

Organocatalytic Enantioselective α -Bromination of Aldehydes with *N*-Bromosuccinimide

George Hutchinson,* Carla Alamillo-Ferrer, Martín Fernández-Pascual, and Jordi Burés*



Cite This: *J. Org. Chem.* 2022, 87, 7968–7974



Read Online

ACCESS |



Metrics & More

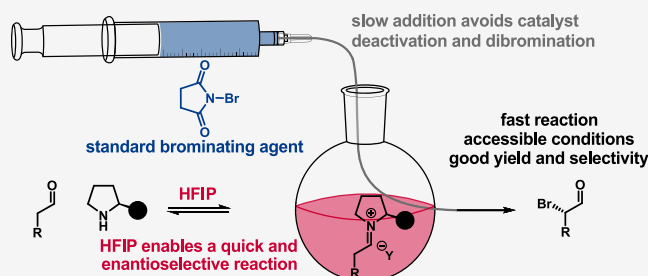


Article Recommendations



Supporting Information

ABSTRACT: Despite the wealth of existing organocatalytic, enantioselective transformations, the α -bromination of aldehydes remains a challenging reaction. The four examples reported to date require expensive, inconvenient brominating agents to achieve the desired products in excellent yields and enantioselectivities. The preferred brominating agent, *N*-bromosuccinimide (NBS), has been repeatedly discarded for these reactions because it results in low yields and relatively poor enantioselectivities. We describe a methodology that uses NBS and performs excellently with low catalyst loadings, short reaction times, and mild temperatures.



INTRODUCTION

Over the past 20 years, asymmetric organocatalysis has emerged as a potent strategy for the formation of a diverse range of useful molecules.¹ This revolutionary work culminated in the 2021 Nobel Prize in Chemistry being awarded to List and MacMillan for their pioneering work. Chiral secondary amines have been used as catalysts in a wealth of stereoselective transformations, such as the installation of heteroatoms at the α -position of aldehydes. While procedures for the enantioselective, organocatalytic fluorination² or chlorination³ of aldehydes have been widely reported, only a few α -bromination reactions provide highly versatile chiral building blocks that can be rapidly derivatized to α -bromoamines,^{8a} azidoalcohols,^{8b} epoxides,^{8c} or bromohydrins (Figure 1).^{4–7}

The first organocatalytic, enantioselective α -bromination of aldehydes was described by the Jørgensen group in 2005 (Figure 2a).⁴ The authors began their investigation using the reaction conditions from their successful chlorination but used *N*-bromosuccinimide (NBS, 2a) instead of *N*-chlorosuccinimide (NCS). The group found that NBS was an unsuitable brominating agent under these reaction conditions, giving just 8% conversion and 19% enantiomeric excess (Figure 2a). The authors attributed these poor results to the “increased reactivity of NBS 2a compared to that of NCS.” Hence, they had to resort to using 4,4-dibromo-2,6-di-*tert*-butyl-cyclohexa-2,5-dienone (2c) as the brominating agent to achieve excellent yields and enantioselectivities. The main handicap of this methodology is the necessity to use the unusual brominating agent 2c, which up to date, has only been used in 48 reactions, whereas the ubiquitous NBS has been used in 4,838,258 reactions.⁹

Later in the same year (Figure 2b),⁵ the Jørgensen group reported an improved methodology that used a more

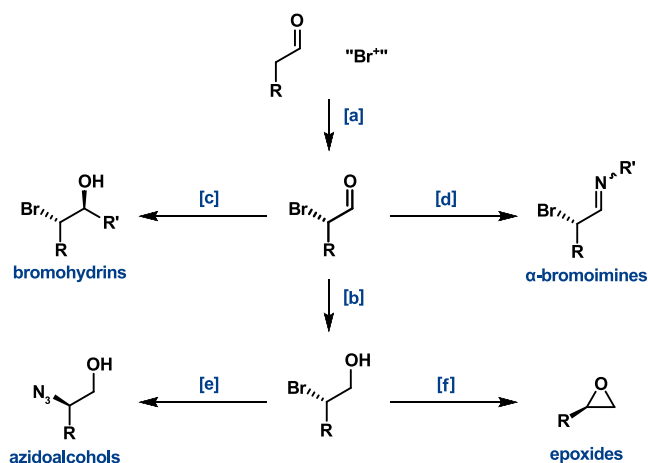


Figure 1. α -Brominated aldehydes are versatile synthons. [a] Any of the previous four methods^{4–7} or this work. [b] NaBH₄, MeOH.^{4–7} [c] R'MgBr.⁶ [d] R'NH₂, MgSO₄.^{8a} [e] (1) Alcohol protection; (2) NaN₃;^{8b} and (3) alcohol deprotection. [f] NaH.^{8c}

convenient catalyst, (*S*)- α,α -bis[3,5-bis(trifluoromethyl)-phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (3b) but still required the use of the unusual brominating agent, 4,4-dibromo-2,6-di-*tert*-butyl-cyclohexa-2,5-dienone 2c, instead of NBS. As in their previous methodology, the authors still

