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Decarboxylative Trichloromethylation of Aromatic Aldehydes and Its Applications in Continuous Flow

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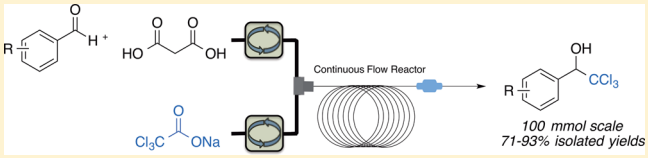
Supporting Information

ABSTRACT: Two new protocols for the efficient synthesis of 2,2,2-trichloromethylcarbinols, starting from aromatic aldehydes, have been developed. A combination of sodium trichloroacetate in the presence of malonic acid proved efficient for the transformation of electron deficient aldehydes using DMSO as solvent. Electron-rich aldehydes did, however, not require the addition of malonic acid, affording the desired 2,2,2-trichloromethylcarbinols without a trace of the competing Cannizzaro reaction. Finally, the reaction of sodium trichloroacetate in THF with a mixture of aldehyde and malonic acid dissolved in DMSO allowed the protocol to be performed in continuous flow. By performing this decarboxylative reaction in continuous flow, scale-up of the reaction could be achieved with a simple and safe setup. In this flow setup, four electron-deficent aldehydes were successfully transformed into their 2,2,2-trichloromethylcarbinol derivatives on a 100 mmol scale.



INTRODUCTION

2,2,2-Trichloromethylcarbinols, formed by the addition of the trichloromethyl anion to aldehydes, serve as important intermediates in organic synthesis (Scheme 1). Probably most commonly known is the Jocic reaction, in which the trichloromethylcarbinol is transformed into α-substituted carboxylic acids.[1] Numerous nucleophiles have been applied in the Jocic reaction, including hydroxide, alcohols, amines, thiols, fluorides, azides, etc.[1,2] Furthermore, 2,2,2-trichloromethyl carbinols (**1**) can be transformed into alkynes,[3] chloromethyl ketones,[4] 2-imino-4-thiazolidinones[5] and other heterocyclic systems,[6] vinyl dichlorides,[7] and α-chloroacetic acids[8] among others (Scheme 1).[9] Finally, silane-protected trichlorocarbinols serve as protecting groups for aldehydes.[10]

Starting from aldehydes, 2,2,2-trichloromethylcarbinols are directly obtained through the addition of chloroform assisted by base.[11] Among the most common bases are hydroxides, but also amidines and even fluoride salts have proven useful.[12] Due to the highly basic and nucleophilic nature of the hydroxide anion, these reactions are often performed at low temperatures to avoid the competing Cannizzaro reaction.[13] Other methods for the formation of trichloromethylcarbinols include Friedel–Craft reactions employing trichloroacetaldehyde (chloral)[1c,14] or trichloromethyl transfer of e.g. CCl_3-TMS in the presence of an activator followed by deprotection.[15] Finally, Corey et al. reported a decarboxylative protocol in which the 1:1 combination of trichloroacetic acid (TCA) and sodium trichloroacetate (NaTCA) in DMF afforded trichlorocarbinols in high yields.[16] Importantly, the last protocol takes advantage of two low-cost reagents and the reaction occurs readily at room temperature.

During work on the decarboxylative formation of trihalomethyl nuclophiles, we became interested in the protocol reported by Corey et al. A simple search in the literature reveals that the method has been applied at numerous occasions. The method performs with both good functional group tolerance and high yields, in particular for the electron-deficient aromatic aldehydes.[17,18] A closer look at the protocol reveals that, in order to obtain full conversion of the starting aldehyde, one or more extra additions of TCA and NaTCA are often required. This in turn results in the evolution of large amounts of CO_2 and heat during the reaction, something that often causes experimental difficulties especially in large-scale preparations. It was therefore decided to investigate this seemingly synergistic effect of the TCA/NaTCA combination in more detail, potentially substituting one of the reagents, in order to establish a more predictable protocol. Furthermore, we envisioned that slightly changed reaction conditions could provide a process that would be adaptable in a continuous flow setup. Allowing a constant portion of the reaction mixture to combine in the flow reactor at any given time, with efficient heat exchange, would provide the operator with full control of the progressing reaction.

In this paper, we wish to report two modified protocols toward the decarboxylative trichloromethylation of aldehydes. Important to our findings was the elimination of TCA in reactions applying electron-rich aromatic aldehydes, with the indication that NaTCA was the main trichloromethylating reagent. Substitution of TCA for malonic acid provided a mild protocol for the reaction with electron-deficient aldehydes. High functional group tolerance was established for both developed protocols, and all desired 2,2,2-trichloromethylcarbinols were obtained in good to excellent yields. Furthermore, with the aim of adapting this decarboxylative transformation to continuous flow, the stabilization of any formed sodium salts in

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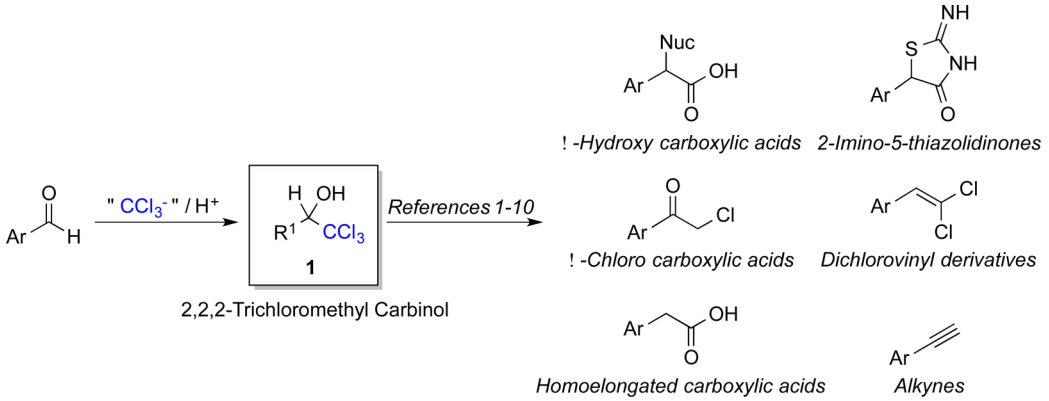
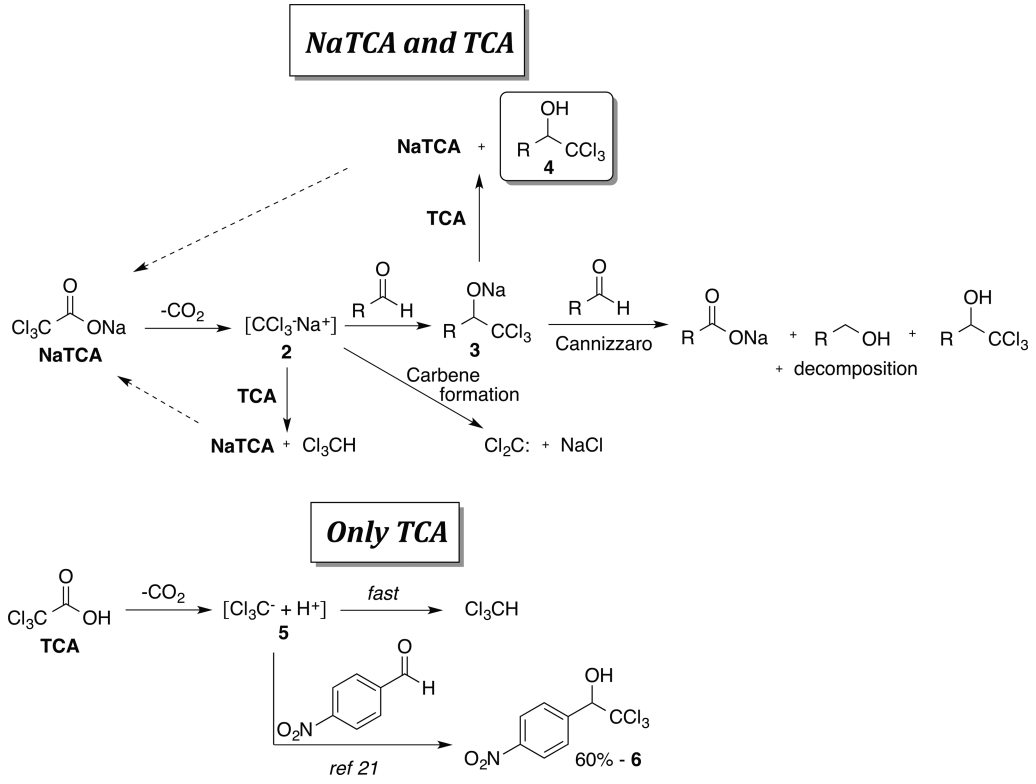
Scheme 1. Formation and Application of 2,2,2-Trichloromethylcarbinols



