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A convenient synthesis of enantioenriched α-haloaldehydes

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α-Haloaldehydes represent an important family of chiral building blocks that are particularly well suited for the synthesis of sp[3]-rich heterocycles and polyketide-derived natural products. While the organocatalytic and enantioselective preparation of α-haloaldehydes has been well-developed, challenges with their purification and stability often complicate their use. Here, we describe a convenient procedure for the enantioselective preparation of *R*- or *S*-configured α-haloaldehydes involving the oxidative cleavage of readily prepared, stable and storable halohydrin aldol products. This operationally simple, two-step process affords α-haloaldehydes in high chemical and enantiomeric purity with minimal manipulation required. This method for preparing α-haloaldehydes should improve their accessibility and inspire new uses in complex molecule synthesis.

Introduction

Due to their predictable reactivity[1] and inherent chirality, α-haloaldehydes are well-recognized as versatile building blocks for the synthesis of epoxides and stereochemically rich heterocycles.[2] While their enantioselective synthesis from amino acids,[3] chiral oxazolidinone amides,[4] chiral epoxides,[5] and chloroenamines[6] are established, over the past two decades, asymmetric organocatalysis has broadened their accessibility and uses.[7,8] For example, a number of groups have described the enantioselective synthesis of α-fluoro,[8a–i] α-chloro,[8j–s] α-bromo[8t–u] and α-iodoaldehydes[8x] using various combinations of electrophilic halogenating agents and organocatalysts, with some reports also documenting stereoselective reactions of the α-haloaldehydes (Fig. 1A).

Despite these successes, α-haloaldehydes suffer from often significant instabilities that make them experimentally challenging to work with. They decompose, epimerize or racemize and polymerize under various conditions.[9] In our own extensive experiences, even storing these substances in solution at temperatures below 0 °C can lead to degradation. Moreover, the catalysts used to prepare α-haloaldehydes are often expensive and require high loadings (~20 mol%). As a result, the preponderance of α-haloaldehyde syntheses are accompanied by an *in situ* or direct reduction to the more stable halohydrin, which can then be purified. We have developed a variety of organometallic addition reactions to α-haloaldehydes that ultimately lead to the formation of sp[3]-rich heterocycles and

natural products.[10] However, in these efforts we found that that the chemical purity of the α-haloaldehyde is critical to the success of these reactions. As crude α-haloaldehydes are often contaminated with over-halogenated aldehydes, organocatalysts, halogentating agents and their by-products, as well as reaction impurities, the wider adoption of these strategies are challenged by idiosyncratic properties of each α-haloaldehyde, which must be understood before successful exploitation. Consequently, these important reagents remain underutilized.

In part to address these challenges, several years ago we developed a one-pot α-halogenation/aldol reaction (CAR: chlorination and aldol reaction; FAR: fluorination and aldol reaction),[11] whereby the α-haloaldehyde is produced in racemic form using proline catalysis and reacted *in situ* in a proline-catalysed aldol reaction. As proline also catalyses racemization of the intermediate α-haloaldehydes (Fig. 1B), these αCAR and αFAR processes effect a dynamic kinetic resolution, producing halohydrins (*e.g.*, **3**) in excellent diastereoselectivity (up to >20 : 1) and enantioselectivity (typically >95%) in a single reaction set up. These processes have been executed on up to ~kg scale[12] and are robust and adaptable to preparing a range of natural product[13] and drug-relevant scaffolds[11b,14] (*e.g.*, **4–7**, Fig. 1C). Notably, in several cases, α-haloaldehydes that are not readily available through organocatalytic procedures (*e.g.*, **7**) can be generated and reacted in this one-pot reaction. Building on these successes, we envisioned a process in which we could exploit the ease and low cost of production, stability, and often crystalline nature of β-ketohalohydrin **3a** (or *ent*-**3a**) for the preparation of enantiomerically enriched and high-purity α-haloaldehydes. Previously, α-chloro-, α-bromo-, and α-iodoaldehydes have

