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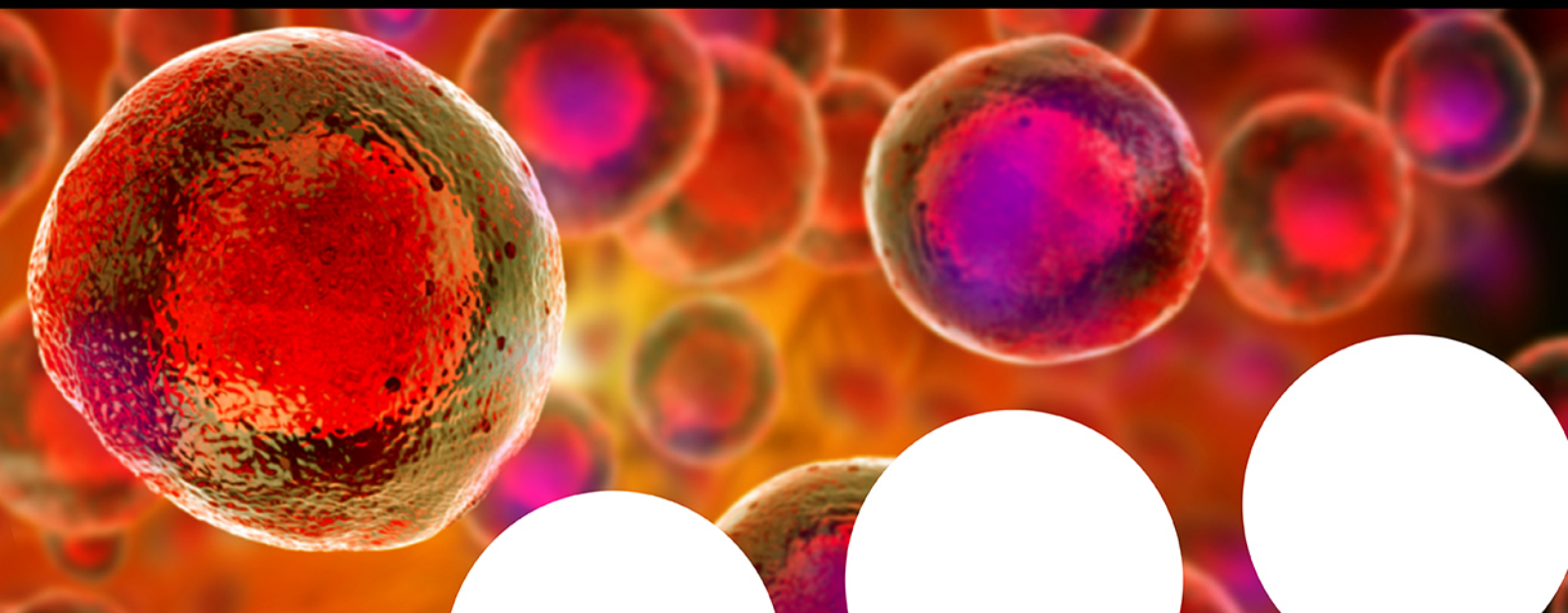
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# Stereoselective Synthesis of Highly Functionalized Structures from $\alpha$ -Bromo $\alpha'$ -Sulfinyl Ketones

Xavier J. Salom-Roig\*<sup>[a]</sup>

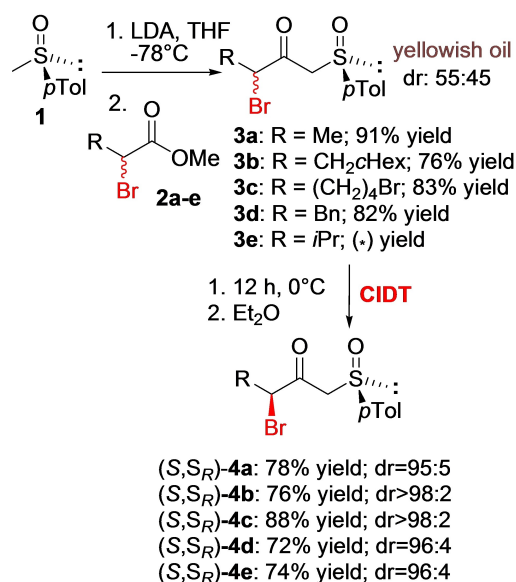
Crystallization-Induced Diastereomer Transformation (CIDT) of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinylketones is reported. The utility of these 1,2-difunctionalized synthons is convincingly demonstrated by their facile conversion into cyanohydrins and bromohydrins.