Scheme 2. Mechanism of 2,2,2-Trichloromethylcarbinol Formation



solution would be imperative. This was secured by applying a small excess of malonic acid to that of NaTCA in DMSO, affording a homogeneous reaction medium throughout the reaction. When the reaction was performed in a continuous plug-flow setup, four aldehydes (100 mmol scale) were converted into the corresponding 2,2,2-trichloromethylcarbinols in a simple and safe laboratory setup. The ability to perform this decarboxylative reaction in a continuous manner allows for the safe preparation of 2,2,2-trichloromethylcarbinols on large scale using a relatively simple setup.

RESULTS AND DISCUSSION

In the paper by Corey et al., they reported that a 1/1 mixture of TCA and NaTCA (1.5 equiv of each), added simultaneously to an aldehyde or ketone in DMF, afforded the desired 2,2,2-trichloromethylcarbinols in good to excellent yields.[16] A closer look at the suggested mechanism suggests that NaTCA dissolved in a polar aprotic solvent such as DMF undergoes decarboxylation affording the CCl_3 carbanion (**2**), a process that occurs at room temperature (Scheme 2).[19] In the presence of TCA, **2** could undergo protonation, affording chloroform and a new 1 equiv of NaTCA. Alternatively, addition of **2** to an aldehyde would afford **3**, which upon protonation by TCA provides the desired 2,2,2-trichloromethylcarbinol (**4**) and NaTCA. In both events, forming either chloroform or **4**, a new 1 equiv of NaTCA is generated which re-enters the reaction (dotted arrows). In the absence of TCA and due to the Brønsted basic nature of **3**, a significant Cannizzaro reaction could occur, especially in the case of electron-deficient aldehydes.[13,20] Hence, by buffering the reaction medium, using TCA, formation of **4** over unwanted byproducts is ensured. In a report by Gold et al. from 1983, it was shown that TCA undergoes rapid decarboxylation in DMSO, and in the presence of 4-nitrobenzaldehyde, the corresponding 2,2,2-

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trichloromethylcarbinol derivative (**5**) was formed.[21] Our own control experiments showed that, without added aldehyde, the DMSO/TCA or DMF/TCA combination lead to the exclusive formation of chloroform in less than 1 h at room temperature (results not shown).[22] The example by Gold et al. indicates that the addition of NaTCA is required if full conversion of 4-nitrobenzaldehyde is to be obtained (Scheme 2, bottom reaction).

By the mechanistic rationale depicted in Scheme 2, the addition of TCA to the reaction medium seems important to guarantee high yields of 2,2,2-trichloromethylcarbinol derivatives. This also hold true for electron-deficient aldehydes, where the absence of TCA leads to complicated reaction mixtures including products from the Cannizzaro reaction and decomposition (results not shown). Substituting TCA for another proton source should ensure the same selectivity toward **3** over formed Cannizzaro byproducts while avoiding the direct formation of chloroform (Scheme 2, bottom reaction). Considering the acidic strength of TCA (pK_a = 0.66 in H_2O), such a substitution should provide a milder protocol toward the synthesis of 2,2,2-trichloromethylcarbinols.[23]

However, in the case of electron-rich aldehydes, with a corresponding slow Cannizzaro reaction, the presence of TCA could potentially become counterproductive. Allowing protonation, by TCA, of **2** to occur instead of its addition to the aldehyde would result in an overall slower reaction rate due to a lower effective concentration of **2**. However, should the addition of **2** to an aldehyde become too slow, resulting in the buildup of **2**, this could result in the formation of a dichlorocarbene, by expelling sodium chloride (Scheme 2).[24]

Even a negative effect of added TCA was detected when performing the reaction of anisaldehyde (**7**) with 1.5 equiv of NaTCA, with and without added TCA (1.5 equiv), the results of which are shown in Scheme 3.

Performing the reaction in DMF at room temperature, adding only 1.5 equiv of NaTCA, led to full conversion of **7** in less than 60 min and upon workup afforded a 92% isolated yield of **8** (Scheme 3a). Importantly, byproducts from the potential Cannizzaro reaction were not observed; however, the reaction mixture became a thick slurry during the reaction, preventing proper stirring. Next, addition of TCA to the reaction mixture, according to the Corey protocol, caused a drop in conversion to 33% of the starting aldehyde after 60 min, as observed by ^{1}H NMR analysis of the crude reaction mixture. Instead, a large peak was detected at 8.32 ppm in the crude ^{1}H NMR spectrum, corresponding to chloroform in DMSO-d_6.[25] Leaving this reaction overnight increased the conversion to 85% and isolation of **8** in 79% yield (Scheme 3b). Treating **7** solely with TCA in DMF provided none of the desired 2,2,2-trichloromethylcarbinol (**8**), and only chloroform was observed, indicating that, in the case of anisaldehyde, carbinol formation occurs solely through NaTCA (Scheme 3c).

Substituting DMF for DMSO as the solvent and performing the reaction without TCA lead to a clean conversion of anisaldehyde (**7**) into **8** in less than 1 h with an isolated yield of 93%. Importantly, no thickening of the reaction medium occurred, ensuring proper stirring throughout the entire transformation (Scheme 3d). Attempts to lower the amount of loaded NaTCA resulted in a slower reaction without full conversion.[26]

The arguments and observations from Schemes 2 and 3 indicate that a proton source is required in order to avoid the competing Cannizzaro reaction, when trichloromethylating electron-deficient aldehydes. However, due to the lack of stability, the application of TCA might not always be the best choice, as it rapidly decomposes into chloroform. Hence, substituting TCA for a more stable alternative, possibly with a higher pK_a in comparison to TCA, should become beneficial. Finally, if this reaction is to be adaptable to continuous flow, a homogeneous reaction medium is required throughout the entire reaction. Should precipitation occur, this typically leads to clogging of the flow tubing, causing reactor shutdown. As mentioned, applying DMSO instead of DMF provided this homogeneous reaction medium (Scheme 3d) and was therefore chosen as the solvent for further optimization.

Next, our attention was turned toward the identification of an acidic buffering alternative to TCA, in the reaction of NaTCA with electron-deficient aldehydes. To this end, 3,4-dichlorobenzaldehyde (**9**) was chosen as the model substrate and the effects of different acids, loadings of NaTCA, and solvent volumes were tested (Table 1). In general, the reactions were stopped after 20 min and the conversion of **9** into **10** was determined by ^{1}H NMR analysis of the crude reaction mixture.

Initial attempts to apply simple carboxylic acids, e.g. acetic acid, pivalic acid, etc. or even longer carbon-chained acids such as dodecanoic acid, all provided the desired reactivity; however, severe precipitation of the formed sodium carboxylates inhibited proper stirring, causing incomplete conversion (results not shown). A lead was provided when citric acid (2 equiv) was tested, affording 86% conversion of **9**, without precipitation (Table 1, entry 1). Given the chelating nature of citric acid in combination with the ability of the monosodium salt of this acid to be stabilized in solution by hydrogen bonding to DMSO could explain the increased solubility.