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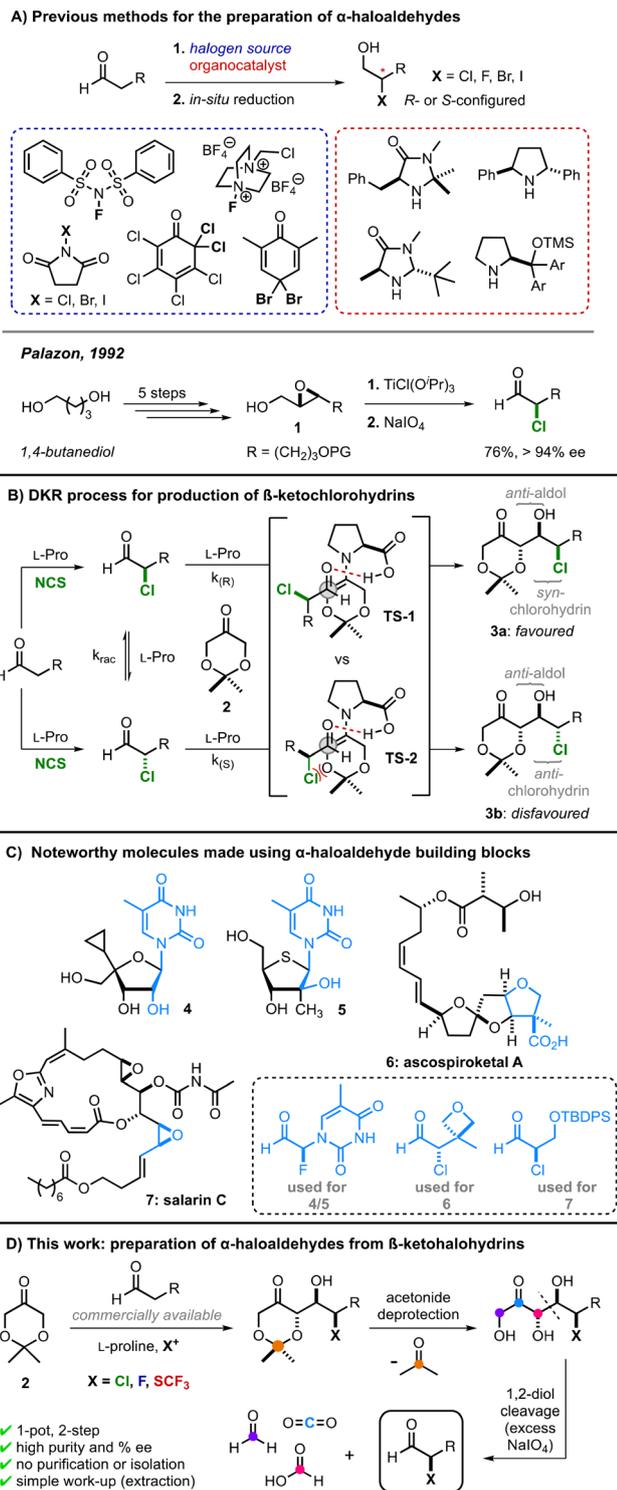
Fig. 1 (A) Previously reported organocatalytic and non-organocatalytic preparations of α-haloaldehydes. (B) Dynamic Kinetic Resolution (DKR) process for the diastereoselective preparation of β-ketochlorohydrins. (C) Noteworthy natural products and drug-relevant scaffolds prepared from α-chloro and α-fluoroaldehydes. (D) Use of β-ketohalohydrins as precursors to access enantioenriched and highly pure α-haloaldehydes.

been prepared from halohydrins *via* oxidative cleavage.[5] However, in these cases, the halohydrin precursors are produced *via* titanium-mediated halogenation and ring-opening of chiral epoxides, which themselves require separate enantioselective synthesis (*e.g.*, **1**, Fig. 1A).[5,15] Here, we describe a one-pot process for converting β-ketohalohydrins into α-haloaldehydes that requires no purification of the α-haloaldehyde (Fig. 1D). Further, we demonstrate that α-haloaldehydes generated by this process are compatible with organometallic addition reactions developed previously by us[10] and others.[16] This new process should support the synthesis of stereochemically rich heterocycles commonly encountered in pharmaceuticals and natural products.