Received: March 15, 2022

Published: May 26, 2022



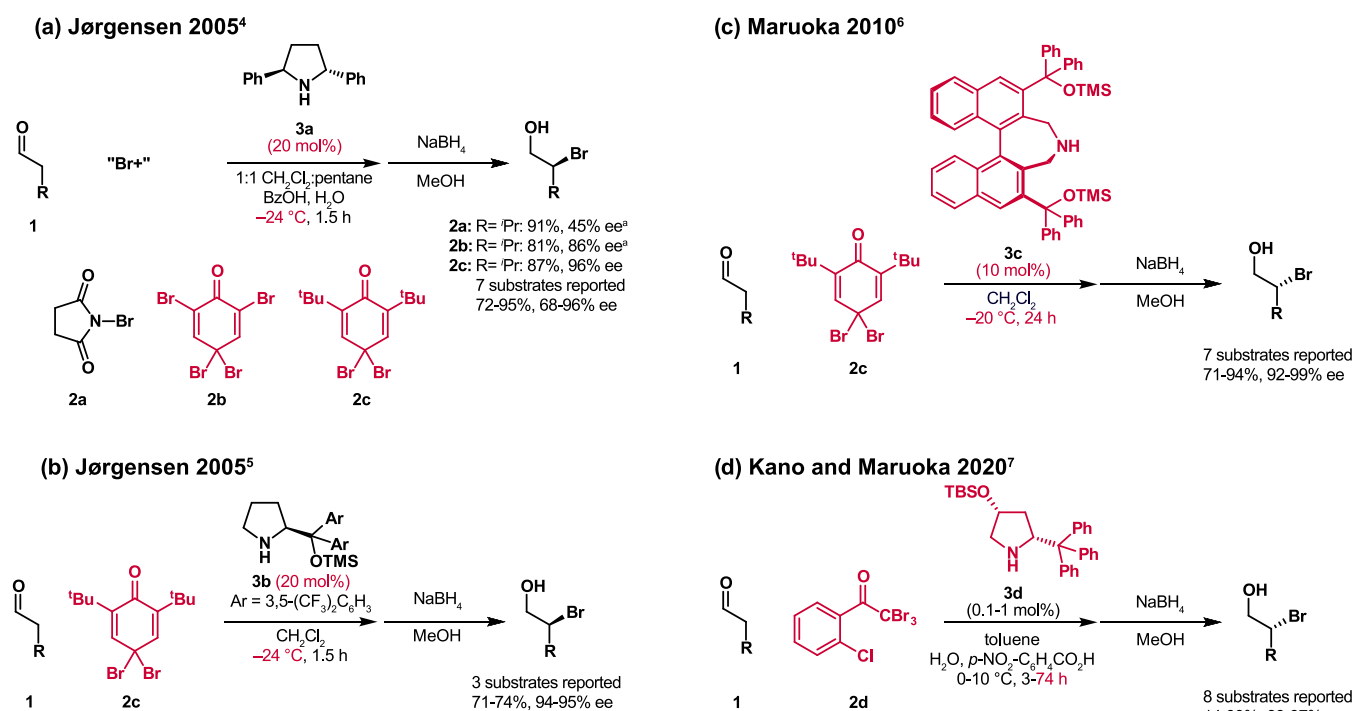


Figure 2. Previous examples of enantioselective aminocatalytic α -brominations of aldehydes. Nonideal conditions and reactants are highlighted in red. ^a1:3 pentane:CH₂Cl₂ and no added water.

required low temperatures ($-24\text{ }^\circ\text{C}$) to prevent side reactions, such as bromination of the catalyst.

Maruoka et al. described another example of an aminocatalytic, enantioselective bromination in 2010 (Figure 2c).⁶ The authors tested seven potential brominating agents and observed that five of them, most notably NBS (2a), gave no conversion (<5%). Therefore, the authors had to use the same nonideal brominating agent as Jørgensen, 2c. They used 10 mol % of the Maruoka's binaphthyl catalyst 3c, which provides the best-reported enantioselectivities but is very laborious to synthesize.^{6,10}

In 2020, Maruoka and Kano explored alternative aminocatalytic methods using pyrrolidine derivatives instead of 3c as catalyst (Figure 2d).⁷ They reported the rapid decomposition of NBS (2a) and 4,4-dibromo-2,6-di-*tert*-butyl-cyclohexa-2,5-dienone (2c) in the presence of pyrrolidine and explored milder brominating agents to avoid the bromination of the pyrrolidine derivatives used as catalysts. They explored several noncommercially available ketone-based brominating agents (KBAs) and chose to use CIPh-KBA 2d (Figure 2d). Even using KBAs, the standard Jørgensen–Hayashi catalyst provided poor yields and enantioselectivities, making necessary the use of noncommercially available pyrrolidine-based catalysts with very large substituents in positions 2 and 4 (e.g., 3d). This original combination of catalyst and brominating agent reduced the catalyst deactivation significantly, allowing the authors to obtain excellent yields even with only 0.1 mol % of catalyst in 74 h.

In brief, both groups pioneering the enantioselective aminocatalytic α -bromination of aldehydes, Jørgensen's and Maruoka's, discarded the possibility of using the commonly preferred brominating agent, NBS. Their original solutions had to compromise on the brominating agent and reaction conditions to get excellent yields and enantioselectivities. All of the brominating agents reported by Jørgensen and Maruoka

generate stoichiometric amounts of organobromine byproducts, which are toxic and environmental hazards.¹¹ Additionally, due to the inherent difficulty of the transformation, the turnover frequencies of their methodologies are generally low, hence requiring either very high catalyst loadings (up to 20 mol %)^{4,5} or very long reaction times (74 h when using 0.1 mol % of catalyst).⁷ Some of the reactions also involve atypical, noncommercially available catalysts and low temperatures (lower than $-20\text{ }^\circ\text{C}$). Herein, we describe a method that achieves excellent turnover frequencies and enantioselectivities using NBS and 2 mol % of a Jørgensen–Hayashi type catalyst at convenient temperatures.

We have recently described an aminocatalytic, enantioselective α -chlorination of aldehydes using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)¹² as the solvent.^{3f} We chose this solvent with the intention of shifting the reaction mechanism to proceed through charged intermediates rather than stable, neutral species. This strategy allowed us to chlorinate a range of aldehydes with good yields and excellent enantioselectivities, using low catalyst loadings, commercially available reagents, short reaction times, and convenient temperatures. We anticipated that the application of a similar knowledge-based strategy would yield comparable improvements for an enantioselective α -bromination of aldehydes.

RESULTS AND DISCUSSION

Although we used our method for the aminocatalytic chlorination in HFIP as starting point, the higher reactivity of NBS with respect to NCS made the development of the bromination methodology much more challenging than the chlorination one. A better control of the reaction conditions is necessary to avoid the deactivation of the aminocatalyst, which occurs quicker with NBS than NCS. The reaction conditions have to be modified to minimize the undesired dihalogenation of the aldehyde, more prevalent in the bromination than the