Furthermore, bromohydrins can be converted into complex arrangements of functionality and stereochemistry through  $S_N2$ -like inter and intramolecular transformations.

## Introduction

$\alpha$ -Halo ketones are 1,2-difunctionalized electrophiles widely used in organic synthesis.<sup>[1]</sup> Despite their large synthetic potential, a survey of the literature reveals that methods for the synthesis of enantiopure chiral unsymmetrical  $\alpha$ -halo ketones that can tautomerize to form enols on both sides of the ketone group is somewhat rare<sup>[2]</sup> due to their stereolability. Therefore, the development of efficient methods to access these synthons is of great importance. In particular, the facile conversion of chiral  $\alpha$ -halo ketones to enantiopure halohydrins makes them particularly useful. Vicinal halohydrins are frequently found in compounds isolated from marine sources.<sup>[3]</sup> They are versatile building blocks and key intermediates for the synthesis of many bioactive derivatives in the pharmaceutical industry and natural products synthesis due to their high reactivity and they allow the preparation of a huge variety of compounds.<sup>[4]</sup> Though a number of methods for their asymmetric synthesis are known,<sup>[5]</sup> there is still need of a general approach to the synthesis of enantiopure chiral halohydrins.

In this context, we recently reported a Crystallization-Induced Diastereomer Transformation (CIDT) of epimeric mixtures of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones, optically pure only at the sulfur atom<sup>[6]</sup> (**3**, Scheme 1), that provides the corresponding enantiopure epimers (*S,S<sub>R</sub>*)-**4**. CIDT is a hybrid process, involving mixtures of two epimeric compounds, that combines the selective crystallization of a desired epimer and the epimerization of the undesired one.<sup>[7]</sup> In contrast to classical resolution, which affords yields lower than 50%, CIDT provides a theoretical yield of 100%. This previous study was performed on substrates **3a–c**. In this paper, we extend the scope of this efficient CIDT to substrates **3d, e** and we demonstrate that  $\alpha$ -



**Scheme 1.** CIDT of epimeric mixtures of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones **3a–e**. (\*): see text.

bromo- $\alpha'$ -(*R*)-sulfinyl ketones (*S,S<sub>R</sub>*)-**4** can be transformed into their corresponding cyanohydrins. Then, we disclose the transformation of bromohydrins that can also be obtained from (*S,S<sub>R</sub>*)-**4**,<sup>[6]</sup> into complex arrangements of functionality and stereochemistry.

## Results and Discussion

Initial attention focused upon the preparation of the required substrates **3a–e** by the nucleophilic addition at  $-78^\circ\text{C}$  of the lithiated anion of (+)-(*R*)-(methyl *p*-tolyl sulfoxide) **1** to the requisite ( $\pm$ )-methyl  $\alpha$ -bromo esters **2a–e**.<sup>[8]</sup> The reaction proceeded with complete regioselectivity on the carboxyl group of  $\alpha$ -bromo esters. Use of one equivalent excess of the nucleophile led to the corresponding  $\alpha$ -bromo  $\alpha'$ -sulfinyl ketone **3a–e** by virtue of their acidity. These compounds were obtained in 76–91% yields as yellowish oils after purification by column chromatography on silica gel. <sup>1</sup>H NMR spectroscopic

