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Enantioselective Haloetherification by Asymmetric Opening of *meso*-Halonium Ions

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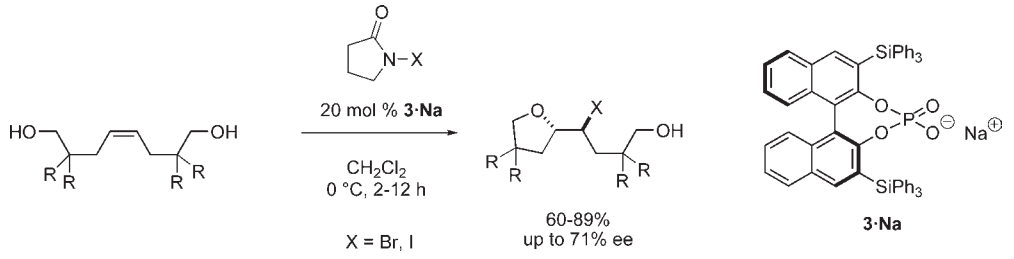
ABSTRACT



A new approach to enantioselective haloetherification reactions via desymmetrization of *in situ*-generated *meso*-halonium ions is described. The combination of *N*-haloamides as a halogen source and sodium salts of chiral phosphoric acids as catalysts can be used for the cyclization of symmetrical ene-diol substrates, yielding the haloetherification products under practical conditions in enantioenriched form.

Halocyclization reactions such as halolactonization or haloetherification are powerful for the preparation of heterocycles. The combination of a cyclization with the stereoselective generation of two new stereocenters and the introduction of a new functional group (halogen) for further transformations have led to their frequent use in natural product synthesis. However, there are only a few reported reagent-controlled asymmetric variants of these reactions.[1] Early examples from the Taguchi group used stoichiometric amounts of titanium taddolates to promote iodocyclizations with enantioselectivities up to 65% ee.[2] Various complexes of iodine-electrophiles with chiral amines have been used in iodocyclization reactions; however, only moderate enantioselectivities were achieved (up to 45% ee).[3] Excellent enantioselectivities (up to 99%) were reported by the Ishihara group in an electrophilic iodine induced polyene cyclization cascade using a stoichiometric quantity of a phosphoramidite promoter.[4] Efficient catalytic asymmetric halocyclization reactions are even scarcer, and only in 2002 did Kang et al. develop the first catalytic asymmetric iodoetherification reaction employing a cobalt salen complex.[5] Very recently asymmetric chloro-, bromo-, and iodolactonizations of alkenenoic acids have been reported by the groups of Borhan,[6] Jacobsen,[7] Yeung,[8]

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(2) Kitagawa, O; Hanano, T.; Tanabe, K.; Shiro, M.; Taguchi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1005.

(3) (a) Grossmann, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233. (b) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297. (c) Hass, J.; Bissmire, S.; Wirth, T. *Chem.—Eur. J.* **2005**, *11*, 5777. (d) Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281. For a related chiral pyridine/bromonium electrophile and its application, see: Cui, X. L.; Brown, R. S. *J. Org. Chem.* **2000**, *56*, 5653.

(4) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.

(5) (a) Kang, S. H.; Sung, B. L.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (b) Kwon, H. Y.; Park, C. M.; Sung, B. L.; Youn, J.-H.; Kang, S. H. *Chem.—Eur. J.* **2008**, *14*, 1023. (c) Kang, S. H.; Park, C. M.; Lee, S. B.; Kim, M. *Synlett* **2004**, 1279. For a recent application of this catalyst system to iodolactonizations, see: Ning, Z.; Jin, R.; Ding, J.; Gao, L. *Synlett* **2009**, 2291.

(6) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298.

(7) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332.

(8) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474.