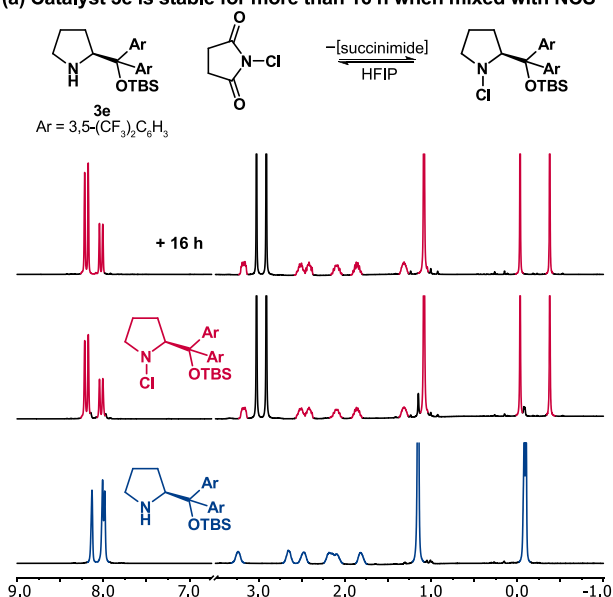
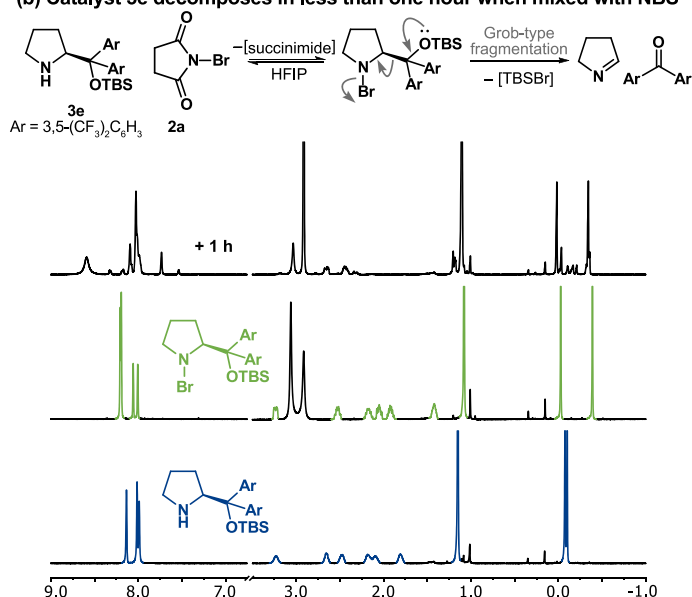
(a) Catalyst **3e** is stable for more than 16 h when mixed with NCS^{3f}(b) Catalyst **3e** decomposes in less than one hour when mixed with NBS

Figure 3. Jørgensen–Hayashi catalyst is far less stable when brominated than when chlorinated.

chlorination. The reaction time has to be precisely controlled to avoid the racemization of the α -brominated aldehydes, which are less stable than the α -chlorinated. Also, the optimization of the reaction conditions could not be guided by in situ FTIR because the IR probe is chemically incompatible with the reaction media.¹³

First, we compared the stability of the Jørgensen–Hayashi type catalysts when mixed with NBS or NCS in HFIP. The OTBS–prolinol derivative bearing 3,5-bis(trifluoromethyl)phenyl groups (**3e**), which is stable for more than 16 h when chlorinated (Figure 3a), decomposes over just 1 h after being brominated (Figure 3b). The faster irreversible deactivation of the halogenated aminocatalyst meant that it was more challenging and more important to control the undesired reaction of the catalyst with the halogenating agent during the bromination than it had been during the chlorination.

A further complication of the bromination reaction is the lower stability of the product of the reaction, the α -brominated aldehyde, compared with the chlorinated analogue. We have observed that the monobrominated aldehyde loses enantiomeric excess not only when mixed with the aminocatalyst in HFIP but also when mixed with the apparently innocuous byproduct of the reaction, succinimide.¹⁴ Maruoka et al. also described the high instability of brominated products when they noticed the loss of enantiomeric excess during NaBH₄ reduction.⁶

When we tested the aminocatalytic reaction with 2 mol % of the Jørgensen–Hayashi catalyst **3f** and NBS under standard conditions in HFIP, we obtained mostly dibrominated aldehyde (13%) with only some of the desired product (4%) after 12 h (Figure 4a). This result is consistent with the yields reported by Jørgensen (8%) and Maruoka (<5%) and confirms the difficulty of using NBS in this transformation. We observed, by NMR, that most of the catalyst was brominated in the first 5 min after starting the reaction, which explains the low yields. We attempted to mitigate the catalyst deactivation by adding succinimide to the reaction mixture. The addition of succinimide shifts the equilibrium between free and bromi-

nated catalyst toward free catalyst and, hence, accelerates the main reaction. In the presence of succinimide, 2 mol % of **3f** was sufficient to consume all of the NBS, but the dibrominated aldehyde was still the main product of the reaction (Figure 4b). The large percentage of dibrominated aldehyde arose because of the over bromination of the brominated enamine, one of the key reaction intermediates of the catalytic reaction, instead of its hydrolysis. In this bifurcation, the branching ratio of products is affected by the concentration of reactants involved in each pathway and therefore water should reduce the percentage of dibromination. Indeed, the addition of water increased the yield of product from 5 to 73% (Figure 4c) and reduced the formation of dibrominated aldehyde from 48 to 15% (Figure 4c), but the enantiomeric ratio of the product was only 78:22. While the additions of succinimide and water to reactions using NBS mitigated the catalyst deactivation and aldehyde dibromination, the enantioselectivity was unsatisfactory. This low enantioselectivity is likely due to the aforementioned erosion of product's enantiomeric excess in the presence of succinimide.

To increase the performance of the aminocatalytic α -bromination of aldehydes using NBS, we explored the slow addition of the brominating agent to the reaction mixture. The slow addition maintains a low concentration of NBS in the reaction media, which reduces the dibromination and favors the irreversible bromination of the aldehyde over the reversible bromination of the catalyst. For each substrate, we increased the time of addition of NBS until we observed full consumption at the end of the addition, which guarantees that the NBS does not build up at any point of the reaction. In addition, we quenched the reaction at the end of the addition of NBS to minimize product racemization.

The amount of water allows us to tune the ratio between the product and the dibrominated aldehyde. Previous studies of the chlorination and fluorination reactions suggest the second halogenation acts as a kinetic resolution, enantioenriching the product of the reaction.^{3,5} However, in the bromination reaction, the correlation between the percentage of dibromination and enantiomeric excess of the product is much smaller.