Decreasing the amount of loaded NaTCA did not seem to affect the conversion (entry 2). Only trace precipitation was observed when applying lactic acid, providing 93% conversion to **10** (entry 3), whereas glycolic acid and maleic acid resulted in severe precipitation (entries 4 and 5). Interestingly, the monoethyl ester of malonic acid afforded a nearly homogeneous reaction, full conversion of **9**, and an isolated yield of 83% of **10** (entry 6). All attempts to increase the isolated yield

Scheme 3. Effect of Added TCA in the Trichloromethylation of Anisaldehyde (7)

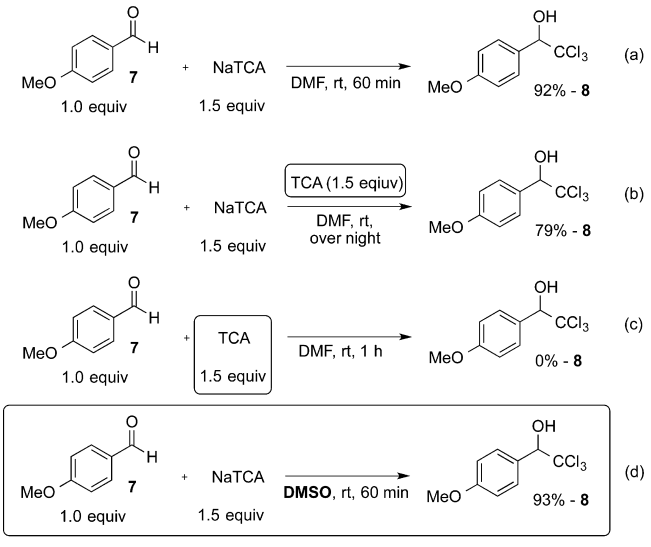

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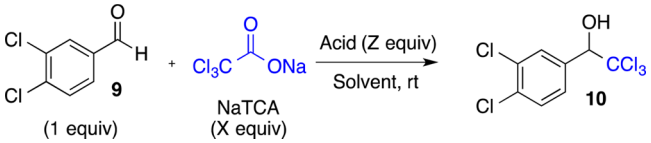
Table 1. Optimization of the Trichloromethylation of 3,4-Dichlorobenzaldehyde[a]



entry	NaTCA (*X* equiv)	acid (*Z* equiv)	DMSO (mL)	conversion (%)[b] [yield (%)][c]
1	1.5	citric acid (2.0)	3	86
2	1.2	citric acid (2.0)	4	88
3	1.2	lactic acid (1.0)	3	93
4	1.2	glycolic acid (1.0)	3	94
5	1.2	maleic acid (1.0)	3	90
6	1.3	ethyl malonate (1.0)	3	100 [83]
7	1.2	malonic acid (1.0)	2	93
8	1.2	malonic acid (0.5)	2	92
9	1.2	malonic acid (0.5)	1	93
10	1.2	malonic acid (1.2)	3	95
11[d]	1.5	malonic acid (1.0)	3	98 [94]
12[d]	1.5	malonic acid (1.0)	2	99
13[d]	1.5	malonic acid (1.0)	1	98

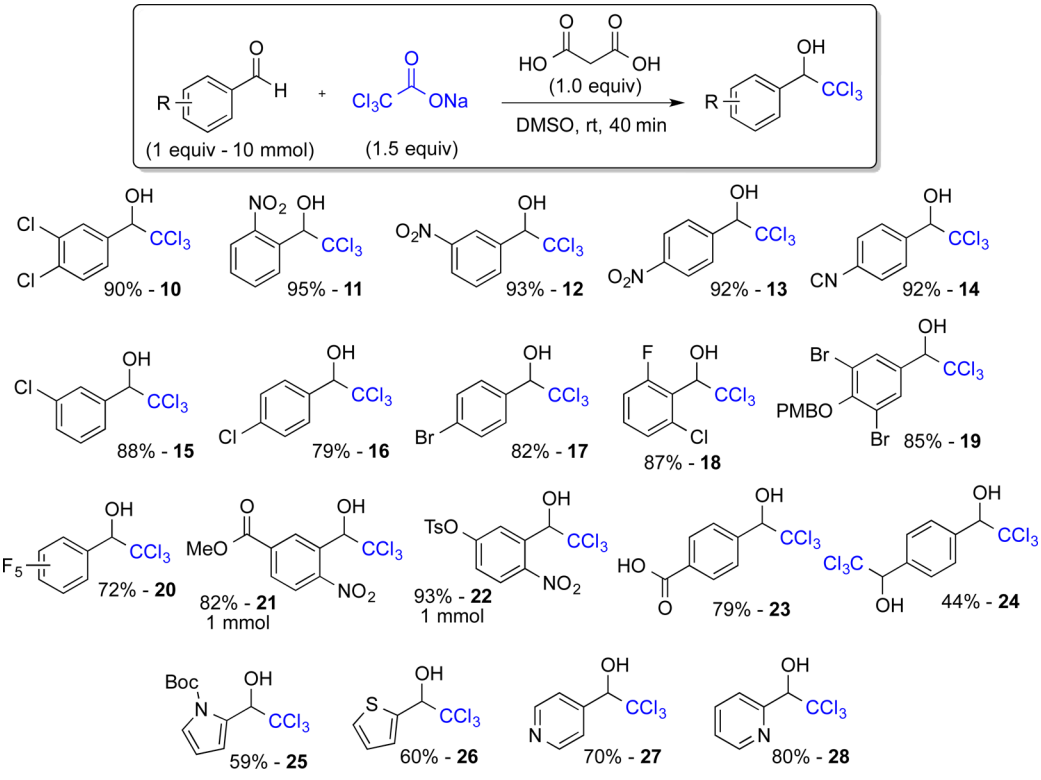
[a]Reaction conditions: **9** (175.0 mg, 1 mmol) and acid (*Z* equiv) were dissolved in DMSO (1−3 mL). Then NaTCA (*X* equiv) was added and the reaction was stirred at room temperature for 20 min. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yields. [d]Reaction time set to 40 min.

of **10** using ethyl malonate as the proton source proved fruitless, and this acid was abandoned. Next, our attention was turned to malonic acid, which provided a completely homogeneous medium for the majority of the reaction time with high conversion (entry 7). Lowering the amount of malonic acid or solvent volume did not affect the conversion; however, precipitation was once again observed (entries 8 and 9). Applying a 1:1 ratio of malonic acid to NaTCA (1.2 equiv) provided a homogeneous reaction with a good 95% conversion (entry 10). Increasing NaTCA to 1.5 equiv in combination with 1.0 equiv of malonic acid and running the reaction for 40 min afforded near-complete conversion with an excellent 94% isolated yield of **10** (entry 11). Finally, the solvent volume could be reduced to 2 and 1 mL without loss of reactivity, both affording near-quantitative conversions (entries 12 and 13).

With the optimized conditions from Table 1, entry 13, in hand, a series of electron-poor aldehydes were trichloromethylated on a 10 mmol scale, starting with the 3,4-dichlorobenzaldehyde from Table 1; the results of this are depicted in Scheme 4.

Increasing the reaction scale to 10 mmol afforded a 90% isolated yield of **10**. Aromatic aldehydes carrying strongly electron withdrawing groups such as nitro, cyano, and a methyl ester all provided high yields of the desired 2,2,2-trichloromethylcarbinols (compounds **11**−**14**, **21**, and **22**). Other halogenated aldehydes with different substitution patterns all proved reactive under the developed conditions, with isolated yields ranging from 79 to 88% (compounds **15**−**19**). Even pentafluorobenzaldehyde was transformed into its 2,2,2-trichloromethylcarbinol (**20**) in 72% isolated yield. Without the addition of malonic acid, 4-formylbenzoic acid was reacted with NaTCA, resulting in a 79% isolated yield of **23**, however, with severe precipitation during the reaction. Ortho substitiuents did not affect the yield of the reaction (compounds **11**, **21**, and **22**). Double trichloromethylation was attempted onto terephthaldehyde; however, only 44% of **24** was secured due to difficulties during workup. Heterocyclic aldehydes also proved reactive under the developed conditions with isolated