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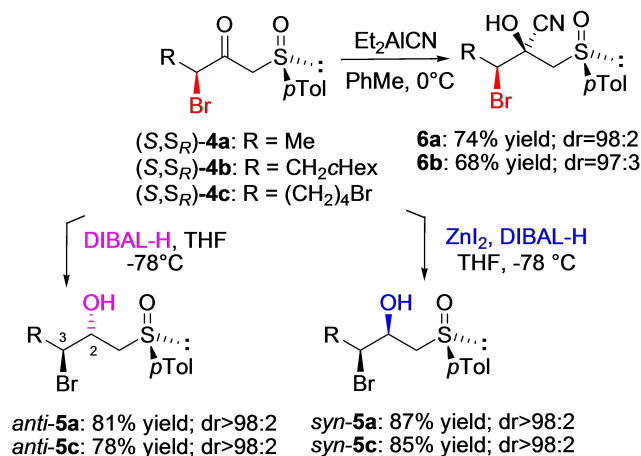
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analysis of the crude reaction mixtures showed clearly that, in each case, an approximate 1:1 mixture of diastereomers was obtained. Stored for 12 h at 0 °C, the epimeric mixtures **3a–e** precipitated giving rise to yellowish solids that after being crushed and washed with diethyl ether provided enantiopure epimers (*S,S<sub>R</sub>*)-**4a–e**. In general, we observed that CIDT of the epimeric mixtures of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones **3a–e** proceeded in good yields (72–88%) and excellent levels of stereochemical control ( $dr > 98:2$ ) with  $\alpha$ -bromo ketones having small or sterically demanding side chains. Interestingly, the epimeric mixture **3e** could not be isolated since it rapidly precipitated providing (*S,S<sub>R</sub>*)-**4e** in 74% yield with a d.r. of 96:4. The stereochemistry of products (*S,S<sub>R</sub>*)-**4a–e** was unequivocally established by X-ray crystallographic analysis of compound (*S,S<sub>R</sub>*)-**4b**.<sup>[6]</sup> This process opened a new access to stereolabile  $\alpha$ -bromoketones.

Solids (*S,S<sub>R</sub>*)-**4a–e** are configurationally stable and can be stored several months at refrigerator temperatures without any epimerization occurring. However, (*S,S<sub>R</sub>*)-**4a–e** smoothly epimerize when redissolved. Indeed, upon standing enantiopure (*S,S<sub>R</sub>*)-**4c** in CDCl<sub>3</sub> at room temperature, after 48 h, <sup>1</sup>H NMR showed a 84:16 epimeric mixture (Figure 1), the epimerization being almost complete after 16 days.

Since epimerization of (*S,S<sub>R</sub>*)-**4a–e** occurs smoothly, we wondered if it would be possible to perform diastereoselective addition reactions to the carbonyl group, by keeping bromo carbon stereochemistry untouched. Thus, we dissolved enantiopure (*S,S<sub>R</sub>*)-**4a, c** in THF and cooled the resulting solutions to –78 °C. To our delight, by treating these stirred solutions with



Scheme 2. Diastereoselective reductions<sup>[6,13]</sup> and hydrocyanations of **4a, c** and **4a, b**.

DIBAL-H<sup>[9]</sup> or with DIBAL-H in the presence of ZnI<sub>2</sub><sup>[10]</sup> in THF at –78 °C (Scheme 2), bromohydrins *anti*-**5a, c** and *syn*-**5a, c** could be readily obtained in 78–87% yields with excellent diastereoselectivities (d.r. > 98:2) and without detectable epimerization of the bromo carbon stereocenter. The absolute stereochemical assignment of bromohydrins *anti*-**5a, c** and *syn*-**5a, c** was initially based on the assumption that these reactions proceeded with the same sense of asymmetric induction as observed with common  $\beta$ -ketosulfoxides.<sup>[9,10]</sup> As it will be