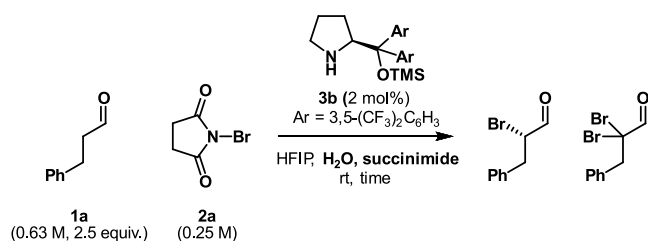
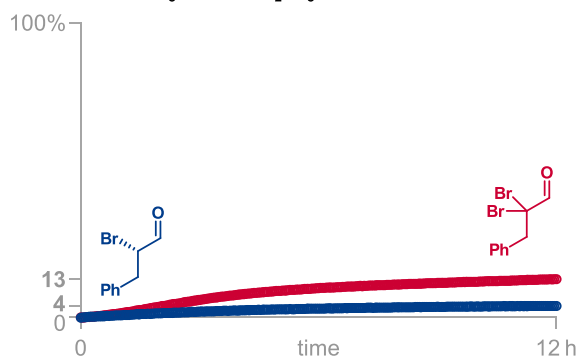
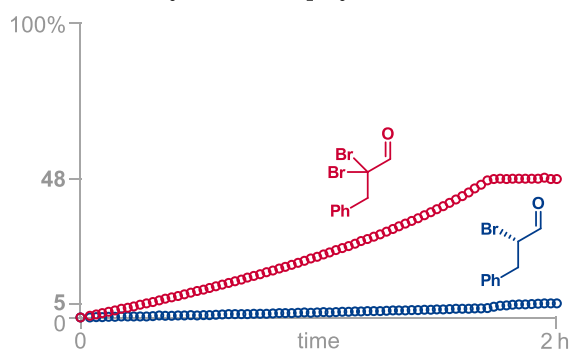
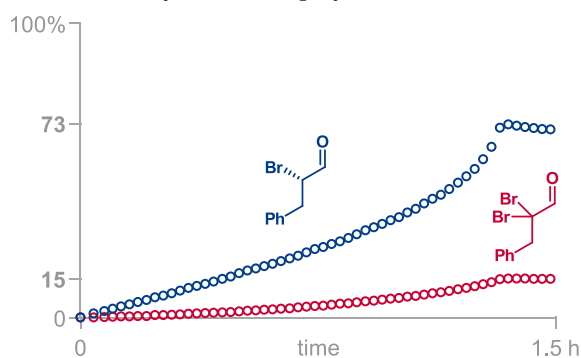
(a) $[\text{succinimide}]_0 = 0 \text{ M}$, $[\text{H}_2\text{O}]_0 = 0 \text{ M}$ (b) $[\text{succinimide}]_0 = 0.25 \text{ M}$, $[\text{H}_2\text{O}]_0 = 0 \text{ M}$ (c) $[\text{succinimide}]_0 = 0.25 \text{ M}$, $[\text{H}_2\text{O}]_0 = 4.63 \text{ M}$ 

Figure 4. Adding succinimide enhanced the reaction rate, while adding water reduced the dibromination, as demonstrated by monitoring the reaction by ^1H NMR.

This is especially the case for short-chain aldehydes,¹⁴ which are challenging substrates absent from the substrate scope of the previous methodologies.^{4–7}

By tuning the time of addition and amount of water, we were able to use NBS for the aminocatalytic α -bromination of aldehydes without sacrificing yield or enantioselectivity. We also achieved great turnover frequencies, which allowed us to run most of the reactions in less than 1.5 h using only 2 mol %

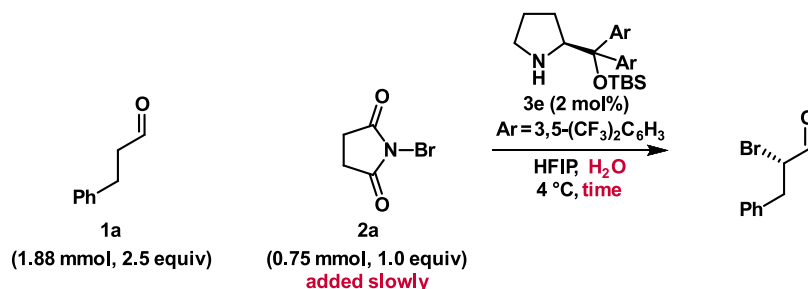
of the Jørgensen–Hayashi type catalyst **3e**. Some substrates, particularly hydrocinnamaldehyde (Table 1, entry 1) and octanal (Table 1, entry 3), performed exquisitely under our reaction conditions, giving good yields and high enantioselectivities after very quick optimization of the reaction conditions. We successfully increased the scale of the bromination of hydrocinnamaldehyde while maintaining a good yield at the cost of some enantiomeric excess (Table 1, entry 2). We found that dodecanal displayed a tendency to dibrominate, giving a lower yield but comparable enantiomeric excess to octanal with the same amount of added water (Table 1, entry 4). For pentanal, a shorter chain substrate, we attained a good yield after increasing the amount of water and time of addition (Table 1, entry 5). The α -bromination of propanal yielded moderate enantioselectivities (Table 1, entry 6), but the result is remarkable given that it is the first reported enantioselective bromination of the shortest utilizable linear aldehyde. We obtained excellent enantioselectivities for isovaleraldehyde, which required longer addition times (4.75 h) because it is β -branched (Table 1, entry 7). Similarly, we found that the bromination of 3-cyclohexylpropanal had to be carried out at room temperature to allow full consumption of the NBS over a reasonable amount of time (Table 1, entry 8).

CONCLUSIONS

In conclusion, the organocatalytic, enantioselective α -bromination of aldehydes is a much more challenging reaction than the analogous chlorination because of the greater reactivity of the brominating agents and instability of the products. We have overcome the limitations of previous methods with respect to the use of NBS as a brominating agent using HFIP as a solvent and tuning the amount of water and dosing the NBS during the reaction. The use of NBS is a more environmentally friendly alternative to the previous brominating agents because it avoids the stoichiometric formation of organobromine byproducts. Our methodology does not require special catalysts or lower temperatures to minimize the catalyst deactivation, which allows us to achieve, in most cases, better turnover frequencies than the previous methodologies.

