached to the backbone of the catalysts (i.e., methyl vs. propyl) did not play a critical role for the reactivity or enantioselectivity. On the other hand, the steric effect of the groups attached to the external nitrogen (methyl vs. isopropyl, Table 4, entries 16 and 17) does have a major influence on the enantioselectivity. This trend is visible with almost all catalysts explored in this study. Most interestingly, catalysts **21k** and **21l**, with a methoxyethyl group attached to the backbone, afforded the highest selectivities, while maintaining very high reactivity. These results clearly support the hypothesis that an additional coordination side in the structure of the catalysts plays an important role for the stabilization of the intermediate bromiranium ions, preventing them from a racemization via an olefin-to-olefin transfer as shown in Scheme 7. However, we cannot rule out the possibility of a dynamic, kinetic asymmetric transformation in which the catalyst–bromiranium ion assembly undergoes equilibration, though if that were operative, then enantioselectivity should be observed with substrate **10**.

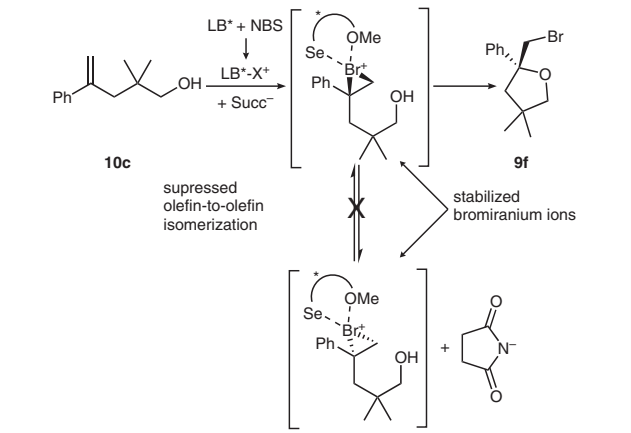
In conclusion, we have shown that bromiranium ion formation is most likely the enantiodetermining step in the Lewis base catalyzed enantioselective bromocycloetherification of Yeung's substrate **7**. We have also been able to identify that fast nucleophilic attack on the bromiranium ion *and* the presence of water is the key for high enantiomeric ratios observed. Two possible strategies to overcome the intrinsic low configurational stability of bromiranium ions were identified. First the Thorpe–Ingold effect, which leads to an increased cyclization rate, can be applied to achieve modest enantioselectivities. Second, stabilization of the bromiranium ion through an additional donating group in the catalyst's structure can effectively suppress the olefin-to-olefin interchange racemization. To our knowledge this strategy has so far not been explored in other designed catalysts, even if first examples of bifunctional Lewis base catalysts have been already published.[15] So far neither strategy alone is effective enough to provide good enantioselectivities. It is hoped that the mechanistic insights presented here will influence the future development of a truly rationally designed and general Lewis base catalyst which is capable of effecting a broad spectrum of enantioselective halofunctionalizations of unactivated olefins.

Table 4 Survey of Seleno- and Thiophosphoramides as Chiral Catalysts



Entry	Catalyst	R^1	R^2	E	Conversion (%)[a]	e.r.[b]
1	**20a** (*R*)	C_3H_7	$CH(CH_3)_2$	S	22	50:50
2	**20b** (*R*)	C_3H_7	$C_2H_4OCH_3$	S	0	–
3	**20c** (*R*)	CH_2OCH_3	CH_3	S	28	50:50
4	**20d** (*R*)	CH_2OCH_3	$CH(CH_3)_2$	S	0	–
5	**20e** (*S*)	$C_4H_4OCH_3$	CH_3	S	0	–
6	**20f** (*R*)	CH_3	$-(CH_2)_5-$	S	<10	50:50
7	**21a** (*S*)	CH_3	CH_3	Se	100	49:51
8	**21b** (*S*)	CH_3	$CH(CH_3)_2$	Se	100	38:62
9	**21c** (*R*)	C_3H_7	CH_3	Se	100	49:51
10	**21d** (*R*)	C_3H_7	$CH(CH_3)_2$	Se	100	62:38
11	**21e** (*R*)	C_3H_7	$C_2H_4OCH_3$	Se	100	52:48
12	**21f** (*R*)	CH_2OCH_3	CH_3	Se	100	57:43
13	**21g** (*S*)	CH_2OCH_3	$CH(CH_3)_2$	Se	95	49:51
14	**21h** (*S*)	CH_2OCH_3	(*R*)-$CH(CH_3)$Ph	Se	100	49:51
15	**21i** (*S*)	CH_2OCH_3	(*S*)-$CH(CH_3)$Ph	Se	100	47:53
16	**21k** (*R*)	$C_2H_4OCH_3$	CH_3	Se	100	41:59
17	**21l** (*R*)	$C_2H_4OCH_3$	$CH(CH_3)_2$	Se	100	21:79

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture.
[b] Determined by CSP-HPLC.