Results and discussion

Reaction optimization

At the outset of this study, we envisioned a one-pot process wherein an intermediate triol produced *via* removal of the acetonide protecting group (step A) from readily available β-ketohalohydrins **3a** could be immediately transformed into the desired α-haloaldehyde by oxidative cleavage (step B) in the same reaction flask. Thus, our initial efforts focused on identifying conditions for acetonide removal that do not impact the other somewhat sensitive functionalities in these types of molecules (Table 1). Starting with the αCAR product of hydrocinnamaldehyde **8**,[11a] we found that treatment of a THF solution of **8** with aqueous HCl followed by NaIO$_4$ in pH 7 buffer gave (2*R*)-2-chlorohydrocinnamaldehyde (**9**) in good yield and enantiomeric excess (entry 1). Notably, isolating the pure α-chloroaldehyde **9** required simple extraction, with all byproducts (acetone, formaldehyde, formic acid and CO$_2$) being volatile or water soluble. Several extraction solvents (*e.g.*, entries 1–3) were examined and ultimately dichloromethane was found to give the best recovery of α-chloroaldehyde **9** (entry 3). We also explored several solvents for the deprotection step (step A, entries 5–8) and found that THF was optimal. Finally, we were concerned by the decrease in ee of α-chloroaldehydes produced using this sequence and examined the impact of several different acids on the stability of the formed α-chloroaldehyde. Ultimately, we found (entry 9) that using aqueous *p*-TsOH the α-chloroaldehyde **9** could be produced with minimal erosion of enantiomeric excess. Importantly, in all cases, isolation of pure (>95%) α-chloroaldehyde (see ^{1}H NMR spectrum; Fig. 2) required only a simple organic extraction. The organic extract could be fully concentrated to provide neat α-chloroaldehyde, or partially concentrated to provide an anhydrous solution of α-chloroaldehyde in THF/CH$_2$Cl$_2$ suitable for direct use in a subsequent reaction (*vide infra*). Quantitative NMR (q-NMR) of an aliquot of the organic extract could be performed, then the remainder of the α-haloaldehyde solution was dried further over 4 Å molecular sieves in preparation for its use as a reactant.

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Table 1 Optimization of a two-step-one-pot α-chloroaldehyde synthesis from β-ketochlorohydrin **8**

#	Acid	Conc. (M)	Reaction solvent	Extraction solvent	Time (h) A	Time (h) B	Yield (%)	ee (%)
1	HCl	0.5	THF	Pentane	4	1.5	53	89
2	HCl	0.5	THF	Et$_2$O	4	1.5	28	ND
3	HCl	0.5	THF	CH$_2$Cl$_2$	4	1.5	68	89
4	HCl	0.2	THF	CH$_2$Cl$_2$	7	1.5	69	88
5	HCl	0.2	THF	CH$_2$Cl$_2$	6	1.5	53[a]	88
6	HCl	0.2	THF/H$_2$O (1:1)	CH$_2$Cl$_2$	4	1.5	66	88
7	HCl	0.2	MeOH	CH$_2$Cl$_2$	4	4	51[b]	ND
8	HCl	0.2	CH$_2$Cl$_2$	CH$_2$Cl$_2$	48	2	48[c]	86
9	p-TsOH	0.2	THF	CH$_2$Cl$_2$	16	2	79	94

Reactions conducted on a 0.1 mmol scale. Yields determined *via* quantitative ^{1}H NMR (q-NMR) using 1,3,5-trimethoxybenzene as internal standard (see SI); enantiomeric excess (ee) determined by chiral HPLC analysis of halohydrin produced following reduction of **9**. [a] Intermediate triol isolated. [b] Mixture of aldehyde and dimethyl acetal product observed. [c] Isolated yield. ND: not determined.
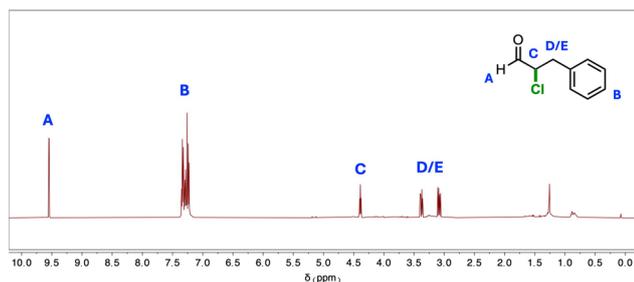

Fig. 2 ^{1}H NMR spectrum (500 MHz – CDCl$_3$) of (2*R*)-2-chlorohydrocinnamaldehyde **9** prepared from β-ketochlorohydrin **8** using the optimized conditions.