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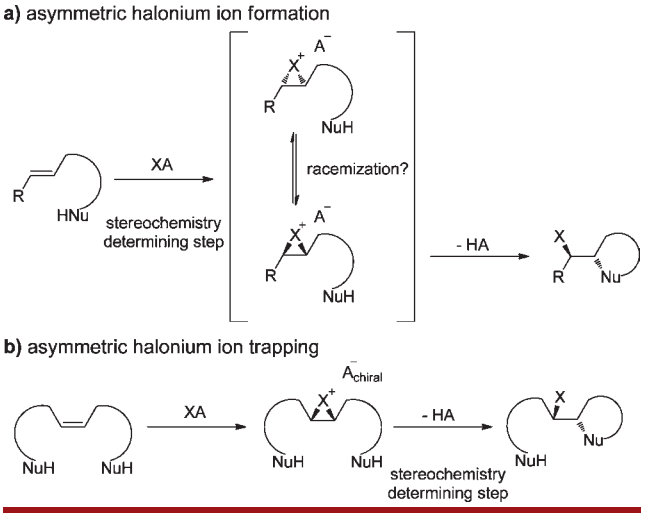
Scheme 1. Stereochemistry-Determining Steps of Halocyclizations



and Fujioka,[9] respectively, using organocatalysts. A related enantioselective bromolactonization of conjugated enynes catalyzed by chinchonidine ureas was reported by Tang et al.[10] With these methods, highly enantioselective halolactonizations of a range of alkenoic acids are now possible. However, asymmetric halocyclization reactions are still regarded as difficult reactions and in many cases only low selectivities were obtained.[11] This is often attributed to the rapid loss of enantiomeric purity of the halonium ion intermediate by rapid alkene-to-alkene transfer as shown by Brown[12] and Denmark.[13] On the other hand, it has been demonstrated by Braddock[14] and Denmark[13,15] that enantiopure halonium ions can be prepared and stereospecifically trapped.

Here we present a conceptually different approach to enantioselective halocyclizations trying to avoid the problems caused by alkene-to-alkene transfer. Up to now, all catalysis attempts have focused on the enantioselective formation of the intermediate halonium ion as the stereochemistry-determining step (Scheme 1, a).

Our approach is instead based on the selective opening of halonium ions in the presence of a suitable chiral counteranion (Scheme 1, b).[16] By catalyzing this second step we should avoid all problems connected to the potentially insufficient stereochemical integrity of halonium ions.

To demonstrate our concept we chose (*Z*)-oct-4-en-1, 8-diol **1a** as our model substrate. Upon treatment with an electrophilic iodine source, a *meso*-iodonium ion should form that further reacts in a 5-*exo* cyclization to the tetrahydrofuran product **2a**. Initial experiments with chiral phosphoric acids to activate the iodine source and as chiral counterion in the iodonium opening gave encouraging results. Reactions were performed using 20 mol % of the catalyst in toluene with *N*-iodosuccinimide (NIS) as iodine source at low temperature. Molecular sieves were added to ensure reproducibility.[17] Yields were generally high, but whereas phosphoric acids based on 3,3′-diarylBINOL[18] **4** or VAPOL[19] **5** led to no detectable enantioselectivity, the combination of NIS and BINOL-derived acid **3**·**H**[20] yielded the product with 22% ee (Table 1, entries 1−4).

Attempts to improve the selectivity using other iodine sources (iodine, 1,3-diiodo-5,5-dimethylhydantoin, bis(collidine)iodonium hexafluorophosphate, and benzyltrimethylammonium dichloroiodate[21]) were not rewarding (data not shown). The combination of silver carbonate and iodine led to a slight improvement (entry 5, 30% ee) but rendered isolation of the product difficult due to the lability of the alkyl iodide **2a** in presence of the silver salt. A first significant improvement was achieved when *N*-iodopyrrolidinone **6** (NIPyr), a iodine source similar to NIS, was tested.[22] Application of NIPyr **6** gave an improved enantioselectivity (entry 6, 34% ee). A second key improvement came with the use of the sodium salt of phosphoric acid **3**·**H**. The identity of this salt, prepared by simply treating the acid with NaOH followed by recrystallization, was proven by X-ray crystallography (see Supporting Information for details). Using **3**·**Na** the enantioselectivity increased to 44% ee (entry 7). Optimization of the solvent (with chlorinated solvents being slightly superior to other solvents, entries 8−11) and reaction temperature led to a further improvement to 62% ee. Experiments with the lithium and the potassium salts of

(9) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew Chem. Int. Ed.* **2010**, *49*, 9174.