Scheme 4. 2,2,2-Trichloromethylcarbinols from Electron-Deficient Aldehydes



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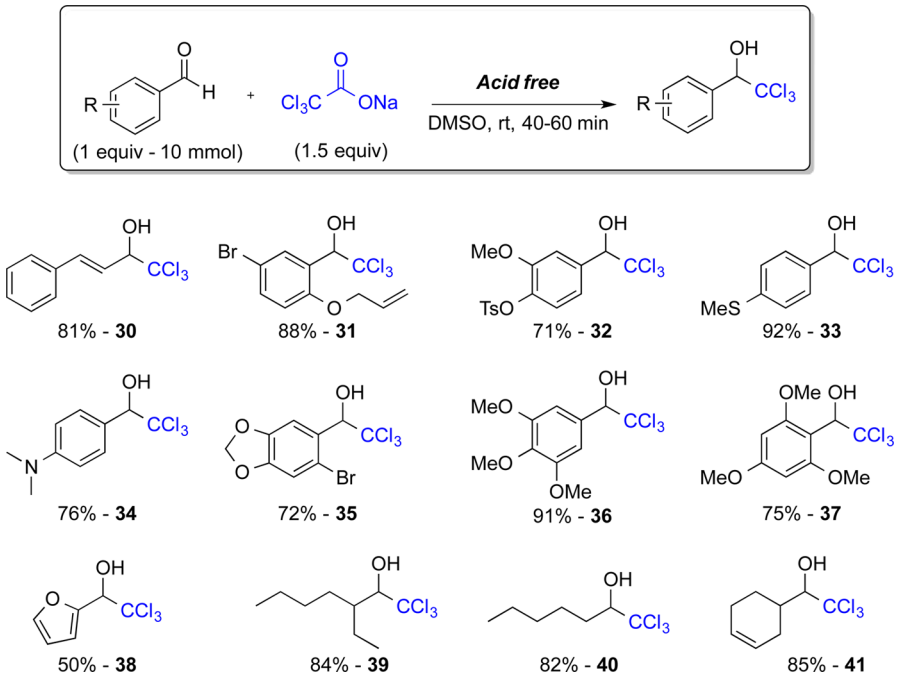
Scheme 5. Trichloromethylations of Electron-Rich Aldehydes



yields ranging from 56 to 80% (compounds **25**–**28**). Finally, it is worth noting that acid-labile protecting groups such as *p*-methoxybenzyl and Boc were tolerated under the developed conditions (compounds **19** and **25**).

Having tested the developed protocol on electron-deficient aldehydes, attention was turned to their electron-rich counterparts. As discussed above, the acid-free approach developed in Scheme 3 was applied, as the competing Cannizzaro reaction is slow for electron-rich aldehydes. Once again, all reactions were performed on a 10 mmol scale in DMSO (10 mL) at room temperature for 40–60 min (Scheme 5).

Starting from cinnamaldehyde, an 81% isolated yield of **30** was obtained. Next, a handful of different phenol-derived aldehydes were tested and all proved highly reactive under these acid-free conditions with yields ranging from 71 to 91% (compounds **31**, **32**, and **35**–**37**). Ortho substituents did have an effect in the case of 2,4,6-trimethoxybenzaldehyde, which required 3 equiv of NaTCA and overnight reaction time to provide an acceptable yield of 75% of **37**. Reaction of 4-methylthiobenzaldehyde afforded an excellent 92% isolated yield of **33**, which is in correspondence with the results obtained from anisaldehyde (Scheme 3d). Even, 4-dimethylaminobenzaldehyde proved reactive, affording **34** in 76% isolated yield, a 2,2,2-trichloromethylcarbinol typically only available through a Friedel–Craft reaction with chloral.[27] Aldehydes carrying free phenols did provide low conversion to the desired 2,2,2-trichloromethylcarbinols, as detected by ^{1}H NMR of the crude reaction mixtures; however, apparent instability during acid workup led to the reisolation of starting material. One heterocyclic aldehyde, furfural, was tested under these acid-free conditions; however, only a 50% isolated yield of the desired product **38** was obtained.

Finally, three aliphatic aldehydes were tested, and all afforded the desired products in yields ranging from 82 to 85% (**39**–**41**). The fact that aliphatic aldehydes are reactive is, however, not too surprising, as they hold α-protons, thereby eliminating the Cannizzaro byproduct formation. Furthermore, if a carboxylate-type intermediate is formed, which is decomposed during workup, then this could explain why the potential aldol-condensation products are also not observed.[28]

Included in our initial setup for this work was the desire to develop a method that could be performed on a large scale under safe circumstances for the operator. A brief look into the literature does provide examples on the Corey protocol being applied in scale-up.[18] In common for these examples was the repeated portionwise addition of a 1:1 mix of TCA and NaTCA reagents to avoid thermal runaway and to control the amount of CO_2 being produced. Since optimization on electron-poor aldehydes indicated that a 1:1 ratio of malonic acid and NaTCA afforded a homogeneous reaction mixture (Table 1, entry 10) and since malonic acid is perfectly stable in DMSO (in comparison to TCA), this indicated that the developed protocol should be applicable toward a continuous-flow setup. When the transformation is performed in a continuous flow, runaway of the reaction is prevented, as the amount of available NaTCA undergoing decarboxylation is kept constant. Furthermore, due to the high surface area to volume ratio, efficient heat transfer is secured, allowing full control of the reaction temperature. It was decided to attempt the reaction in a classic plug-flow reactor setup with an internal pressure of 1000 psi, thereby forcing the formed CO_2 to stay dissolved in the reaction medium (DMSO) until release upon exit of the reactor. This setup ensures a controllable release of CO_2 with minimum expansion of the reaction medium. Trichloromethylation of 3-nitrobenzaldehyde was chosen as the model reaction. As it turned out, NaTCA did not prove sufficiently stable in solution, applying DMSO as the solvent, with visible discoloration and the distinct smell of dimethyl sulfide, by leaving the mixture at room temperature overnight.[29] A small screen of solvents revealed THF to be a suitable alternative, and a 1 M solution of NaTCA proved stable for 24 h at room temperature. The addition of THF to the reaction medium did not affect the reactivity (Scheme 6). Hence, application of a stock solution containing both starting aldehyde (0.5 M) and

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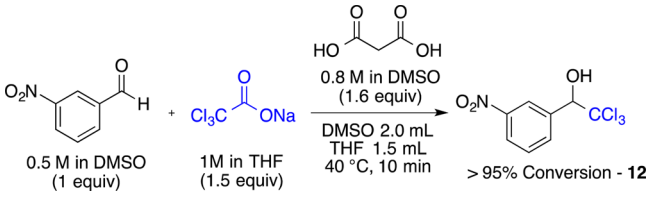
Scheme 6. Test Reaction for Continuous-Flow Setup



malonic acid (0.8 M) in DMSO combined with the NaTCA (1 M) solution in THF afforded an excellent 95% conversion to **12** in batch mode. Notably, increasing the reaction temperature to 40 °C allowed the transformation to complete in just 10 min (Scheme 6).

Next, this batch model system was tested in continuous flow on a 15 mmol scale. The continuous-flow setup, depicted in Scheme 7, consists of a stainless steel reactor (inner diameter 2.0 mm and length 5 m) fitted with a 1000 psi back-pressure regulator (BPR). The crude reaction mixture coming off the flow reactor was collected directly into a round-bottom flask containing water with vigorous stirring. The presence of water quenches the reaction immediately, thereby providing the correct conversion rates obtained in the flow reactor. Three runs were performed testing the reaction settings, the results of which are shown in Table 2. To ensure that the crude reaction mixture coming off the reactor had reached steady state, the flow setup was run for 1.5 times the retention time before collection was initiated. Performing the reaction according to the conditions selected in Scheme 6 provided a good 93% conversion with an isolated yield of 89% (entry 1). Decreasing the retention time led to a small drop in isolated yield (entry 2). Finally, increasing the reactor temperature to 50 °C did not improve the overall conversion (entry 3).