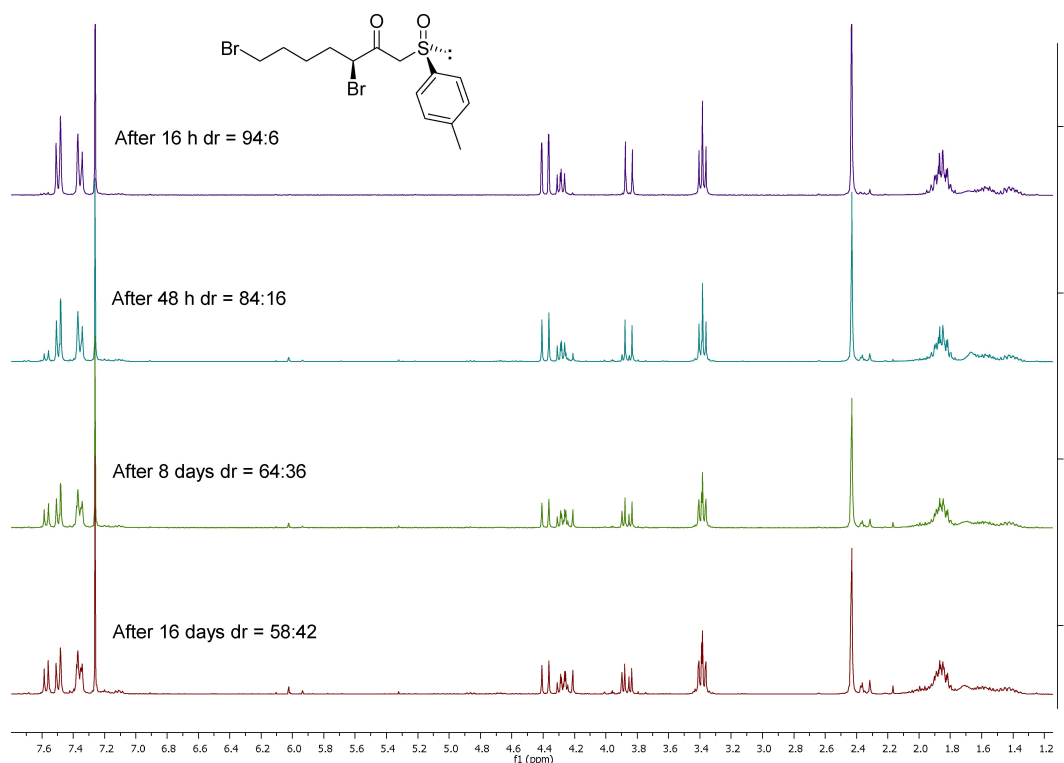


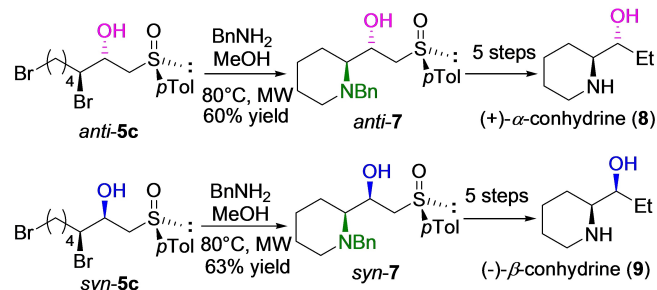
Figure 1. Epimerization study of (*S,S<sub>R</sub>*)-**4c** in CDCl<sub>3</sub> at room temperature.

described later on, this assignment was subsequently confirmed through the synthesis of  $\beta,\gamma$ -epoxysulfoxides *anti*-14 and *syn*-14 (Scheme 5) (*vide infra*).

