Asymmetric Catalysis

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Desymmetrization of Diolefinic Diols by Enantioselective Amino-thiocarbamate-Catalyzed Bromoetherification: Synthesis of Chiral Spirocycles**

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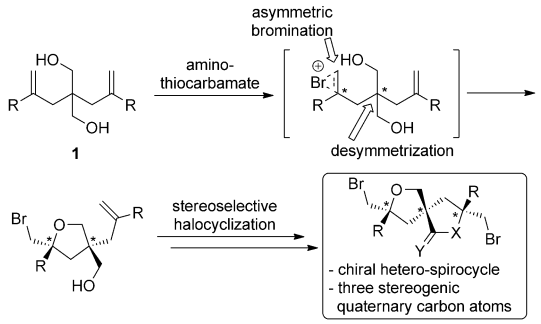
Abstract: *A facile, efficient, and highly diastereo- and enantioselective bromoetherification of diolefinic diols has been developed using an amino-thiocarbamate catalyst. Further manipulations of the bromoether products enabled entry into a new class of spirocycles which are distinctively lacking in the literature.*

Chiral spirocycles are a special class of compounds which has attracted much attention over the past decades. Because of the inherent rigidity and well-defined three-dimensional molecular structure, chiral nonracemic spiromolecules have been used in various areas, including catalysis, metal complexation, and molecular architecture.[1] The unique structural features of spirocycles also open a new avenue for exploring new pharmacological spacing.[2] Recently, multifunctional chiral hetero-spirocycles, having readily modifiable handles, have garnered significant interest as they are particularly useful in modern drug discovery.[3] However, facile and efficient asymmetric pathways towards enantioenriched spirocycles remain sparse. The tremendous difficulty encountered in controlling the regio- and stereochemistry of quaternary carbon centers has caused the synthesis of these privileged scaffolds to remain a challenge for synthetic chemists.[1]

Halocyclization of olefinic compounds, an important synthetic transformation that was discovered more than a century ago,[4] is a powerful method for the construction of heterocycles. However, it was not until recently that significant efforts were devoted to the development of catalytic enantioselective halolactonization, haloetherification, and haloaminocyclization.[5] The resulting heterocyclic intermediates, having modifiable halogen handles, are important building blocks for synthetic chemists as they typically resemble the fundamental cores of many valuable pharmaceutical intermediates as well as biologically active natural products.[6]

The challenge in developing an efficient method for halocyclization lies in improving the rate of nucleophilic capture as opposed to the racemization of halonium ions through olefin-to-olefin transfer.[7] Recently, we reported asymmetric bromolactonizations and bromoaminocyclizations using amino-thiocarbamate catalysts.[8] Herein we are pleased to disclose the catalytic enantioselective synthesis of hetero-spirocycles through a double halocyclization strategy. The first cyclization involves a desymmetrization/asymmetric halogenation process which gives rise to two quaternary stereogenic carbon atoms in the cyclic ether products (Scheme 1). Subsequently, a diastereoselective halocyclization can be performed to yield a series of chiral hetero-spirosystems. This protocol allows access to a class of novel chiral spirocycles which are distintively missing in the literature.[1] To the best of our knowledge, this report also represents the first case of desymmetrizing bromoetherification of a diolefinic diol system.[9]



Scheme 1. Synthesis of hetero-spirocycles through the asymmetric bromination and desymmetrization of **1**.

At the initial stage of this project, we screened our library of cinchona-alkaloid-derived amino-thiocarbamates to look for a suitable catalyst with which to carry out the desymmetrization with good enantioselectivity and diastereoselectivity. The compound **1** ($R = C_6H_5$; for structure see Table 1) and *N*-bromosuccinimide (NBS) were used as the substrate and the halogen source, respectively. We first screened for a suitable catalyst core and observed that quinine and quinidine gave better d.r. and e.r. values as compared to cinchonine and cinchonidine. We then proceeded to examine various phenyl handles and the 6-alkoxy substituents of quinoline, and the

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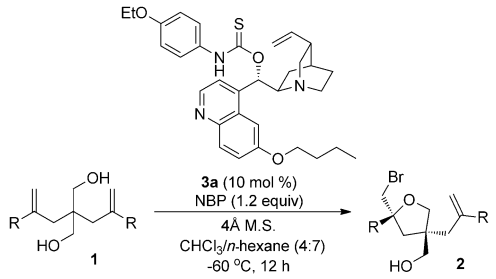
quinidine-derived catalyst **3a** was identified to be superior (see Table S1 in the Supporting Information).[10]