Satisfied with the conditions in Table 2, entry 1, we changed the scale to 100 mmol by running the reactor for 3 h and 43 min. After workup, 24.8 g of the desired trichlorocarbinol **12** was secured, corresponding to an isolated yield of 92% (Scheme 7). Three other aldehydes were then tested under identical conditions. *o*-Nitrobenzaldehyde was cleanly converted into its 2,2,2-trichloromethylcarbinol (**11**) in 93% yield (25.2 g). A yield of 71%, comparable to that of the batch reaction, was obtained starting from 4-pyridinecarboxaldehyde, resulting in 16.0 g of isolated **28**. Finally, compound **18** was secured in 82% isolated yield (22.8 g).[30]

CONCLUSION

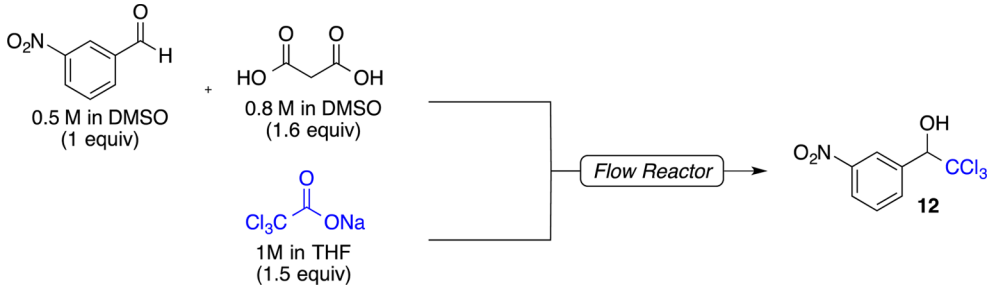
Realizing that addition of TCA to the reaction mixture in the trichloromethylation of aldehyde was not always beneficial, two sets of alternative conditions were developed. Electron-rich aromatic aldehydes and aliphatic aldehydes were transformed rapidly to the 2,2,2-trichlorocarbinols in the precense of NaTCA in DMSO. Electron-deficient aldehydes proved sufficiently protected in the presence of NaTCA using malonic acid as the proton source, with no formation of undesired Cannizzaro byproducts. Both protocols ensure a more effective utilization of the added trichloromethyl donor (NaTCA) by reducing excess chloroform formation in the presence of TCA. All desired 2,2,2-trichloromethylcarbinols were isolated in good to excellent yields with a broad spectrum of tolerable functional groups in only 40−60 min for most cases. Finally, slightly modified conditions proved adaptable to continuous flow, allowing the transformation to be performed on a large scale. By performing the transformation in continuous flow, the possibility of reaction runaway or uncontrollable CO_2 degassing was avoided, both factors that significantly improve operator safety. Increasing the reaction temperature to 40 °C allowed a retention time of only 10 min on the plug-flow reactor. Four aldehydes were successfully converted on a 100 mmol scale in isolated yields ranging from 71 to 93%, a clear indication of the advantages of performing the reaction in a continuous-flow setup.

EXPERIMENTAL SECTION

General Considerations. All purchased chemicals were used as received without further purification. Flash chromatography was carried out on silica gel 60 (230−400 mesh). The chemical shifts are reported in ppm relative to the solvent residual peak.[25] ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 MHz, ^{31}P NMR spectra were recorded at 162 MHz, and ^{19}F NMR spectra were recorded at 376.8 MHz on a 400 MHz spectrometer. MS spectra were recorded on an LC TOF (ES) apparatus.

General Methods. *General Procedure for the Decarboxylative Trichloromethylation of Electron-Poor Aldehydes: Method A.* Sodium trichloroacetate (1.5 equiv), malonic acid (1 equiv), and the aryl aldehyde (1 equiv) were dissolved in DMSO (10 mL) in a round-bottomed flask (50 mL). The reaction mixture was stirred at room temperature for 40−60 min (if not otherwise stated). Then sodium bisulfate (40 w/w %, 30 mL) was added and the reaction mixture was stirred at room temperature for another 30 min. At this point toluene (100 mL) was added and the organic phase was washed with water (3

Table 2. Optimization of Trichloromethylations in Continuous Flow[a]



entry	retention time (min)	temp (°C)	conversion (%)	yield (%)
1	10	40	93	89
2	8	40	85	83
3	10	50	91	88

[a]See the Supporting Information for specific conditions.

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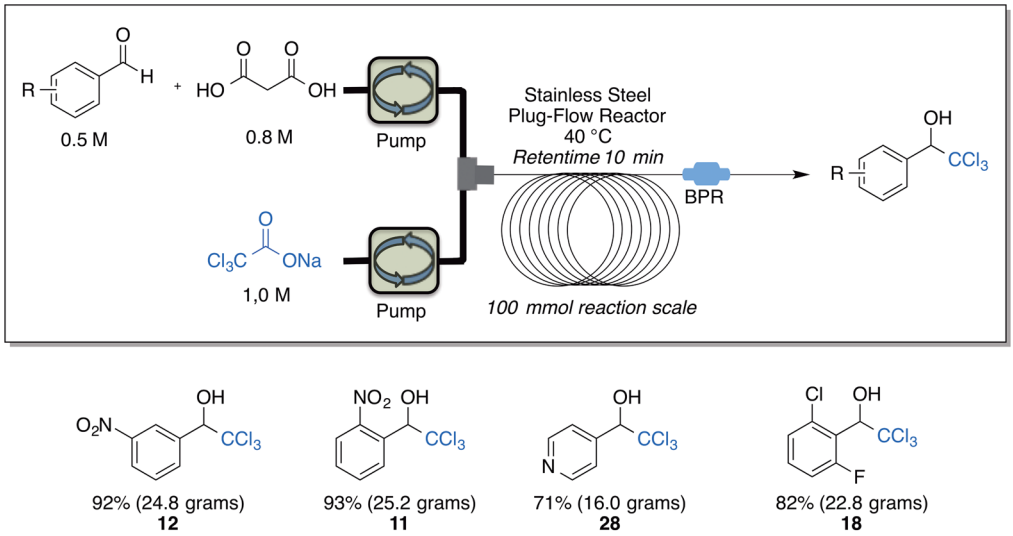
Scheme 7. Trichloromethylations Performed in Continuous Flow



× 20 mL) and brine (25 mL). The organic phase was dried using Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Unless otherwise stated, no further purification was required.

General Procedure for the Decarboxylative Trichloromethylation of Electron-Rich Aldehydes: Method B. Sodium trichloroacetate (1.5 equiv) and the aryl aldehyde were dissolved in DMSO (10 mL) in a round-bottomed flask (50 mL). The reaction mixture was stirred at room temperature for 40−60 min (if not otherwise stated). Then sodium bisulfate (40 w/w %, 30 mL) was added and the reaction mixture was stirred at room temperature for another 30 min. Then toluene (100 mL) was added and the organic phase was washed with water (3 × 20 mL) and brine (25 mL). The organic phase was dried using Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Unless otherwise stated, no further purification was required.

Setup of the Decarboxylative Trichloromethylation of Electron-Poor Aldehydes in Continuous Flow (Scheme 7). Stock solution A: aldehyde (0.5 M) and malonic acid (0.8 M) in DMSO. Stock solution B: trichloroacetic acid (1.0 M) in THF. Stock solutions A and B were connected to separate HPLC pumps. These were set to pump at 0.897 mL/min (stock solution A) and 0.673 mL/min (stock solution B), respectively. These feeds were combined in a T-connector (o.d. $^1/_{16}$ in., i.d. 0.75 mm) attached by a $^1/_{16}$−$^1/_8$ in. adaptor to a plug-flow reactor (stainless steel tubing, o.d. $^1/_8$ in., i.d. 2.0 mm, length 5 m, reactor volume 15.7 mL) placed in an oil bath heated to 40 °C, providing an overall retention time of the reaction of 10.0 min. The flow reactor was allowed to run for 15 min (1.5 times the retention time), before collection was initiated. The crude reaction mixture coming off the reactor was collected into a round-bottom flask loaded with water, quenching the reaction immediately. Collection was continued for 3 h 42 min and 56 s, corresponding to the turnover of 100 mmol of starting aldehyde.

To the crude reaction mixture was added sodium bisulfate (40 w/w %, 50 mL), and the reaction mixture was stirred at room temperature for another 60 min. The crude reaction mixture was extracted with toluene (3 × 150 mL). The combined organic phases were washed with water (3 × 100 mL) and brine (100 mL), dried using Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. No further purification was required.

Derivatized MS Procedure: Phosphorylation of 2,2,2-Trichloromethylcarbinols. Obtaining HRMS data proved difficult for several entries and these were therefore derivatized prior to HRMS analysis as their corresponding phosphorylated products.