(10) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664.

(11) (a) Ahmad, S. M.; Braddock, D. C.; Cansell, G.; Hermitage, S. A.; Redmond, J. M.; White, A. J. P. *Tetrahedron Lett.* **2007**, *48*, 5948. (b) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874. For an extensive study of achiral Lewis base catalysis in halocyclization reactions, see: Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655.

(12) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1996**, *61*, 962.

(13) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232. For related work on thiiranium and seleniranium ions, see: Denmark, S. E.; Collins, W. R.; Cullen, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 3490.

(14) Braddock, D. C.; Hermitage, S. A.; Kwok, L.; Pouwer, R.; Redmond, J. M.; White, A. J. P. *Chem. Commun.* **2009**, 1082.

(15) For a related study on thiiranium and seleniranium ions, see: Denmark, S. E.; Vogler, T. *Chem.—Eur. J.* **2009**, *15*, 11737.

(16) For related desymmetrization reactions of aziridines and thiiranium ions, see: (a) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084. (b) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984–14986. (c) Larson, S. E.; Baso, J. C.; Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 5186. For chiral counter anion catalysis in general, see:(a) Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373. (b) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193–4195. (c) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (d) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (e) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903. (f) Lacour, J.; Moraleda, D. *Chem. Commun.* **2009**, 7073.

(17) Trace amounts of water led to lower enantioselectivities.

(18) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

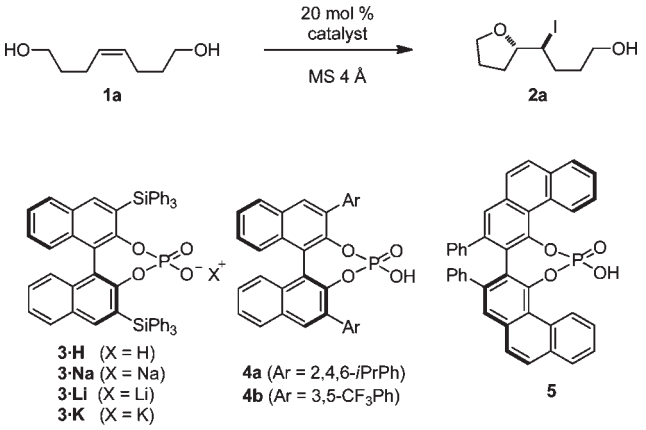
(19) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696.

(20) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.

(21) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600.

(22) For details on the preparation see Supporting Information.

Table 1. Optimization of Reaction Conditions



entry	catalyst (20 mol %)	iodine source (1.2 equiv)	solvent	temp (°C)	ee (%)[d]
1	**3·H**	NIS	toluene	−78 to rt	22
2	**4a**	NIS	toluene	−78 to rt	0
3	**4b**	NIS	toluene	−78 to rt	0
4	**5**	NIS	toluene	−78 to rt	0
5	**3·H**	I_2, Ag_2CO_3	toluene	−78	30
6	**3·H**	NIPyr	toluene	−78 to rt	34
7	**3·Na**	NIPyr	toluene	0	44
8	**3·Na**	NIPyr	CH_2Cl_2	0	62
9	**3·Na**	NIPyr	DCE	0	60
10	**3·Na**	NIPyr	$PhCF_3$	0	46
11	**3·Na**	NIPyr	CH_2Cl_2	−78 to rt	58
12	**3·Li**[a]	NIPyr	CH_2Cl_2	0	56
13	**3·K**	NIPyr	CH_2Cl_2	0	46
14	**3·H**[b]	NIPyr	CH_2Cl_2	0	62
15	**3·Na**[c]	NIPyr	CH_2Cl_2	0	50