Once a suitable catalyst was identified, optimizations of temperature, solvent, and halogen source were conducted. The reaction was observed to perform better when carried out using *N*-bromophthalimide (NBP) with a chloroform/*n*-hexane (4:7) solvent blend at −60 °C (see Tables S2 and S3).[10] Under these reaction conditions, the diastereomeric ratio was determined to be 84:16 and enantioselectivity as 96:4 for the cyclization of **1a** (Table 1, entry 1). The reaction was found to be readily scalable without diminishing the yield, and d.r. and e.r. values (entry 2). By using the optimized reaction conditions, we examined substrates with symmetrical olefinic systems. In general, the reactions with different diolefinic diols (**1**) proceeded smoothly to give the corresponding bromoethers with good to excellent d.r. and e.r. values, especially for those which have electron-rich substituents (Table 1). The catalyst loading that was required to maintain the performance was also examined. It was observed that even under a low catalyst loading of 2 mol%, the d.r. and e.r. values of the reaction remain almost unchanged (entries 3 and 4).

Diols with unsymmetrical unsaturated systems were also investigated and the results are shown in Table 2. Again, good to excellent d.r. values were obtained. For the relatively bulkier alkyl-substituted olefinic substrates **4a** and **4b**, the cyclization favored the phenyl olefin with good e.r. values (Table 2, entries 1 and 2). In contrast, the methyl-substituted mixed olefin **4c** gave rise to **5c**, as a result of cyclization at the less hindered methyl olefin (entry 3).[11] The substrate **4d**, which contains a 1,1- and a 1,2-disubstituted olefin, delivered **5d** (94%) with a good e.r. value of 92:8 (entry 4). The alkene-alkyne **4e** was also examined and gave **5e** exclusively in excellent enantioselectivity (99:1 e.r.; entry 5).

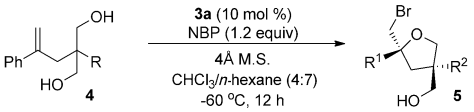
Table 1: Desymmetrizing bromoetherification of **1**.[a]

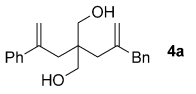
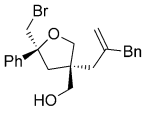
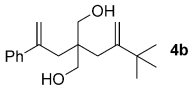
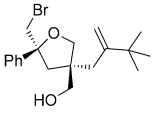
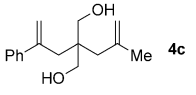
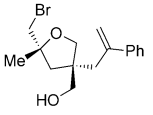
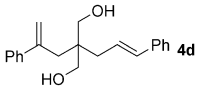
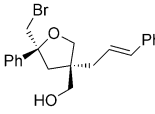
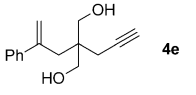
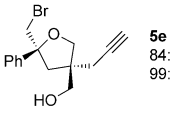


Entry	R	Product	Yield [%][b]	d.r.	e.r.
1	C_6H_5	**2a**	93	84:16	96:4
2[c]	C_6H_5	**2a**	91	83:17	95:5
3[d]	C_6H_5	**2a**	90	81:19	96:4
4[e]	C_6H_5	**2a**	93	83:17	94:6
3	2-MeC_6H_4	**2b**	90	95:5	96:4
4	3-MeC_6H_4	**2c**	89	80:20	82:18
5	4-MeC_6H_4	**2d**	92	82:18	95:5
6	1-naphthyl	**2e**	96	95:5	93:7
7	4-FC_6H_4	**2f**	93	79:21	82:18
8	4-ClC_6H_4	**2g**	92	76:24	82:18

[a] Reactions were carried out with **1** (0.05 mmol), catalyst **3a** (0.005 mmol), and NBP (0.06 mmol) in $CHCl_3$/*n*-hexane (4:7) (5.5 mL) at −60 °C for 12 h in the absence of light. [b] Yield of the isolated product. [c] Reaction was carried out using 1 mmol of **1a**. [d] 5 mol% of **3a** was used. [e] 2 mol% of **3a** was used. M.S. = molecular sieves.

Table 2: Desymmetrizing bromoetherification of mixed olefins.[a]



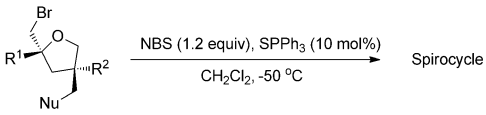
Entry	Substrate	Product
1	 **4a**	 **5a** (90%) 88:12 d.r. 93:7 e.r.
2	 **4b**	 **5b** (91%) 94:6 d.r. 90:10 e.r.
3	 **4c**	 **5c** (90%) 86:14 d.r. 70:30 e.r.
4	 **4d**	 **5d** (94%) 79:21 dr 92:8 er
5	 **4e**	 **5e** (91%) 84:16 d.r. 99:1 e.r.