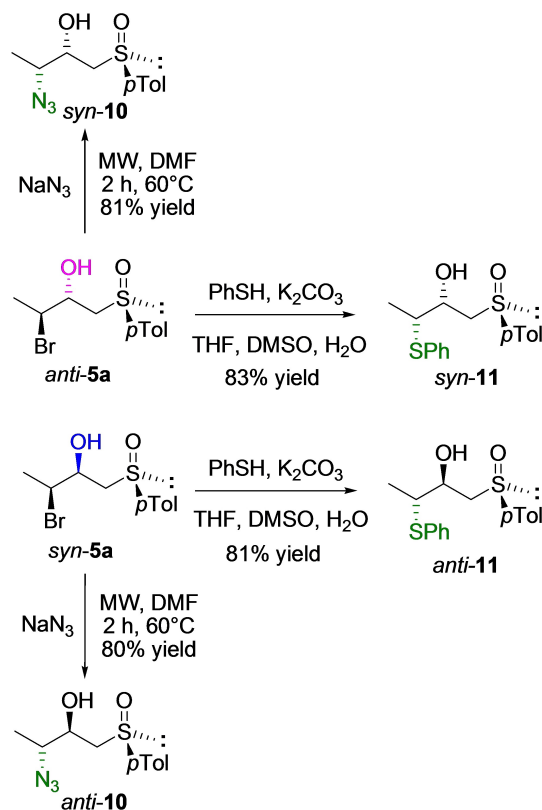
Encouraged by the high levels of asymmetric induction observed in the carbonyl reduction, our focus turned toward the diastereoselective hydrocyanation of (*S,S*<sub>R</sub>)-4 aiming the preparation of the corresponding non-racemic cyanohydrins 6. Thus, reaction of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones (*S,S*<sub>R</sub>)-4 a, c with Et<sub>2</sub>AlCN in toluene at 0 °C<sup>[11]</sup> afforded  $\beta$ -cyanosulfoxides 6 a and 6 b in 74% and 68% yield and 98:2 and 97:3 of diastereomeric excess.<sup>[12]</sup> The sulfoxide group strictly controls the facial selectivity of cyano group delivery in a 1,3-induction process that resulted from an intramolecular transfer of the cyano group from a pentacoordinated aluminum intermediate arising from the association of Et<sub>2</sub>AlCN with the sulfinyl oxygen.<sup>[11b]</sup>

The remarkable stereocontrol observed on the synthesis of enantiopure bromohydrins *anti*-5 a, c and *syn*-5 a, c along with their versatility, in particular with the ease of displacement of bromine atom in S<sub>N</sub>2-like processes, made these bromohydrins highly appealing substrates to undertake their conversion into complex functionalized structures useful in particular for natural products synthesis. In this context, as we described recently,<sup>[6,13]</sup> bromohydrins *anti*-5 c and *syn*-5 c can be converted into piperidinic alcohols *anti*-7 and *syn*-7, respectively via an epoxide intermediate, in a double inversion of the configuration of the bromo carbon stereocenter (Scheme 3). A five-step sequence let us to transform *anti*-7 and *syn*-7 into (+)- $\alpha$  and (-)- $\beta$ -conhydrins (8 and 9, respectively), two alkaloids isolated from the seeds and leaves of hemlock *Conium maculatum* L. Umbelliferae, a highly poisonous plant used in ancient Greece for the execution of criminals, which caused the death of the Greek philosopher Socrates in 399 B.C.<sup>[14]</sup>

Ongoing our efforts to illustrate the synthetic possibilities of our bromohydrins as valuable chiral building blocks, we used compounds *anti*-5 a and *syn*-5 a as model substrates to develop a divergent and efficient strategy allowing access to relevant valuable moieties. Thus, we first investigated the introduction of an azide-functionality by a S<sub>N</sub>2 type substitution reaction of bromine atoms in *anti*-5 a and *syn*-5 a by sodium azide used as the nucleophile (Scheme 4). The reaction was run under microwave irradiation in DMF at 60 °C and provided the azido derivatives *anti*-10 and *syn*-10 in 81 and 80% yields, respec-