Reaction scope

Using these optimized reaction conditions, we evaluated the scope of this process starting from readily prepared chloro-, fluoro-, and trifluoromethylthio-hydrin precursors (Fig. 3). We were pleased to find that chlorohydrins bearing alkene, alkyl halide, and benzyl functionality (**9–12**) were successfully transformed into their α-chloroaldehyde counterparts in good yield and enantiomeric excess (Fig. 3A). The αCAR product of 2-phenylacetaldehyde was also subjected to our optimized conditions but the corresponding α-chloroaldehyde was unstable to excess NaIO$_4$ and formed benzaldehyde as the major product. Notably, the α-chloroaldehyde **12** was previously used as a key building block in the synthesis of the alkaloid (−)-swainsonine,[10i] however its preparation *via* organocatalytic α-chlorination required impractical reaction conditions that included low temperatures over a prolonged period of time (−35 °C, 19 days),[17] and still only gave modest levels of enantioselectivity (82% ee). The enantiomeric or diastereomeric α-chloro and α-fluoroaldehydes **13–17** are also now readily available *via* this process and each was produced with

>20:1 diastereoselectivity. Here, it was found that removal of the acetonide protecting group at a higher temperature (60 °C) and for a shorter amount of time (3 h) prevented removal of the TIPS protecting group and facilitated production of these highly functionalized compounds in good yield. The α-fluoroaldehydes **18–21** feature tertiary nitro or benzylic functionalities and each was prepared with high levels of enantiopurity using this strategy. These results are particularly noteworthy given the challenges with the preparation and isolation of enantiomerically enriched α-fluoroaldehydes.[9] Finally, we examined both the aldol reaction and deprotection/oxidative cleavage sequence using an α-trifluoromethylthioaldehyde (Fig. 3B). Notably, while α-trifluoromethylthioketones,[18] esters,[19] amides,[20] and β-ketoesters[21] have been prepared enantioselectively (80–100% ee),[22] the preparation of enantioenriched α-trifluoromethylthioaldehydes has been limited to a single example with low enantiopurity (11% ee) facilitated by the Hayashi–Jørgenson organocatalyst, and the products were only isolated after reduction to the corresponding alcohol derivatives.[23] Thus, the preparation of α-trifluoromethylthioaldehyde **23** from β-ketotrifluoromethylthiohydrin **22** represents the highest level of enantioselectivity for the preparation of this class of compounds. Here, we found that our standard conditions gave the α-trifluoromethylthioaldehyde **23** in modest enantiopurity (51% ee). Further optimization of the process, which included performing the oxidative cleavage step at 3 °C, allowed preparation of **23** in good yield and enantiopurity (84% ee).

Having established a robust process for generating α-haloaldehydes in pure form, we sought to target the particularly problematic α-chloroaldehyde **25**. We have previously attempted to produce this compound *via* organocatalysis as it proved to be a key building block for the synthesis of the marine macrolide biselide A.[24] In this prior work, the organocatalytic chlorination of the parent aldehyde gave predomi-
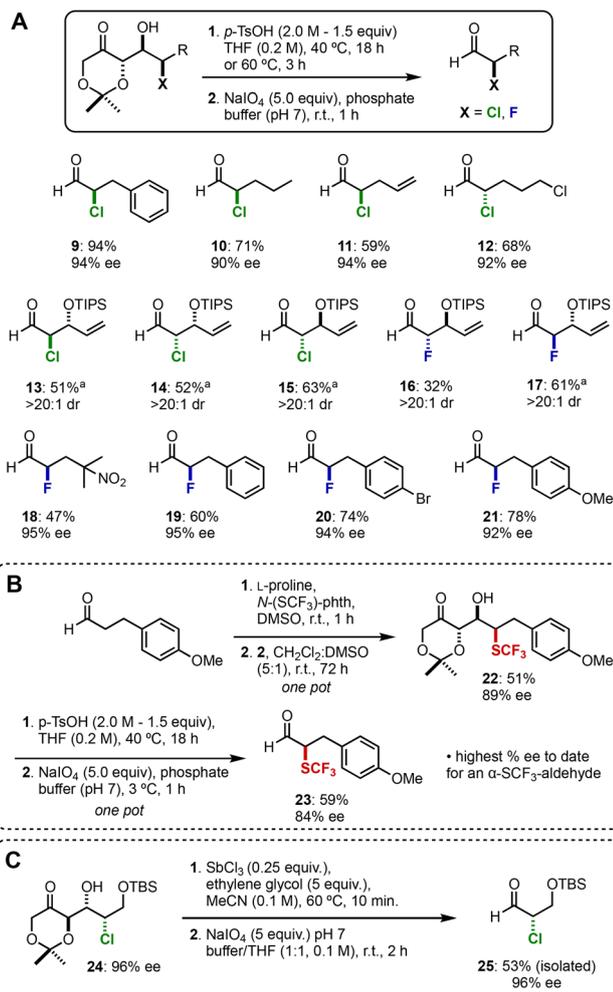
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Fig. 3 (A) Scope of α-haloaldehydes prepared from chloro-, fluoro-, or trifluoromethylthio-hydrins on reaction scales between 0.1–1.0 mmol; [a] 60 °C, 3 h instead of 40 °C, 18h for step 1. (B) Preparation of β-ketotrifluoromethylthiohydrin **22** and its conversion to α-trifluoromethylthioaldehyde **23**. (C) Conversion of β-ketochlorohydrin **24** into α-chloroaldehyde **25**. Yields determined via q-NMR using 1,3,5-trimethoxybenzene as internal standard. Enantiomeric excess (ee) determined via chiral HPLC on reduction products. Diastereomeric ratios determined by ^{1}H NMR spectroscopic analysis.