EXPERIMENTAL SECTION

General Information. Commercially available aldehydes were carefully distilled under vacuum into an LN₂ trap immediately prior to use. The 3-cyclohexylpropanal was synthesized by Dess–Martin periodinane (DMP) oxidation of 3-cyclohexylpropanol, following GP1. The N-bromosuccinimide (NBS) was recrystallized from water. The (*S*)- α,α -bis[3,5-bis(trifluoromethyl)-phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**3c**) and (*S*)- α,α -bis[3,5-bis(trifluoromethyl)-phenyl]-2-pyrrolidinemethanol *tert*-butyldimethylsilyl ether (**3e**) catalysts were purified from commercial sources by flash column chromatography (CH_2Cl_2) to remove any deprotected alcohol. All other reagents and solvents were used as-purchased from Merck, Fluorochem, Alfa Aesar, and TCI. All NMR spectra were recorded on a Bruker AVII 500 MHz spectrometer or a Bruker AVIII HD 400 MHz spectrometer with BBO prodigy probe. ^1H NMR and ^{13}C NMR chemical shifts (δ) are quoted in ppm relative to residual solvent peaks (for ^1H and ^{13}C , respectively, given in ppm, for CDCl_3 : 7.26, 77.16). Any nondeuterated NMR spectra were recorded after shimming on the solvent peak closest to the middle of the spectrum and are reported with respect to the shift of this solvent peak aligned with its position in CDCl_3 (for ^1H and ^{13}C , respectively, given in ppm, for HFIP: 4.49, 69.20). Chiral HPLC was carried out on an Agilent 1260 Infinity II LC equipped with a diode array detector. Slow additions were carried out using a Harvard Apparatus standard

Table 1. Examples of Optimized Reaction Conditions for the α -Bromination of Aldehydes

entry	deviation from above	H ₂ O (μ L)	time of addition of NBS (min)	yield ^a (%)	er ^b
1	none	50	60	71 (65)	98:2
2	3 mmol scale (4x) instead of 0.75 mmol	200	60	72 (58)	92:8
3	octanal instead of hydrocinnamaldehyde	80	60	73 (59)	95:5
4	dodecanal instead of hydrocinnamaldehyde	80	60	44 (40)	96:4
5	pentanal instead of hydrocinnamaldehyde	100	75	65 (47)	92:8
6	propanal instead of hydrocinnamaldehyde	200	150	61 (33 ^c)	76:24
7	isovaleraldehyde instead of hydrocinnamaldehyde	85	285	69 (51)	95:5
8 ^d	3-cyclohexylpropanal instead of hydrocinnamaldehyde	50	90	72 (62)	90:10

^aYield of α -bromoaldehyde measured by qNMR with an internal standard (see [Electronic Supporting Information \(ESI\)](#)) after reduction of the α -bromoaldehyde to the bromohydrin. The number in parenthesis indicates the isolated yield of the bromohydrin after purification from a repeated reaction. ^bEnantiomeric ratio determined by chiral high-performance liquid chromatography (HPLC) after reduction of the α -bromoaldehyde to the bromohydrin. Entries 3–8 were benzoylated for UV detection during HPLC analysis. ^cProduct was volatile and was isolated after benzoylation of the bromohydrin. ^dReaction run at room temperature.

infuse/withdraw pump 11 elite programmable syringe pump calibrated to the syringe, a Henke-Saas-Wolf Air-tight 2.5 mL. The brominating agent was added as a stock solution through poly-(tetrafluoroethylene) (PTFE) tubing with an internal diameter of 0.50 mm. All bromination reactions were carried out in a STEM Integrity 10 set to the desired temperature. Flash column chromatography was performed using 230–400 mesh silica, with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography were performed on precoated glass-backed silica gel plates (Supelco TLC Silica gel 60 F₂₅₄). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or anisaldehyde stain. The time of addition and amount of water required for each substrate were optimized following the procedure described for chlorination in our previous work.^{3f} Yields were calculated after reduction of the α -bromoaldehydes to the corresponding bromohydrins using qNMR with an internal standard (see [ESI](#)).

General Procedure 1 (GP1): DMP Oxidation of 3-Cyclohexylpropan-1-ol.¹⁵ To a stirred solution of alcohol (2.0 g, 14 mmol, 1 equiv) in dry CH₂Cl₂ (50 mL, 0.28 M) under N₂ was added DMP (7.2 g, 17 mmol, 1.2 equiv). The reaction mixture was stirred for 3 h before Et₂O (200 mL) and sat. NaHCO_{3(aq)} (100 mL) was added. After stirring for 10 min, the mixture was filtered through a short plug of celite and transferred to a separating funnel. The organic phase was washed with sat. NaHCO_{3(aq)} (2 × 100 mL) and brine (50 mL) before the organic phase was collected, dried over MgSO₄, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (9:1 hexane:EtOAc) to afford a colorless oil (1.70 g, 12 mmol, 86%).

General Procedure 2 (GP2): Bromination of Aldehydes. Solutions of aldehyde (1.88 mmol in 500 μ L, 2.5 equiv), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)-phenyl]-2-pyrrolidinemethanol *tert*-butyldimethylsilyl ether **3e** (0.015 mmol in 500 μ L, 2 mol %) and H₂O (determined amount in 500 μ L) in HFIP were added to a stirred vial containing HFIP (500 μ L) at 4 °C. The reaction mixture was stirred for 2 min before a solution of NBS (0.75 mmol in 1000 μ L, 1 equiv) in HFIP was added over the determined time. Immediately after the end of the addition, the reaction mixture was transferred to a stirred flask containing MeOH (1 mL) and CH₂Cl₂ (1 mL) before NaBH₄ (approximately 5 equiv) was added. This mixture was stirred for 2

min before sat. NH₄Cl_(aq) (5 mL), H₂O (5 mL) and a stock solution of internal standard were added. The mixture was extracted with CH₂Cl₂ (4 × 15 mL), before the combined organic phase was washed with brine (15 mL), dried over MgSO₄, and concentrated under reduced pressure (care should be taken as some of the bromohydrins, particularly 2-bromo-3-methylbutan-1-ol, 2-bromo-pentan-1-ol and 2-bromo-propan-1-ol, are volatile). The products were isolated after purification by flash column chromatography.