In a vial (4 mL) were added the 2,2,2-trichloromethylcarbinol (10 mg), K_2CO_3 (35 mg, 0.25 mmol), diethyl chlorophosphate (36 uL, 0.25 mmol), and acetone (1 mL). The reaction mixture was stirred for 2 h at room temperature. The crude reaction mixture was filtered, and an aliquot was sampled for MS analysis detecting the corresponding diethyl (2,2,2-trichloro-1-arylethyl)phosphate.

Diethyl (2,2,2-Trichloro-1-(2-nitrophenyl)ethyl)phosphate: HRMS Derivatization Test Reaction. In a round-bottomed flask were added 2,2,2-trichloro-1-(2-nitrophenyl)ethanol (2.70 g, 10 mmol), diethyl chlorophosphate (1.73 mL, 12 mmol), K_2CO_3 (4.15 g, 30 mmol), and acetone (10 mL). The reaction mixture was stirred for 2 h at room temperature. Then Et_2O (100 mL) was added and the organic phase was washed using water (3 × 25 mL) and brine (25 mL). The organic phase was dried using Na_2SO_4 and filtered, and the solvents were removed under reduced pressure. The crude product was purified using flash column chromatography with 1/1 pentane/dichloromethane as eluent. This afforded the title compound as a yellow oil (3.89 g, 96%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (dd, 1H, J = 7.9, 1.3 Hz), 8.00(dd, 1H, J = 8.1, 1.2 Hz), 7.71(td, 1H, J = 7.9, 1.3 Hz), 7.61(td, 1H, J = 8.1, 1.2 Hz), 7.06(d, 1H, J = 9.2 Hz), 4.22−4.04(m, 4H), 1.26 (qd, 6H, J = 7.1, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.7, 132.6, 130.7, 130.6, 128.1, 124.7, 98.8, 98.7, 79.3 (d, J = 4.0 Hz), 64.8 (dd, J = 10.2, 5.9 Hz), 15.9 (dd, J = 6.8, 2.9 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ −3.49 (sep, J = 5.0 Hz); HRMS m/z $C_{12}H_{15}Cl_3NO_6P$ [M + H$^+$] calculated 405.9781, found 405.9777.

*2,2,2-Trichloro-1-(4-methoxyphenyl)ethan-1-ol (**8a**).*[2b] DMF (10 mL), trichloroacetic acid (1.5 equiv), and sodium trichloroacetate (1.5 equiv) were added to a mixture of anisaldehyde in a round-bottomed flask (50 mL). The reaction mixture was stirred at room temperature overnight. Otherwise, the procedure was the same as general method B. The compound was isolated as a dark yellow oil (2.03 g, 79%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, 2H, J = 8.7 Hz), 6.92 (d, 2H, J = 8.7 Hz), 5.18 (s, 1H), 3.83 (s, 3H), 3.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.6, 130.6, 127.0, 113.4, 103.7, 84.4, 55.4.

*2,2,2-Trichloro-1-(4-methoxyphenyl)ethan-1-ol (**8b**).*[2b] The reaction was run in DMF instead of DMSO; otherwise the reaction followed general method B. The compound was isolated as a dark yellow oil (2.35 g, 92%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, 2H, J = 8.7 Hz), 6.92 (d, 2H, J = 8.7 Hz), 5.18 (s, 1H), 3.83 (s, 3H), 3.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.6, 130.6, 127.0, 113.4, 103.7, 84.4, 55.4.

*2,2,2-Trichloro-1-(4-methoxyphenyl)ethan-1-ol (**8d**).*[2b] The compound was obtained using general method B and was isolated as a dark yellow oil (2.38 g, 93%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, 2H, J = 8.7 Hz), 6.92 (d, 2H, J = 8.7 Hz), 5.18 (s, 1H), 3.83 (s, 3H), 3.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.6, 130.6, 127.0, 113.4, 103.7, 84.4, 55.4.

*2,2,2-Trichloro-1-(3,4-dichlorophenyl)ethan-1-ol (**10**).*[31] This compound was obtained using general method A and was isolated as a colorless oil (2.64 g, 90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (s, 1H), 7.46 (s, 2H), 5.18 (s, 1H), 3.35 (s, 1H); ^{13}C NMR ($CDCl_3$,

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100 MHz) δ 134.9, 133.9, 132.3, 131.9, 129.9, 128.7, 102.5, 83.4. HRMS was determined using the derivatized MS procedure: HRMS m/z $C_{12}H_{14}Cl_5O_4P$ [M + H$^+$] calculated 428.9151, found 428.9143.

*2,2,2-Trichloro-1-(2-nitrophenyl)ethan-1-ol (**11**).*[32] The compound was obtained using general method A and was isolated as a pale brown solid (2.57 g, 98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (dd, 1H, J = 8.0, 1.1 Hz), 7.89 (dd, 1H, J = 8.1, 1.2 Hz), 7.69 (dt, 1H, J = 8.0, 1.1 Hz), 7.56 (dt, 1H, J = 8.1, 1.2 Hz), 6.45 (d, 1H, J = 4.3 Hz), 3.63 (d, 1H, J = 4.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.1, 132.6, 130.6, 130.3, 129.2, 124.5, 102.1, 77.1. HRMS was determined using the derivatized MS procedure: HRMS m/z calculated for $C_{12}H_{15}Cl_3NO_6P$ [M + H$^+$] 405.9781, found 405.9777.

This compound was also produced in continuous flow, affording **11** (25.2 g, 93%) as a pale brown solid.

*2,2,2-Trichloro-1-(3-nitrophenyl)ethan-1-ol (**12**).*[33] The compound was obtained using general method A and was isolated as a colorless solid (2.52 g, 93%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (s, 1H), 8.26 (dd, 1H, J = 8.0, 1.3 Hz), 7.97 (d, 1H, J = 8,0), 7.58 (t, 1H, J = 8.0 Hz), 5.34 (d, 1H, J = 3.7 Hz), 3.59 (d, 1H, J = 3.7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.9, 136.8, 135.5, 128.9, 124.6, 124.5, 102.3, 83.5.

This compound was also produced in continuous flow, affording **12** (24.8 g, 92%) as a pale yellow solid.

*2,2,2-Trichloro-1-(4-nitrophenyl)ethan-1-ol (**13**).*[2b] The compound was obtained using general method A and was isolated as a yellow solid (2.43 g, 90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, 2H, J = 8.8 Hz), 7.84 (d, 2H, J = 8.8 Hz), 5.34 (d, 1H, J = 3.3 Hz), 3,58 (d, 1H, J = 3.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 141.6, 130.5, 122.9, 102.2, 83.6.

*4-(2,2,2-Trichloro-1-hydroxyethyl)benzonitrile (**14**).* The compound was obtained using general method A and was isolated as a colorless solid (2.29 g, 92%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, 2H, J = 8.4 Hz), 7.69 (d, 2H, J = 8.4 Hz), 5.27 (s, 1H), 3.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.9, 131.6, 130.2, 118.5, 113.3, 102.3, 83.7. HRMS was determined using the derivatized MS procedure: HRMS m/z calculated for $C_{13}H_{15}Cl_3NO_4P$ [M + H$^+$] 385.9883, found 385.9878.

*2,2,2-Trichloro-1-(3-chlorophenyl)ethan-1-ol (**15**).*[34] The compound was obtained using general method A and was isolated as a pale brown oil (2.23 g, 86%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 1H), 7.51 (d, 1H, J = 8.0 Hz), 7.40 (d, 1H, J = 8.0 Hz), 7.32 (t, 1H, J = 8.0 Hz), 5.19 (d, 1H, J = 3.8 Hz), 3.32 (d, 1H, J = 3.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.7, 133.9, 129.8, 129.5, 129.1, 127.7, 102.7, 83.9. HRMS was determined using the derivatized MS procedure: HRMS m/z calculated for $C_{12}H_{15}Cl_4O_4P$ [M + H$^+$] 394.9549, found 394.9537.

*2,2,2-Trichloro-1-(4-chlorophenyl)ethan-1-ol (**16**).*[8] The compound was obtained using general method A and was isolated as a colorless solid (2.05 g, 80%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, 2H, J = 8.5 Hz), 7,38 (d, 2H, J = 8.5 Hz), 5.21 (d, 1H, J = 3.4 Hz), 3.28 (d, J = 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.7, 133.3, 130.7, 128.2, 102.9, 84.0.