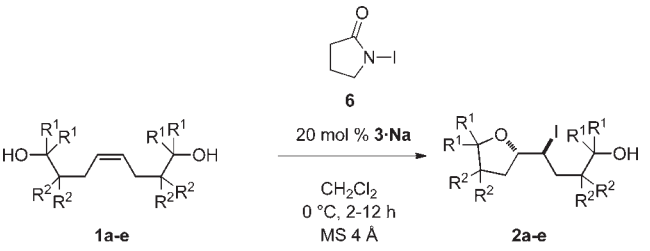
[a] Prepared *in situ* from **3·H** and LiOH. [b] 0.5 equiv of sodium carbonate was added to generate **3·Na** *in situ*. [c] 5 mol % catalyst **3·Na** was used. [d] Determined by HPLC on a chiral stationary phase.

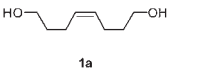
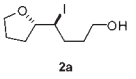
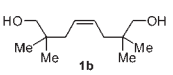
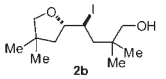
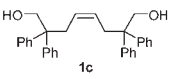
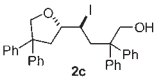
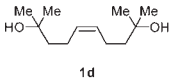
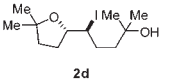
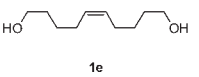
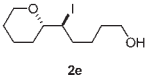
3·H (**3·Li**, **3·K**; entries 12, 13) gave slightly inferior results. Instead of **3·Na** a combination of **3·H** and sodium carbonate can be used to generate **3·Na** *in situ* leading to the same enantioselectivity then using **3·Na** directly (entry 14). If the amount of catalyst **3·Na** is decreased to 5 mol %, the enantioselctivity is reduced from 62% to 50% (entry 15).

To test the substrate scope of this reaction, the optimized reaction conditions were applied to a range of oct-4-en-1, 8-diol substrates (Table 2). Substitution at the 2,7-positions (Me, Ph) was well tolerated and led to even better enantioselectivities if 1 equiv of sodium carbonate was added (entries 2, 3). Methyl-substitution at the 1,8-positions, on the other hand, had a detrimental effect, leading to an almost racemic product. Application of the optimized conditions to the cyclization of dec-5-en-1,10-diol **1e** (6-*exo*) yielded the pyran product with moderate 18% ee. The absolute configuration of the excess enantiomer was determined

(23) See Supporting Information for details.

Table 2. Substrate Scope of the Iodoetherification Using NIPyr **6**



entry	substrate	product	yield [%]	ee (%)[b]
1			81	62
2[a]			60	68
3[a]			82	71
4			82	6
5			75	17

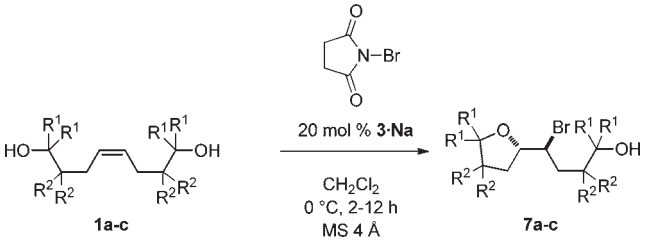
[a] 1 equiv of Na_2CO_3 was added to the reaction. [b] Determined by HPLC on a chiral stationary phase.

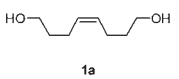
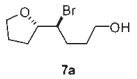
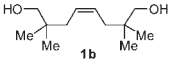
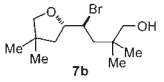
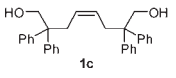
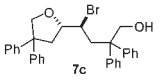
by dehalogenation of **2a** and comparison with an authentic standard prepared from enantiopure tetrahydrofurfuryl alcohol.[23] This established *S,S*-**2a** as the major enantiomer derived from catalyst (*S*)-**3·Na**.