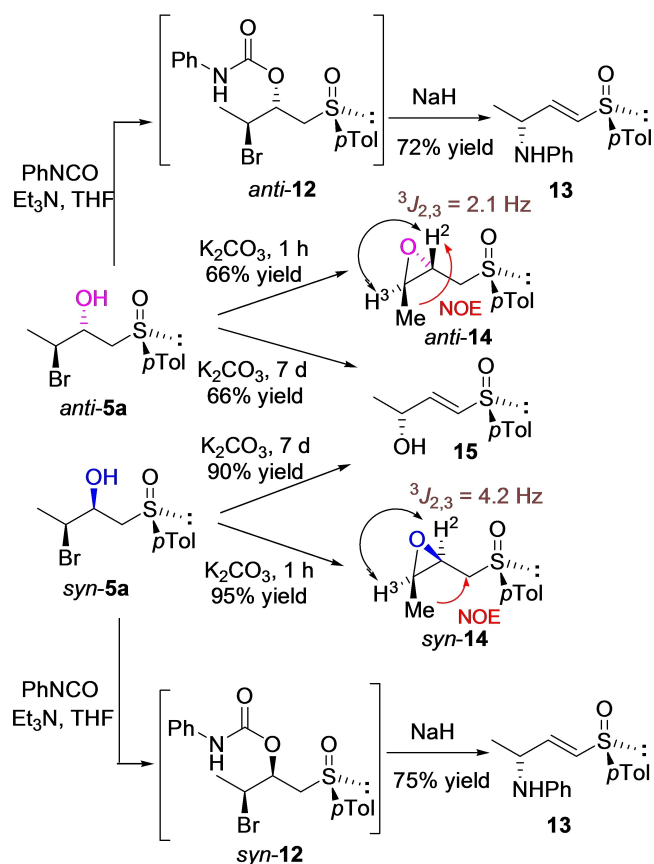
Scheme 3. Synthesis of (+)- $\alpha$  and (-)- $\beta$ -conhydrins from bromohydrins *anti*-5 c and *syn*-5 c.<sup>[6,13]</sup>



Scheme 4. Synthesis of azido derivatives *anti*-10 and *syn*-10 and hydroxyl sulfurs *anti*-11 and *syn*-11.

tively with inversion of configuration at C-3. Next, we focussed our attention to the creation of sulfur-carbon bonds, of considerable importance in biological processes, material science, medicinal chemistry, and synthetic methodologies.<sup>[15]</sup> For this meaning, *anti*-5 a and *syn*-5 a were successfully reacted with thiophenol, using K<sub>2</sub>CO<sub>3</sub> as the base, providing the corresponding thioether derivatives *syn*-11 and *syn*-11 in 83 and 81% yield, respectively by an S<sub>N</sub>2 reaction.

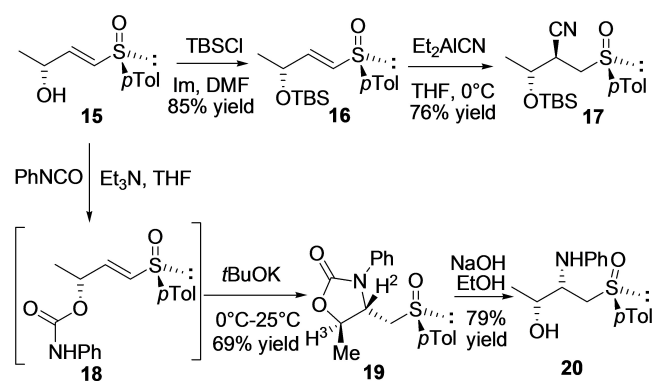
We explored then in the stereospecific intramolecular bromo atom displacement. Thus, reaction of *anti*-5 a and *syn*-5 a with phenyl isocyanate in the presence of triethyl amine produced carbamates *anti*-12 and *syn*-12, which convergently afforded, upon addition of NaH,  $\gamma$ -amino vinyl sulfoxide 13 after a nitrogen-carbon bond formation (Scheme 5). The synthetic potential of  $\gamma$ -amino vinyl sulfoxides has been well documented.<sup>[16]</sup> Next, we took advantage of the vicinal alcohol and triggered the intramolecular cyclization by exposure of bromohydrins *anti*-5 a and *syn*-5 a to K<sub>2</sub>CO<sub>3</sub> in a 8:5 mixture of CH<sub>3</sub>CN and MeOH to provide the corresponding  $\beta,\gamma$ -epoxysulfoxides *anti*-14 and *syn*-14 in good yields. The coupling constants values between H-2 and H-3 obtained from <sup>1</sup>H NMR spectra of these compounds confirmed the *anti* relative configuration in epoxide *anti*-14 (<sup>3</sup>J<sub>2,3</sub> = 2.1 Hz) and the *syn* configuration could be assigned to epoxide *syn*-14 (<sup>3</sup>J<sub>2,3</sub> = 4.2 Hz). These stereochemistries were confirmed by an NOE measurement in the <sup>1</sup>H NMR spectra: *anti*-14 shows an NOE