Scheme 7 Mechanistic rationale for a suppressed olefin-to-olefin isomerization through a stabilization of the intermediate bromiranium ion by a Lewis base catalyst with an additional coordination side in the catalyst´s structure

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590951.

References and Notes

(1) New current address: Dietrich Böse, Boehringer Ingelheim RCV GmbH & Co KG, Dr.-Boehringer-Gasse 5-11, 1121 Vienna, Austria; e-mail: dietrich.boese@boehringer-ingelheim.com.

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(12) **Experimental Procedures: Enantioselective Bromocycloetherification of 2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4-phenylpent-4-en-1-ol (12)**
A stock solution of 2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4-phenylpent-4-en-1-ol (*rac*-**12**) (30 mg/1.0 mL) in CH_2Cl_2 was added (1.0 mL, 0.1 mmol) to cyclic sulfide **8** (0.01 mmol, 0.1 equiv) in a septum sealed sample vial at 20 °C. The solution was cooled to –78 °C, and a second stock solution of chloroacetic acid in CH_2Cl_2 (0.1 M, 1.0 mL, 0.1 mmol, 1.0 equiv) was added. After 10 min at this temperature a stock solution of NBS (0.1 M, 1.0 mL, 0.10 mmol, 1.0 equiv) was slowly added. After 13 h 1 mL of a stock solution of $NaBH_4$ in EtOH (50 mg/5 mL) was added. Then the reaction was slowly warmed to 0 °C (over approx. 2 h). Then 1 mL of H_2O and 1 mL of hexanes (HPLC grade) were added, and the mixture was stirred at 20 °C for 15 min. After phase separation, the organic phase was filtered through a plug of $MgSO_4$ and Celite and evaporated using a stream of nitrogen. The residue was dissolved in $CDCl_3$ and a ^1H NMR spectrum was collected to estimate conversion and product distribution. The diastereomeric ratio was found to be **13**/**14** = 41:59. Then the products were dissolved in THF (2 mL) at 20 °C and TBAF was added (95 mg, 0.3 mmol, 3.0 equiv). The reaction was stirred at 20 °C until full conversion was observed by TLC analysis (hexanes/EtOAc, 90:10). After 2.5 h 10 mL of diethyl ether were added, and the mixture was washed with sat. aq NH_4Cl solution (1 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated. Purification by column chromatography (hexanes/EtOAc, 90:10) yielded the pure products as a diastereomeric mixture. HPLC analysis revealed that both diastereoisomers were formed with an enantiomeric ratio of 60:40

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(14) For all screening experiments CH_2Cl_2 with a water content of >500 µg/mL was applied. A stock solution (0.12 M) of 2,2-dimethyl-4-phenylpent-4-en-1-ol (**17**) in CH_2Cl_2 (0.25 mL, 0.03 mmol) was added to the indicated Lewis base (0.003 mmol, 0.1 equiv) in a septum-sealed sample vial at 20 °C. The solution was cooled to –78 °C, and a second stock solution of chloroacetic acid (CAA) in CH_2Cl_2 (0.12 M, 0.25 mL, 0.03 mmol, 1.0 equiv) was added. After 10 min at this temperature a stock solution of NBS (0.12 M, 0.25 mL, 0.03 mmol, 1.0 equiv) was slowly added. After 18 h 1 mL of a stock solution of $NaBH_4$ in EtOH (50 mg/5 mL) was added. Then the reaction was slowly warmed to 0 °C (over approx. 2 h). Then 1 ml of H_2O and 1 mL of hexanes (HPLC grade) were added, and the mixture was stirred at 20 °C for 15 min. After phase separation, the organic phase was filtered through a plug of $MgSO_4$ and Celite and evaporated using a stream of nitrogen. The residue was dissolved in $CDCl_3$ and a ^1H

NMR spectrum was collected to estimate conversion and product distribution (d.r.). HPLC analysis was used to establish the enantioselectivities. HPLC: **18** t_R = 8.2 min; *ent*-**18** t_R = 8.8 min (Chiralcel OJH, hexanes/2-propanol; 99:01, 0.4 mL/min, 220 nm, 20 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 1.21 (s, 3 H, 1″-H), 2.25 (d, *J* = 12.8 Hz, 1 H, 3-Ha), 2.35 (d, *J* = 12.8 Hz, 1 H, 3-Hb), 3.63 (s, 2 H, 1′-H), 3.66 (d, *J* = 8.2 Hz, 1 H, 5-Ha), 3.82 (d, *J* = 8.3 Hz, 1 H, 5-Hb), 7.24–7.33 (m, 1 H), 7.37 (dd, *J* = 8.6, 6.9 Hz, 2 H), 7.43–7.48 (m, 2 H, PhH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.0, 27.1, 40.8, 43.5, 51.9, 80.6, 86.0, 125.7, 127.3, 128.3, 144.7.

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