General Procedure 3 (GP3): Benzoylation of Alcohols. The crude or purified product from GP2 was dissolved in dry CH₂Cl₂ (10 mL, 0.075 M) before BzCl (3 mmol, 347 μ L, 4 equiv) was added. NEt₃ (3 mmol, 413 μ L, 4 equiv) was added dropwise over 30 s. The reaction mixture was stirred overnight before sat. NaHCO_{3(aq)} (10 mL) was added. The mixture was transferred to a separating funnel, and the organic phase was collected, dried over MgSO₄, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography or preparative TLC.

General Procedure 4 (GP4): Synthesis of Racemic Bromohydrins. To a stirred solution of the aldehyde (3.75 mmol, 1 equiv) in CH₂Cl₂ (10 mL, 0.375 M) was added NBS (800 mg, 4.5 mmol, 1.2 equiv) and DL-proline (86 mg, 0.75 mmol, 20 mol %) at room temperature. The reaction mixture was stirred for 2 h before being transferred to a stirred vial containing MeOH (5 mL) and NaBH₄ (approximately 5 equiv). The reduction was stirred for 2 min before sat. NH₄Cl_(aq) (10 mL) and H₂O (5 mL) were added. The mixture was extracted with CH₂Cl₂ (4 × 30 mL) before the combined organic phase was washed with brine (30 mL), dried over MgSO₄, and concentrated under reduced pressure.

Stability of Catalyst 3e When Brominated. To a stirred solution of (*S*)- α,α -bis[3,5-bis(trifluoromethyl)-phenyl]-2-pyrrolidinemethanol *tert*-butyldimethylsilyl ether (0.06 mmol, **3e**) in HFIP (0.6 mL, 0.1 M) in an NMR tube was added *N*-bromosuccinimide (0.132 mmol, 2.2 equiv). Sequential ¹H NMR spectra were collected over 90 min.

Reactions with an Instantaneous Injection of NBS Solution. A stock solution of catalyst **3b** (100 μ L of a 0.03 M solution in HFIP, 2 mol %) was added to a mixture of hydrocinnamaldehyde (0.38 mmol, 2.5 equiv), NBS (0.15 mmol), and the desired amounts of succinimide and water in HFIP (500 μ L). Sequential ¹H NMR spectra were collected over the reaction course. The integrals of the

aldehyde protons on the starting material (9.72 ppm) and mono- (9.43 ppm) and dibrominated aldehydes (9.26 ppm) were compared to determine the conversion.

Assessment of the Configurational Stability of the α -Bromoaldehyde Products. 2-Bromo-3-phenylpropanal was obtained following GP2 with catalyst **3b**, a 90 min addition of NBS, and 100 μ L of added water without NaBH₄ reduction. The monobrominated aldehyde was purified by column chromatography (100% CH₂Cl₂) to give a pale-yellow oil (82 mg, 51% isolated yield, 86:14 er). The isolated monobrominated aldehyde was mixed separately with catalyst **3b** (5 mol %) and with NHS (1.0 equiv). These reactions were sampled and the enantiomeric ratio of the aldehyde in each sample was determined by chiral HPLC after reduction to the corresponding bromohydrin.

2-Bromo-3-phenylpropan-1-ol.⁷ 2-Bromo-3-phenylpropan-1-ol was obtained following GP2 with an initial amount of 50 μ L of water and an addition of NBS over 60 min (71% by qNMR, 98:2 er). The product was isolated after column chromatography (100% CH₂Cl₂) to give a pale-orange oil (105 mg, 65% isolated yield). When performed at a 3 mmol scale (4 \times GP2) with an initial amount of 200 μ L of water and an addition of NBS over 60 min, the yield by qNMR was 72%. The product was isolated after column chromatography (100% CH₂Cl₂) to give a pale-orange oil (374 mg, 58% isolated yield, 92:8 er). ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.28 (m, 3H), 7.24–7.22 (m, 2H), 4.33 (tdd, *J* = 7.3, 6.2, 3.7 Hz, 1H), 3.83 (ddd, *J* = 12.4, 7.1, 3.7 Hz, 1H), 3.74 (dt, *J* = 12.4, 6.2 Hz, 1H), 3.27 (dd, *J* = 14.2, 7.3 Hz, 1H), 3.18 (dd, *J* = 14.2, 7.5 Hz, 1H), 2.01 (t, *J* = 6.9 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 137.8, 129.3, 128.8, 127.2, 66.2, 58.9, 41.5.

2-Bromo-octan-1-ol.⁶ 2-Bromo-octan-1-ol was obtained following GP2 with an initial amount of 80 μ L of water and an addition of NBS over 60 min (73% by qNMR, 95:5 er). The product was isolated after column chromatography (100% CHCl₃) to give a colorless oil (92 mg, 59% isolated yield). ¹H NMR (400 MHz, CDCl₃) δ 4.18–4.12 (m, 1H), 3.82 (ddd, *J* = 11.8, 7.7, 3.9 Hz, 1H), 3.82 (dt, *J* = 12.3, 6.1 Hz, 1H), 1.99 (dd, *J* = 7.9, 5.7 Hz, 1H), 1.85 (q, *J* = 7.4 Hz, 2H), 1.47–1.39 (m, 1H), 1.38–1.25 (m, 7H), 0.89 (t, *J* = 6.7 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 67.5, 60.4, 35.0, 31.7, 28.8, 27.6, 22.7, 14.2.

2-Bromo-dodecan-1-ol.¹⁶ 2-Bromo-dodecan-1-ol was obtained following GP2 with an initial amount of 80 μ L of water and an addition of NBS over 60 min (44% by qNMR, 96:4 er). The product was isolated after column chromatography (100% CHCl₃) to give a colorless oil (79 mg, 40% isolated yield). ¹H NMR (400 MHz, CDCl₃) δ 4.17–4.11 (m, 1H), 3.81 (dd, *J* = 12.3, 4.0 Hz, 1H), 3.74 (dd, *J* = 12.3, 6.9 Hz, 1H), 1.91 (bs, 1H), 1.87–1.81 (m, 2H), 1.58–1.49 (m, 1H), 1.45–1.38 (m, 1H), 1.33–1.23 (m, 14H), 0.87 (t, *J* = 6.8 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 67.4, 60.4, 35.0, 32.0, 29.71, 29.68, 29.54, 29.45, 29.1, 27.6, 22.8, 14.3.