*1-(4-Bromophenyl)-2,2,2-Trichloroethan-1-ol (**17**).*[8] The compound was obtained using general method A and was isolated as a colorless solid (2.51 g, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (q, J = 8.7 Hz, 4H), 5.18 (s, 1H), 3.32 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.8, 131.2, 131.0, 124.0, 102.8, 83.1.

*2,2,2-Trichloro-1-(2-chloro-6-fluorophenyl)ethanol (**18**).*[35] The compound was obtained using general method A and was isolated as a colorless solid (2.43g, 87%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.28 (m, 2H), 7.09−7.04 (dd, 1H, J = 8.4, 2.8 Hz), 5.87 (d, 1H, J = 9.6), 4.01 (t, 1H, J = 9.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.1 (d, J = 995.3 Hz), 136.6 (d, J = 24.5 Hz), 131.2 (d, J = 43.4 Hz), 126.2, 121.1 (d, J = 45.6 Hz), 115.9 (d, J = 99.3 Hz), 101.8, 82.5; ^{19}F NMR ($CDCl_3$, 377 MHz) δ 105.64. HRMS was determined using the derivatized MS procedure: HRMS m/z calculated for $C_{12}H_{14}Cl_4FO_4P$ [M + H$^+$] 412.9446, found 412.9442.

This compound was also produced in continuous flow, affording **18** (22.8 g, 82%) as a colorless solid.

*2,2,2-Trichloro-1-(3,5-dibromo-4-((4-methoxybenzyl)oxy)-phenyl)ethan-1-ol (**19**).* The compound was obtained using general method A and was isolated as a colorless solid (4.41 g, 85%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (s, 2H), 7.54 (d, 2H, J = 7.7 Hz), 6.95 (d, 2H, J = 7.7 Hz), 5.12 (s, 1H), 4.99 (s, 2H), 3.83 (s, 3H), 3.44 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 153.7, 133.6, 133.4, 130.5, 128.2, 118.1, 114.1, 102.5, 82.8, 74.79, 55.48 HRMS m/z calculated for $C_{16}H_{13}Br_2Cl_3O_3$ [M + Na$^+$] 538.8189, found 538.8166.

*2,2,2-Trichloro-1-(perfluorophenyl)ethanol (**20**).*[36] The compound was obtained using general method A and was isolated as a colorless solid (2.29 g 72%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.59 (d, 1H, J = 10.0 Hz), 3.72 (d, 1H, J = 10.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, only nonaromatic carbons reported) δ 101.3, 79.36; ^{19}F NMR ($CDCl_3$, 377 MHz) δ −136.0, 150.6 (m), 160.6.

*Methyl 4-Nitro-3-(2,2,2-trichloro-1-hydroxyethyl)benzoate (**21**).* The reaction scale was 1 mmol in 1 mL of DMSO, otherwise following general method A. The compound was isolated as a pale yellow solid (269 mg, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.74 (d, 1H, J = 1.5 Hz), 8.21 (dd, 1H, J = 8.0, 1.5 Hz), 7.94 (d, 1H, J = 8.0 Hz), 6.39 (s, 1H), 3.98 (s, 3H), 3.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 152.5, 133.8, 132.3, 131.5, 129.8, 124.7, 101.87, 77.08, 53.23; HRMS m/z calculated for $C_{10}H_8Cl_3NO_5$ [M + Na$^+$] 349.9360, found 349.9359.

*4-Nitro-3-(2,2,2-trichloro-1-hydroxyethyl)phenyl 4-Methylbenzenesulfonate (**22**).* The reaction scale was 1 mmol in 1 mL of DMSO, otherwise following general method A. The compound was isolated as a thick brown oil (408 mg, 93%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, 1H, J = 9.0 Hz), 7.73 (d, 2H, J = 8.3 Hz), 7.64 (d, 1H, J = 2.6 Hz), 7.34 (d, 2H, J = 8.3 Hz), 7.33 (d, 1H, J = 9.0 Hz), 6.38 (s, 1H), 3.57 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.9, 147.9, 146.4, 131.9 (d, J = 5.6), 130.3, 129.2, 128.7, 128.4, 126.4, 125.4, 124.8, 124.3, 101.5, 76.7, 21.9; HRMS m/z calculated for $C_{15}H_{12}Cl_3NO_6S$ [M + Na$^+$] 461.9343, found 461.9337.

*4-(2,2,2-Trichloro-1-hydroxyethyl)benzoic Acid (**23**).* The reaction was carried out according to general method B. The compound was isolated as a colorless solid (2.13, 79%): ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.06 (d, 2H, J = 8.0 Hz), 7.84 (d, 2H, J = 8.0 Hz), 6.45 (s, 1H), 5.45 (s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 167.3, 142.7, 131.8, 130.5, 129.5, 104.0, 84.2; HRMS m/z calculated for $C_9H_7Cl_3O_3$ [M − H$^+$] 266.9388, found 266.9394.

*1,1′-(1,4-Phenylene)bis(2,2,2-trichloroethan-1-ol) (**24**).* An dditional 5 mL of DMSO was added to the reaction mixture, and the reaction mixture was stirred overnight at room temperature, otherwise following general method A, followed by chromatography with 1/1 pentane/dichloromethane as eluent. The compound was isolated as a colorless solid (1.66 g, 44%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (s, 4H), 5.24 (d, 2H, J = 3.8 Hz), 3.36 (d, 2H, J = 3.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.2, 128.8, 102.9, 84.3, 84.2. HRMS was determined using the derivatized MS procedure: HRMS m/z calculated for $C_{14}H_{17}Cl_6O_5P$ [M + H$^+$] 506.9023, found 506.9020.

*tert-Butyl 2-(2,2,2-Trichloro-1-hydroxyethyl)-1H-pyrrole-1-carboxylate (**25**).* The compound was obtained using general method A and was isolated as a dark red oil (1.93 g, 59%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (m, 1H), 6.64 (m, 1H), 6.19 (t, 1H, J = 3.3 Hz), 5.98 (d, 1H, J = 7.7 Hz), 4.82 (d, 1H, J = 7.7 Hz), 1.61 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 128.8, 123.9, 117.0, 110.3, 102.7, 85.4, 78.5, 27.9; HRMS m/z calculated for $C_{11}H_{14}Cl_3NO_3$ [M + Na$^+$] 335.9931, found 335,9926.

*2,2,2-Trichloro-1-(thiophen-2-yl)ethan-1-ol (**26**).*[2b] The compound was obtained using general method A and was isolated as a colorless solid (1.40 g, 60%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 1H, J = 5.0 Hz), 7.32 (d, 1H, J = 3.3 Hz), 7.05 (t, 1H, J = 5.0 Hz), 5.49 (d, 1H, J = 4.0 Hz), 3.29 (d, 1H, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 100 M Hz) δ 137.4, 129.3, 127.2, 126.5, 102.6, 81.7.

*2,2,2-Trichloro-1-(pyridin-4-yl)ethanol (**27**).*[37] The compound was obtained using general method A and was isolated as a yellow solid (1.59 g, 70%): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.61 (d, 2H, J = 6.0 Hz), 7.62 (d, 2H, J = 6.0 Hz), 7.55 (d, 1H, J = 5.9 Hz), 5.32 (d, 1H, J = 5.9 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 148.9, 145.8, 124.2,

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102.7, 81.5; HRMS m/z calculated for $C_7H_6Cl_3NO$ [M + H]$^+$ 225.9593, found 225.9589.

This compound was also produced in continuous flow, affording **28** (16.0 g, 71%) as a colorless solid.

*2,2,2-Trichloro-1-(pyridin-2-yl)ethan-1-ol (**28**).*[38] The compound was obtained using general method A and was isolated as a pale yellow solid (1.83 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (d, 1H, J = 4.5 Hz), 7.76 (t, 1H, J = 7.8 Hz), 7.67 (d, 1H, J = 7.8 Hz), 7.37 (dd, 1H, J = 7.8, 4.5 Hz), 5.99 (d, 1H, J = 7.6 Hz), 5.22 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 148.1, 136.5, 125.2, 124.6, 102.3, 82.1; HRMS m/z calculated for $C_7H_6Cl_3NO$ [M + H$^+$] 225.9593, found 225.9585.