The use of catalyst **3·Na** in combination with electrophilic reagents derived from other elements gave mixed results. The cyclization of **1a** with *N*-(phenylseleno)-phthalimide, *N*-(phenylthio)phthalimide, and *N*-chloro-succinimide gave almost no conversion, even at room temperature. With *N*-bromosuccinimide, however, full conversion to the bromoetherification product **7a** was achieved at 0 °C. Again, oct-4-en-1,8-diol substrates with or without substituents at the 2,7-position could be cyclized using NBS (Table 3). The enantioselctivities observed for these cyclizations are generally lower than those for the iodocyclization but can reach up to 67% ee.

Iodolactonization using catalyst **3·Na** was also attempted using diacide **8** as a model substrate, but only

Table 3. Substrate Scope of the Bromoetherification Using NBS



entry	substrate	product	yield [%]	ee (%)[b]
1	 1a	 7a	89	44
2[a]	 1b	 7b	68	25
3[a]	 1c	 7c	82	67

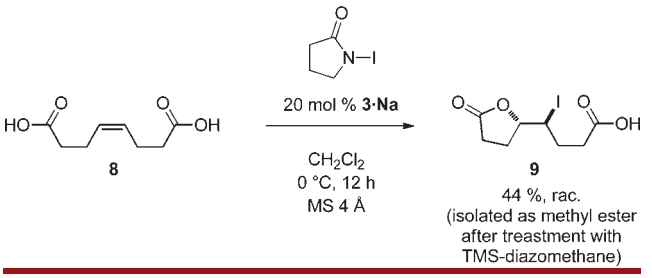
[a] 1 equiv of Na_2CO_3 was added to the reaction. [b] Determined by HPLC on a chiral stationary phase.

the racemic cyclization product **9** was obtained (Scheme 2). This is an interesting observation highlighting the differences between the described catalytic system and most of the recently reported systems for asymmetric halolactonizations.[6–9] Whereas catalyst **3·Na** can be used for asymmetric haloetherifications but not for lactonizations, all other newly described organocatalysts are potent in halolactonizations, and no applications to etherifications have been described.

The higher catalytic activity of the sodium salt **3·Na** as compared to the acid **3·H** suggests an interesting role for BINOL phosphate in these halogenation reactions. Although the role of the sodium cation is currently unclear, the similar selectivities of the sodium and the lithium salts

(24) For BINOL-phosphates salts as Lewis acids, see: (a) Inanaga, J.; Sugimoto, Y.; Hanamoto, T. *New J. Chem.* **1995**, *19*, 707. (b) Furuno, H.; Hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, *2*, 49. (c) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350. For an application of a chiral sodium phosphate, see: Shen, K.; Liu, X.; Cai, Y.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2009**, *15*, 6008.

Scheme 2. Iodolactonization with Catalyst **3·Na**



in the catalytic reactions suggest that **3·Na** is not primarily acting as a Lewis acid in these reactions.[24] Instead of acting as a (Lewis) acid the phosphate anion might initially act as Lewis base toward the halogenating agent forming a phosphate NIPyr complex[25] and thereby activating the NIPyr via Lewis base activation.[26] Iodination of the double bond to the iodonium ion is then quickly followed by an asymmetric opening controlled by the chiral counteranion. This would mean that the mode of activation of the NIPyr by the phosphate is distinctly different from other reactions catalyzed by BINOL phosphoric acids.

In summary, we present a new desymmetrizing approach to asymmetric haloetherification reactions. Using the sodium phosphate **3·Na** good yields and enantioselectivities can be achieved under practical reaction conditions.

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Supporting Information Available. Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(25) Mixing **3·Na** and NIPyr (ratio 1:1) in CD_2Cl_2 leads to upfield shifts of the ^1H NMR signals of NIPyr **6** (0.11 ppm for the 5-CH_2, see Supporting Information for details). For complexes of halide anions with NIS, see: (a) Eberson, L.; Finkelstein, M.; Folkesson, B.; Hutchins, G. A.; Jönsson, L.; Larsson, R.; Moore, W. M.; Ross, S. D. *J. Org. Chem.* **1986**, *51*, 4400. (b) Ghassemzadeh, M.; Dehnicke, K.; Goesmann, H.; Fenske, D. *Z. Naturforsch.* **1994**, *49b*, 602.

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