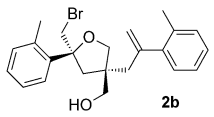
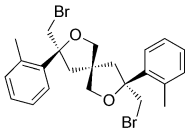
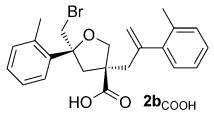
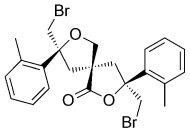
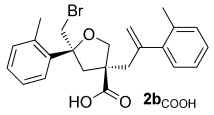
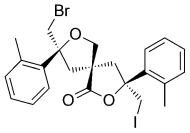
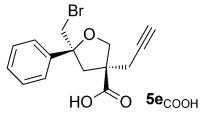
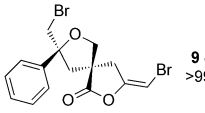
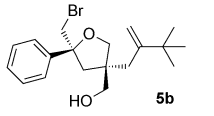
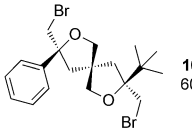
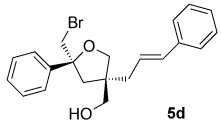
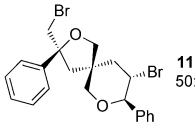
[a] Reactions were carried out with **4** (0.05 mmol), catalyst **3a** (0.005 mmol), and NBP (0.06 mmol) in $CHCl_3$/*n*-hexane (4:7) (5.5 mL) at −60 °C for 12 h in the absence of light. The yields within parentheses are those of the isolated products.

The substituted tetrahydrofurans **2** and **5**, which contain two stereogenic quaternary carbon centers, were further cyclized to yield the corresponding hetero-spirocycles (Table 3). Treatment of **2b** with NBS and a catalytic amount of triphenylphosphine sulfide in dichloromethane furnished **6** with an excellent d.r. value (94:6).[12] $\mathbf{2b}_{COOH}$, which was obtained by oxidizing **2b**, using PCC followed by $NaClO_2$, could also be cyclized stereoselectively to yield the spirocycle **7** in 98% yield and 93:7 d.r. NIS could also be used in place of NBS to give the mixed spirocycle **8** which contains both a Br and I handle. The reactivity between Br and I can readily be differentiated and is beneficial for subsequent manipulation. Under similar reaction conditions, the carboxylic acid derivative $\mathbf{5e}_{COOH}$ (obtained by oxidizing **5e**) could be cyclized to yield the spirocycle **9** which contains a vinyl bromide substituent. A lower diastereoselectivity was obtained when cyclizing **5b** and **5d**. The absolute configuration of the bromoethers, as well as the corresponding spirocycles, were established based on the X-ray crystallographic study of **7**.[13]

It is noteworthy that the spirocycle can be prepared in a one-pot fashion. For instance, double cyclization of **1b** in one pot under the optimized reaction conditions gave **6** in 70% overall yield. Attempts to manipulate the Br handles in **6** by heating it in pyrrolidine with 10 mol% of NaI furnished **6′** in 72% yield (Scheme 2).

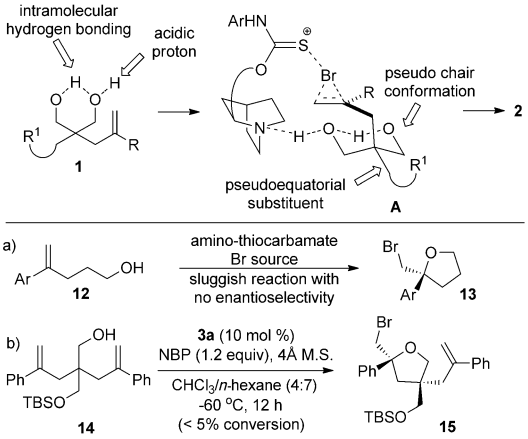
Table 3: Second cyclization to spirocycles.[a]



Entry	Substrate	Spirocycle
1	 **2b**	 **6** (96%) 94:6 d.r.
2	 **2b**$_{COOH}$	 **7** (98%) 93:7 d.r.
3[b]	 **2b**$_{COOH}$	 **8** (93%) 93:7 d.r.
4[c]	 **5e**$_{COOH}$	 **9** (98%) >99:1 d.r.
5	 **5b**	 **10** (91%) 60:40 d.r.
6	 **5d**	 **11** (92%) 50:50 d.r.

[a] Reactions were carried out with substrate (0.05 mmol), $SPPh_3$ (0.005 mmol), and NBS (0.06 mmol) in CH_2Cl_2 (5.0 mL) at −50 °C for 12 h in the absence of light. The yields within parentheses are those of the isolated products. [b] NIS was used instead of NBS. [c] $NaHCO_3$ (1.1 equiv) was used instead of $SPPh_3$.