2-Bromo-pentan-1-ol.⁶ 2-Bromo-pentan-1-ol was obtained following GP2 with an initial amount of 100 μ L of water and an addition of NBS over 75 min (65% by qNMR, 92:8 er). The product was isolated after column chromatography (100% CH₂Cl₂) to give a pale-yellow oil (59 mg, 47% isolated yield). ¹H NMR (400 MHz, CDCl₃) δ 4.16 (tdd, *J* = 7.1, 5.8, 4.0 Hz, 1H), 3.82 (dd, *J* = 12.3, 4.0 Hz, 1H), 3.74 (dd, *J* = 12.3, 7.0 Hz, 1H), 1.93 (bs, 1H), 1.86–1.78 (m, 2H), 1.65–1.52 (m, 1H), 1.52–1.39 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 67.5, 60.0, 37.0, 20.8, 13.6.

2-Bromopropylbenzoate.¹⁷ 2-Bromopropylbenzoate was obtained following GP2 with an initial amount of 200 μ L of water and an addition of NBS over 150 min (61% by qNMR, 76:24 er). This product was benzoylated following GP3 as the unprotected alcohol is volatile. The benzoylated product was isolated after column chromatography (100% CH₂Cl₂) and preparative TLC (95:5 hexane:EtOAc) to give a colorless oil (60 mg, 33% isolated yield). ¹H NMR (400 MHz, CDCl₃) δ 8.08–8.06 (m, 2H), 7.60–7.57 (m, 1H), 7.48–7.44 (m, 2H), 4.55–4.45 (m, 2H), 4.40–4.32 (m, 1H), 1.79 (d, *J* = 6.8 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.4, 133.7, 130.6, 130.2, 128.9, 69.7, 45.2, 23.0.

2-Bromo-3-methylbutan-1-ol.⁷ 2-Bromo-3-methylbutan-1-ol was obtained following GP2 with an initial amount of 85 μ L of water and an addition of NBS over 285 min (69% by qNMR, 95:5 er). The product was isolated after column chromatography (100% CH₂Cl₂) to give a pale-yellow oil (69 mg, 51% isolated yield). ¹H NMR (400 MHz, CDCl₃) δ 4.10 (ddd, *J* = 6.3, 5.6, 4.8 Hz, 1H), 3.84–3.79 (m, 2H), 2.02 (hept, *J* = 6.7, 4.8 Hz, 1H), 1.95 (bs, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 68.4, 65.9, 31.6, 21.0, 19.2.

2-Bromo-3-cyclohexylpropan-1-ol.⁶ 2-Bromo-3-cyclohexylpropan-1-ol was obtained following GP2 with an initial amount of 50 μ L of water and an addition of NBS over 90 min at room temperature (72% by qNMR, 90:10 er). The product was isolated after column chromatography (100% CH₂Cl₂) to give a pale-yellow oil (102 mg, 62% isolated yield). ¹H NMR (400 MHz, CDCl₃) δ 4.25 (dddd, *J* = 10.4, 7.0, 4.5, 3.7 Hz, 1H), 3.81 (ddd, *J* = 12.2, 8.0, 3.7 Hz, 1H), 3.72 (ddd, *J* = 12.2, 7.0, 5.6 Hz, 1H), 2.03 (dd, *J* = 8.0, 5.6 Hz, 1H), 1.82–1.52 (m, 8H), 1.31–1.22 (m, 2H), 1.18–1.10 (m, 1H), 1.02–0.94 (m, 1H), 0.88–0.78 (m, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 67.9, 58.3, 47.4, 35.6, 33.8, 32.2, 26.6, 26.3, 26.1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.2c00600>.

Experimental procedures and spectral and chromatographic data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

George Hutchinson – *The University of Manchester, Department of Chemistry, M13 9PL Manchester, U.K.*;
 orcid.org/0000-0001-5477-9521;

Email: george.hutchinson@manchester.ac.uk

Jordi Burés – *The University of Manchester, Department of Chemistry, M13 9PL Manchester, U.K.*;
 orcid.org/0000-0002-7821-9307; Email: jordi.bures@manchester.ac.uk

Authors

Carla Alamillo-Ferrer – *The University of Manchester, Department of Chemistry, M13 9PL Manchester, U.K.*;
 orcid.org/0000-0003-3607-846X

Martín Fernández-Pascual – *The University of Manchester, Department of Chemistry, M13 9PL Manchester, U.K.*;
 orcid.org/0000-0002-2855-0069

Complete contact information is available at:

<https://pubs.acs.org/doi/10.1021/acs.joc.2c00600>

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research leading to these results has received funding from the EPSRC (EP/S005315/1 and EP/RS13131/1).

■ REFERENCES

- (1) (a) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. The Diarylprolinol Silyl Ethers: Ten Years After. *Angew. Chem., Int. Ed.* **2015**, *54*, 13860. (b) Vega-Peñaloza, A.; Paria, S.; Bonchio, M.; Dell'Amico, L.; Companyó, X. Profiling the Privileges of Pyrrolidine-Based Catalysts in Asymmetric Synthesis: From Polar to Light-Driven Radical Chemistry. *ACS Catal.* **2019**, *9*, 6058. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. Asymmetric Aminocatalysis—Gold Rush in Organic Chemistry. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138.