Table 2 Chemical and enantiomeric purity of α-chloro- and α-fluoroaldehydes produced via 1- or 2-step processes

Entry	Compound	2-Step process[a]		1-Step process[c]	
		ee (%)	Purity[b]	ee (%)	Purity[b]
1	**9**	94	*****	94	****
2	**11**	94	*****	92	***
3	**12**	92	*****	92	***
4	**25**	96	*****	94[24]	***
5	**19**	95	*****	NA	*

[a] Process reported in this manuscript. [b] See text above for description of how purity was determined. [c] Process reported in ref. 8s for entries 1–3. Enantiomeric excess (ee) determined by chiral HPLC analysis of halohydrin produced following reduction of α-haloaldehyde.

generation catalyst[8m] and N-chlorosuccinimide (Table 2, entries 1–4). Also, we included a product produced using the α-fluorination method reported by Barbas (entry 5) in this comparison.[8b] As these α-halogenation reactions are executed in MeCN (chlorination) or DMF (fluorination), the products can be extracted directly into pentane. We note that the original procedures in all cases involve direct reduction of the α-haloaldehyde and isolation of the readily purifiable halohydrin, and that the table below only reflects the purity of α-haloaldehydes directly extracted from these reaction mixtures. To assess purity, we analyzed ^{1}H NMR spectra of the pentane extracts and assigned each compound a purity score (1 to 5 stars) based on sum of the integration of product signals above 2 ppm divided by the sum of the integration of all non-solvent signals above 2 ppm (***** >95%, **** >90%, *** >80%, ** >60%, * <60%). All ^{1}H NMR spectra are included in the SI. As indicated in Table 2, while the enantiomeric purities were comparable, the chemical purities were lower utilizing 1-step protocols. Thus, the use of these capricious materials would require additional purification steps that often compromises enantiomeric purity and yield.

Reactions of α-substituted aldehydes 13, 14, 16, and 23

Finally, to demonstrate the synthetic utility of α-substituted aldehydes prepared via the methods reported here, we engaged select examples in stereoselective lithium aldol reactions[2] with various ketones. α-Chloroaldehydes **13** and **14** (Fig. 4A) were engaged in separate aldol reactions with the lithium enolate derived from 3′-bromoacetophenone to provide anti-β-ketochlorohydrins **26** and **27** in good yield and diastereoselectivity. Notably, the increased diastereoselectivity observed for the formation of **27** when compared to **26** (>20 : 1 vs. 8 : 1) is likely a result of the favourable stereochemical relationship between the functional groups in **27**, which support both 1,2-anti[25] and 1,3-anti[26] selectivity.[27] Unlike α-chloroaldehydes, the use of enantioenriched α-fluoroaldehydes as electrophilic partners is much less common though the reaction of chiral or achiral dicyclohexylboron enolates[28] with pre-formed α-fluoroaldehydes[4] or in situ organocatalytic generation of α-fluoroaldehydes followed by copper-catalyzed decarboxylative

nantly the elimination product acrolein using various catalysts. With proline, **25** could be formed in good yield but in near racemic form (<15% ee). Ultimately, **25** was produced from ʟ-Ser by adopting a 5-step process originally developed by De Kimpe.[3,24] Now, the readily prepared αCAR aldol product **24** could be deprotected using a combination of SbCl₃ and ethylene glycol in acetonitrile (see SI for optimization of this reaction). Oxidative cleavage then gave α-chloroaldehyde **25** in pure form (Fig. 3C).