With regard to the reactivity of the substrate, we realized that the diol system was critical, as almost no reaction occurred when cyclizing the olefinic alcohol **12** under the optimized reaction conditions (Scheme 3a). In our previous studies on amino-thiocarbamate catalysis, the nucleophiles (e.g. carboxylic acid) in the olefinic substrates have relatively low pK_a values, which allowed deprotonation by the quinuclidine and in turn helped to increase the rate of nucleophilic capture.[8] By comparison, we believe that the deprotonation of the alcohol is not favorable because of its higher pK_a value,

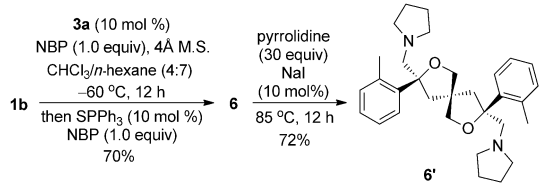


Scheme 3. A plausible reaction mechanism.

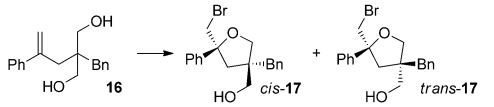
thus forbidding the stereoselective etherification. For diol systems, it has been reported that the acidity of the proton is enhanced because of the intramolecular hydrogen bonding.[14] As such, we believe that the acidic proton in the 1,3-diol may interact with the quinuclidine nitrogen atom of the amino-thiocarbamate catalyst. A plausible mechanistic picture was constructed as indicated in Scheme 3. We speculate that the transition-state **A** may consist of several important components: 1) an intramolecular hydrogen bond which helps to lock the 1,3-diol in a pseudo six-membered ring chair conformation; 2) the bulkier substituent sits at the pseudoequatorial position; and 3) the amino-thiocarbamate bifunctional pocket helps to restrict the geometry of the intermediate.

To gain further information on the mechanism, the substrate **14**, having one of the hydroxy groups protected as a TBS ether, was prepared (Scheme 3b). Subjecting **14** to the optimized bromocyclization conditions resulted in a sluggish reaction, which further supports the importance of the hydrogen bonding. In fact, we also examined the benzyl-substituted substrate **16** which reacted to give good product d.r. and e.r. values (Scheme 4). Poor diastereoselectivity was observed when using triphenylphosphine sulfide or potassium carbonate to mediate the reaction. This result reinforces the importance of the bis(functionality) in which the catalyst is controlling both the diastereoselectivity and the enantioselectivity.

In summary, a facile, efficient, and highly diastereo- and enantioselective desymmetrizing bromoetherification of diolefinic diols has been developed using an amino-thiocarbamate catalyst. Further manipulation of the bromoether products enabled entry into a new class of spirocycles which



Scheme 2. Synthesis of **6** in one pot from **1b**.



Catalyst	Yield [%]	*cis*-**17**:*trans*-**17**	e.r. of *cis*-**17**
3a (10 mol%)	91	84/16	89:11
K_2CO_3 (100 mol%)	92	45/55	-
Ph_3PS (10 mol%)	95	59/41	-

Scheme 4. Cyclization of **16** using different catalysts.

are distinctively lacking in the literature. The importance of the diol functionality also substantiated the mode of action of the catalyst as proposed in earlier studies.

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Keywords: asymmetric catalysis · chemoselectivity · cyclization · furans · Lewis base

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[10] For details, see the Supporting Information.

[11] The chemoselectivity in the cyclization of **4c** was also examined using other catalysts. For details, see Table S4.

[12] Triphenylphosphine sulfide was found to be superior in catalyzing the cyclization reactions after screening some catalysts. For details, see Tables S5 and S6. For a related study on using triphenylphosphine sulfide as the catalyst in halocyclization, see: S. E. Denmark, M. T. Burk, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20655.

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Communications

Asymmetric Catalysis

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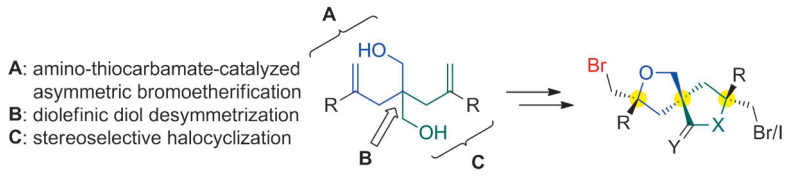
Desymmetrization of Diolefinic Diols by Enantioselective Amino-thiocarbamate-Catalyzed Bromoetherification: Synthesis of Chiral Spirocycles



Seeing double: A facile, efficient, and highly diastereo- and enantioselective bromoetherification of diolefinic diols has been developed using an amino-thiocarbamate catalyst. Further manipulations of the bromoether products enabled entry into a new class of spirocycles, having three stereogenic quaternary carbon centers, which are distinctively lacking in the literature.