*(E)-1,1,1-Trichloro-4-phenylbut-3-en-2-ol (**30**).*[12b] The compound was obtained using general method B and was isolated as a pale yellow solid (2.04 g, 81%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, 2H, J = 7.1 Hz), 7.38−7.31 (m, 3H), 6.93 (d, 1H, J = 15.8 Hz), 6.39 (dd, 1H, J = 15.8, 5.8 Hz), 4.77 (t, 1H, J = 5.8 Hz), 2.99 (d, 1H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.9, 135.7, 128.9, 128.8, 127.1, 122.7, 102.9, 83.5.

*1-(2-(Allyloxy)-5-bromophenyl)-2,2,2-trichloroethanol (**31**).* The compound was obtained using general method B and was isolated as a pale yellow oil (3.16 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, 1H, J = 2.1 Hz), 7.45 (dd, 1H, J = 8.8, 2.1 Hz), 6.81 (d, 1H, J = 8.8 Hz), 6.02 (m, 1H), 5.68 (d, 1H, J = 5.9 Hz), 5.44 (d, 1H, J = 17.2 Hz), 5.33 (d, 1H, J = 9.8 Hz), 4.59 (d, 2H, J = 5.0 Hz), 3.78 (d, 1H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.8, 133.2, 132.9, 132.3, 125.7, 118.2, 113.9, 112.9, 102.9, 78.7, 69.6; HRMS m/z calculated for $C_{11}H_{10}BrCl_3O_2$ [M + Na$^+$] 380.8822, found 380.8818.

*2-Methoxy-4-(2,2,2-trichloro-1-hydroxyethyl)phenyl 4-Methylbenzenesulfonate (**32**).* The compound was obtained using general method B and was further purified using flash chromatography, with 1/1 pentane/dichloromethane as eluent and isolated as a colorless solid (71%, 3.02 g): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, 2H, J = 8.1 Hz), 7.33 (d, 2H, J = 8.1 Hz), 7.19- 7.12 (m, 3H), 5.19 (d, 1H), 3.61 (s, 3H), 3.38 (d, 1H, J = 2.3 Hz), 2.46 (s, 3H); HRMS m/z calculated for $C_{16}H_{15}Cl_3O_5S$ [M + Na$^+$] 446.9598, found 446.9614.

*2,2,2-Trichloro-1-(4-(methylthio)phenyl)ethanol (**33**).* The compound was obtained using general method B and was isolated as a yellow solid (2.48 g, 92%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, 2H, J = 8.3 Hz), 7.25 (d, 2H, J = 8.3 Hz), 5.18 (s, 1H), 3.27 (s, 1H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.6, 131.4, 129.7, 125.5, 103.3, 84.3, 15.5. HRMS was determined using the derivatized MS procedure: HRMS m/z calculated for $C_{13}H_{18}Cl_3O_4PS$ [M + H$^+$] 406.9807, found 406.9809.

*2,2,2-Trichloro-1-(4-(dimethylamino)phenyl)ethanol (**34**).*[39] The compound was obtained using general method B and was isolated as a colorless solid (2.05 g, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, 2H, J = 8.8 Hz), 6.62 (d, 2H, J = 8.8 Hz), 5.13(d, 1H, J = 3.6 Hz), 3.20 (d, 1H, J = 3.6 Hz), 2.98 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.2, 130.0, 122.3, 111.4, 104.1, 88.7, 40.4; ESI HRMS m/z calculated for $C_{10}H_{12}Cl_3NO$ [M + H$^+$] 268.0063, found 268.0061.

*1-(6-Bromobenzo[d][1,3]dioxol-5-yl)-2,2,2-trichloroethan-1-ol (**35**).* The compound was obtained using general method B and was isolated as a yellow oil (2.51 g, 72%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 1H), 7.48 (s, 2H), 6.24 (d, 2H, J = 3.3 Hz), 5.98 (s, 1H), 3.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.4, 147.4, 128.0, 116.9, 112.7, 109.6, 103.3, 103.1, 82.1. HRMS was determined using the derivatized MS procedure: HRMS m/z calculated for $C_{13}H_{15}BrCl_3O_6P$ [M + H$^+$] 482.8933, found 482.8930.

*2,2,2-Trichloro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (**36**).* The compound was obtained using general method B and was isolated as a yellow solid (2.87 g, 91%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.82 (s, 2H), 5.14 (d, 1H, J = 3.2 Hz), 3.86 (s, 6H), 3.85 (s, 3H), 3.51 (d, 1H, J = 3.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.7, 138.9, 130.5, 106.8, 103.2, 84.6, 61.1, 56.4; HRMS m/z calculated for $C_{11}H_{13}Cl_3O_4$ [M + Na$^+$] 336.9772, found 336.9758.

*2,2,2-Trichloro-1-(2,4,6-trimethoxyphenyl)ethan-1-ol (**37**).* The reaction was run with 3 equiv of sodium trichloroacetate, in 15 mL of DMSO; otherwise the reaction followed the general method B. The compound was isolated as a purple solid (2.34 g, 75%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.16 (s, 2H), 5.68 (s, 1H), 5.62 (s, 1H), 3.86 (s, 3H), 3.82 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1, 160.0, 159.9, 104.6, 104.3, 91.5, 91.4, 80.3, 55.9, 55.5; HRMS m/z calculated for $C_{11}H_{13}Cl_3O_4$ [M + Na$^+$] 336.9772, found 336.9758.

*2,2,2-Trichloro-1-(3-methylfuran-2-yl)ethan-1-ol (**38**).*[2b] The compound was obtained using general method B and was isolated as a brown oil (1.08 g, 50%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (s, 1H), 6.61 (d, 1H, J = 3.3 Hz), 6.43 (t, 1H, J = 1.6 Hz), 5.24 (s, 1H), 3.51 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 143.2, 111.0, 110.8, 101.3, 79.4.

*1,1,1-Trichloro-3-ethylheptan-2-ol (**39**).*[40] The compound was obtained using general method B and was further purified using flash chromatography with 7/3 pentane/dichloromethane as eluent. The compound was isolated as a colorless oil in a diastereomeric ratio of 1:1 (2.08 g, 84%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.04 (d, 1H, J = 4.9 Hz), 2.77 (d, 1H, J = 4.9 Hz), 1.97−181 (m, 2H), 1.62−1.45 (m, 2H), 1.40−1.21 (m, 5H), 0.99−0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 104.7, 104.6, 84.3, 83.9, 41.0, 40.8, 32.4, 29.9, 28.8, 27.1, 26.0, 22.9, 22.8, 20.7, 14.1, 14.0, 12.1, 11.0.

*1,1,1-Trichloroheptan-2-ol (**40**).*[16] The compound was obtained using general method B and was further purified using flash chromatography with 7/3 pentane/dichloromethane as eluent. The compound was isolated as a colorless oil (1.80 g, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.01 (d, 1H, J = 6.9 Hz), 2.67 (s, 1H), 2.06−2.00 (m, 1H), 1.66−1.58 (m, 2H), 1.48−1.45 (m, 1H), 1.39−1.34 (m, 4H), 0.93−0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 104.4, 83.0, 31.48, 31.47, 25.8, 22.5, 13.9.

*2,2,2-Trichloro-1-(cyclohex-3-en-1-yl)ethanol (**41**).*[41] The compound was obtained using general method B and was isolated as a colorless oil in a diastereomeric ratio of 1:1 (1.95 g, 85%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.68 (s, 2H), 4.04 (dd, 1H, J = 5.9, 2.8 Hz), 2.77(dd, 1H, J = 5.9, 2.8 Hz), 2.46−2.31 (m, 1H), 2.28−2.12 (m, 4H), 1.82−1.67 (m, 1H), 1.57−1.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.4, 126.5, 126.1, 125.8, 104.2, 103.8, 86.3, 85.6, 36.3, 35.7, 31.6, 28.5, 25.23, 25.2, 25.1, 23.2.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H NMR, ^{19}F NMR, ^{31}P NMR, and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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