Scheme 5. Synthesis of epoxides *anti*-14 and *syn*-14, allylic alcohol 15<sup>[6]</sup> and allylic amine 13.

between H-2 hydrogen and C-4 methyl group whereas *syn*-14 shows an NOE between C-1 hydrogens and C-4 methyl group. Furthermore, when reactions of bromohydrins *anti*-5a and *syn*-5a with  $K_2CO_3$  were stirred during seven days, (*E*)- $\gamma$ -hydroxy- $\alpha,\beta$ -unsaturated sulfoxide 15 was obtained in both cases, with a d.r. > 98%, confirming that the stereochemistry at the bromo carbon atom was kept during the diastereoselective reduction of the carbonyl group. (*E*)- $\gamma$ -hydroxy- $\alpha,\beta$ -unsaturated sulfoxides have shown to be useful building blocks in synthetic chemistry.<sup>[17]</sup>

With this result in hand, we turned our attention to the further elaboration of 15 (Scheme 6). First, the hydroxyl group was masked as its *tert*-butyl-dimethyl silyl ether by reaction with TBSCl in the presence of imidazole affording 16 in 85% yield. The latter was subjected to a diastereoselective hydrocyanation upon reaction with  $Et_2AlCN$  in THF at 0 °C delivering nitrile 17 in 76% yield with excellent diastereoselectivity (d.r. > 98:2).<sup>[18]</sup> In this intramolecular hydrocyanation, the sulfoxide group controls the diastereoselectivity by virtue of its previous association with  $Et_2AlCN$  in a chair-like transition stage. Configurational assignment of the resulting stereocenter was confidently assigned by reference to the known stereochemical outcome of this nucleophilic addition of cyanide when applied to (*E*)-vinyl sulfoxides.<sup>[16,18]</sup> Moreover, 15, after a two-step sequence involving reaction with phenyl isocyanate in the



Scheme 6. Synthesis of  $\beta$ -cyano- $\gamma$ -hydroxy sulfoxides 17 and amino alcohol 20.

presence of triethyl amine and treatment of the ensuing carbamate intermediate 18 with potassium *tert*-butanolate at 0 °C, resulted in the formation of disubstituted oxazolidinone 19 in 69% yield as a sole diastereomer. A NOE interaction between H-2 hydrogen and C-4 methyl group in the 2D NOESY spectrum of 19 provided strong support for the *anti* relative stereochemistry (see supporting information). Finally, 19 was successfully converted into 1,2-amino alcohol 20 by reaction with an excess of NaOH using EtOH as a solvent in 79% yield.

## Conclusion

In conclusion, we have developed an efficient CIDT of epimeric mixtures of  $\alpha$ -bromo- $\alpha'$ -(*R*)-sulfinyl ketones, which combined to diastereoselective  $\beta$ -ketosulfoxides reduction and hydrocyanation reaction allowed access to enantiopure bromohydrins and cyanohydrins, respectively. By taking bromohydrins *anti*-5a and *syn*-5a as common building blocks, we have highlighted the synthetic potential of these molecular scaffolds, that can be accessed by our methodology, by exploring the intermolecular and intramolecular bromo atom displacement to form nitrogen, sulfur and oxygen-carbon bonds. Moreover, further elaboration of our allylic alcohol scaffold led to a protected  $\beta$ -cyano- $\gamma$ -hydroxy sulfoxide, to an *anti*-disubstituted oxazolidinone and to a 1,2-amino alcohol. It is noteworthy that the ready availability of methyl-*p*-tolylsulfoxide in either enantiomerically pure form renders this approach equally applicable to the preparation of the remaining stereoisomeric forms of all the new compounds described in this article. Moreover, the synthetic versatility of the sulfoxide group present in the final targets, which could be transformed into other functional groups,<sup>[6,13]</sup> could increase the interest of our methodology for future synthetic applications. Additional studies with regard to the scope of this CIDT are currently investigated.

## Acknowledgements

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Asymmetric synthesis · Bromohydrins · Chiral sulfoxide · Cyanohydrins · Synthetic methods

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