- (2) For pioneering examples, see (a) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. Enantioselective Formation of Stereogenic Carbon–Fluorine Centers by a Simple Catalytic Method. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (b) Steiner, D. D.; Mase, N.; Barbas, C. F., III Direct Asymmetric α -Fluorination of Aldehydes. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706. (c) Beeson, T. D.; MacMillan, D. W. C. Enantioselective Organocatalytic α -Fluorination of Aldehydes. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (d) Enders, D.; Hüttel, M. R. M. Direct Organocatalytic α -Fluorination of Aldehydes and Ketones. *Synlett* **2005**, *2005*, 0991.
- (3) (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. Direct and Enantioselective Organocatalytic α -Chlorination of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. Direct Organocatalytic Asymmetric α -Chlorination of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 4790. (c) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. Enantioselective Linchpin Catalysis by SOMO Catalysis: An Approach to the Asymmetric α -Chlorination of Aldehydes and Terminal Epoxide Formation. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121. (d) Jimeno, C.; Cao, L.; Renaud, P. Trichloromethanesulfonyl Chloride: A Chlorinating Reagent for Aldehydes. *J. Org. Chem.* **2016**, *81*, 1251. (e) Ponath, S.; Menger, M.; Grothues, L.; Weber, M.; Lentz, D.; Strohmam, C.; Christmann, M. Mechanistic Studies on the Organocatalytic α -Chlorination of Aldehydes: The Role and Nature of Off-Cycle Intermediates. *Angew. Chem., Int. Ed.* **2018**, *57*, 11683. (f) Hutchinson, G.; Alamillo-Ferrer, C.; Burés, J. Mechanistically Guided Design of an Efficient and Enantioselective Aminocatalytic α -Chlorination of Aldehydes. *J. Am. Chem. Soc.* **2021**, *143*, 6805.
- (4) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. Organocatalytic Asymmetric α -Bromination of Aldehydes and Ketones. *Chem. Commun.* **2005**, 4821.
- (5) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. A General Organocatalyst for Direct α -Functionalization of Aldehydes: Stereoselective C–C, C–N, C–F, C–Br, and C–S Bond-Forming Reactions. Scope and Mechanistic Insights. *J. Am. Chem. Soc.* **2005**, *127*, 18296.
- (6) Kano, T.; Shirozu, F.; Maruoka, K. Direct Asymmetric Bromination of Aldehydes Catalyzed by a Binaphthyl-based Secondary Amine: Highly Enantio- and Diastereoselective One-Pot Synthesis of Bromohydrins. *Chem. Commun.* **2010**, *46*, 7590.
- (7) Takeshima, A.; Shimogaki, M.; Kano, T.; Maruoka, K. Development of Ketone-Based Brominating Agents (KBA) for the Practical Asymmetric α -Bromination of Aldehydes Catalyzed by Tritylpyrrolidine. *ACS Catal.* **2020**, *10*, 5959.
- (8) Additional references for the reactions shown in Figure 1: (a) Jiang, H.; Elsner, P.; Jensen, K. L.; Falcicchio, A.; Marcos, V.; Jørgensen, K. A. Achieving Molecular Complexity by Organocatalytic One-Pot Strategies—A Fast Entry for Synthesis of Sphingoids, Amino Sugars, and Polyhydroxylated α -Amino Acids. *Angew. Chem., Int. Ed.* **2009**, *48*, 6844. (b) Epifanov, M.; Mo, J. Y.; Dubois, R.; Yu, H.; Sammis, G. M. One-Pot Deoxygenation and Substitution of Alcohols Mediated by Sulfuryl Fluoride. *J. Org. Chem.* **2021**, *86*, 3768. (c) Tercenio, Q. D.; Alexanian, E. J. Stereospecific Nickel-Catalyzed Reductive Cross-Coupling of Alkyl Tosylate and Allyl Alcohol Electrophiles. *Org. Lett.* **2021**, *23*, 7215.
- (9) A reaction search carried out on 10/03/2022 using SciFinder revealed that 4,4-dibromo-2,6-di-*tert*-butyl-cyclohexa-2,5-dienone (**2c**) was listed as a reactant or reagent in 48 reactions, whereas NBS (**2a**) was listed as a reactant or reagent in 4,881,021 reactions. The 42,763 reactions where succinimide was attached to a non-H atom in the product were excluded from this total.
- (10) (a) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. Direct Asymmetric Hydroxyamination Reaction Catalyzed by an Axially Chiral Secondary Amine Catalyst. *J. Am. Chem. Soc.* **2006**, *128*, 6046. (b) Kano, T.; Mii, H.; Maruoka, K. Metal-Free Direct Asymmetric Aminoylation of Aldehydes Catalyzed by a Binaphthyl-Based Chiral Amine. *Angew. Chem., Int. Ed.* **2010**, *49*, 6638. (c) Liang, D.-C.; Luo, R.-S.; Yin, L.-H.; Chana, A. S. C.; Lu, G. A new synthetic route for axially chiral secondary amines with binaphthyl backbone and their applications in asymmetric Michael reaction of aldehydes to nitroalkenes. *Org. Biomol. Chem.* **2012**, *10*, 3071.
- (11) (a) 4-Bromo-2,6-di-*tert*-butylphenol: Classification according to Regulation (EC) No 1272/2008: H315, H319, H335; GHS Classification in accordance with 29 CFR 1910 (OSHA HCS): H315, H319, H335. (b) 2,4,6-tribromophenol: Classification according to Regulation (EC) No 1272/2008: H317, H319, H400; GHS Classification in accordance with 29 CFR 1910 (OSHA HCS): H317, H319, H400. (c) Rae, I. D. The trouble with bromine: health and environmental impacts of organobromine compounds. *Global Environ.* **2014**, *7*, 106.
- (12) While HFIP is not a usual solvent, it can be recovered and recycled because of its low boiling point. (a) Albanese, D. C. M.; Gaggero, N.; Fei, M. A practical synthesis of 2,3-dihydro-1,5-benzothiazepines. *Green Chem.* **2017**, *19*, 5703. (b) Herold, S.; Bafaluy, D.; Muñoz, K. Anodic benzylic C(sp³)-H amination: unified access to pyrrolidines and piperidines. *Green Chem.* **2018**, *20*, 3191.
- (13) Potential bromine generation would oxidize the gold seal of the ReactIR 15 probe, which would ruin the instrument. Additionally, NBS had to be added through PTFE capillaries because it oxidized the standard stainless-steel needles.
- (14) See [Electronic Supporting Information](#).
- (15) Grünenfelder, C. E.; Kisunzu, J. K.; Wennemers, H. Peptide-Catalyzed Stereoselective Conjugate Addition Reactions of Aldehydes to Maleimide. *Angew. Chem., Int. Ed.* **2016**, *55*, 8571.
- (16) Braddock, D. C.; Hermitage, S. A.; Kwok, L.; Pouwer, R.; Redmond, J. M.; White, A. J. P. The generation and trapping of enantiopure bromonium ions. *Chem. Commun.* **2009**, 1082.
- (17) Soroka, M.; Goldeman, W.; Maysa, P.; Stochaj, M. Comments on a Conversion of Epoxides to Halohydrins with Elemental Halogen Catalyzed by Phenylhydrazine: Tandem Electrophilic Halogenation of Aromatic Compounds and Epoxide Ring Opening to Halohydrins. *Synthesis* **2003**, *15*, 2341.