At the request of a Referee, we also compared the purity (chemical and enantiomeric) of α-haloaldehydes produced via this 2-step process with those produced using the convenient α-chlorination method reported by Christmann (1-step process),[8s] which utilizes the MacMillan's imidazolidinone 1st

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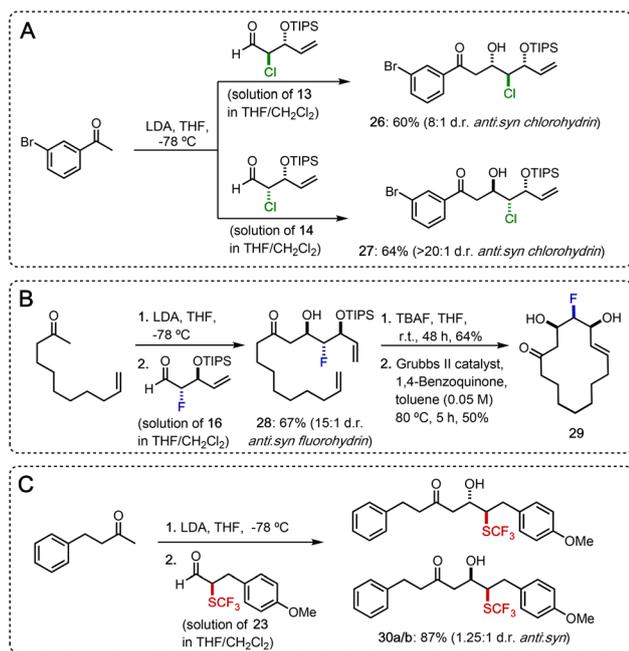
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Fig. 4 Stereoselective lithium-aldol reactions involving (A) α-chloroaldehydes, (B) α-fluoroaldehydes and (C): α-trifluoromethylthioaldehydes. Diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of crude reaction products.

aldolization has been reported.[29] Here, α-fluoroaldehyde **16** was successfully engaged in an aldol reaction with the lithium enolate derived from undec-10-en-2-one to provide 1,2-*anti*-β-ketofluorohydrin **28** in excellent yield (Fig. 4B). Removal of the TIPS protecting group then afforded a mixture of the β-ketofluorohydrin and the corresponding hemiacetal. RCM using Grubbs second generation catalyst facilitated the synthesis of the unusual polyketide-like macrocyclic ketone **29**. Finally, α-trifluoromethylthioaldehyde **23** was engaged in a lithium aldol reaction with the enolate derived from 4-phenylbutan-2-one (Fig. 4C). The resulting mixture of *anti*- and *syn*-β-ketotrifluoromethylthiohydrin diastereomers **30a** and **30b** was generated in excellent yield and were separable by flash chromatography with stereochemistry assigned based on Mosher's ester analysis of the separated diastereomers. Notably, this is the first example of an organometallic addition to an α-trifluoromethylthioaldehyde.

Conclusions

In summary, we describe a process for the preparation of high purity and enantioenriched α-haloaldehydes from their corresponding chloro-, fluoro-, and trifluoromethylthiohydrins. These later compounds are storable and made readily available through robust and scalable α-halogenation/aldol reactions that require only proline catalysis. Thus, overall, this is an inexpensive and general process for accessing high value but often unstable α-haloaldehydes in pure form. We expect that

this new process will support the broader use of these versatile building blocks in heterocycle and complex molecule synthesis.

Author contributions

A. J. B. and M. S. carried out the experimental work. R. B., A. J. B. and M. S. planned the study and A. J. B. and R. B. drafted the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article, including experimental protocols, characterization data, and NMR spectra, have been included as part of the Supplementary Information. See DOI: **https://doi.org/10.1039/d5qo01415h**.

Acknowledgements

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