CHEMISTRY
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To be cited as: *Chem. Eur. J.* 10.1002/chem.201704972

Link to VoR: http://dx.doi.org/10.1002/chem.201704972

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Organocatalyzed Decarboxylative Trichloromethylation of Morita-Baylis-Hillman Adducts in Batch and Continuous Flow

Martin V. Enevoldsen,[a] Jacob Overgaard,[b] Maja S. Pedersen,[a] Anders T. Lindhardt*[a]

Abstract: Two protocols for the organocatalyzed decarboxylative trichloromethylation of Morita-Baylis-Hillman (MBH) substrates have been developed. Applying simple sodium trichloroacetate, as the trichloromethyl anion precursor, in combination with an organocatalyst, and acetylated MBH-alcohols the desired trichloromethylated products were obtained in good yields at room temperature in batch. The method was next extrapolated into a two-step continuous flow protocol, starting directly from the MBH alcohols, in combination with tributylamine acting both as base and catalyst. The flow process proved superior to the batch approach, reducing the reaction time from 16 hours to *only 20 minutes*, with increased yields for all investigated entries. Two examples were also taken to scale-up in flow producing more than 10 grams of both trichloromethylated targets. Finally, substitution of the organocatalyst to $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ induced chiral transfer to the generated stereocenter in the reaction attaining selectivities with nearly 90% ee.

Introduction

To date, thousands of naturally occurring and biologically active compounds, carrying a halogen in its structure, have been identified.[1] Among these structures, substitution with chlorine is observed with the highest frequency, and especially the fully chlorinated trichloromethyl-group (CCl_3) holds a particularly interest. Besides being observed in natural occurring pool of compounds, the CCl_3 group is also found within the human made repertoire of pharmaceuticals and agrochemicals.[2] Furthermore, the CCl_3-functionality serves as a versatile synthetic platform in chemical synthesis, being a known precursor to carboxylic acids, heterocycles, etc.[3] Consequently, the development of chemical methods towards trichloromethyl derivatized and highly functionalized compounds is of continued interest. This argument is further strengthened if the installation of the CCl_3 group occurs in an enantioselective fashion.

In 2016, the group of Shibata reported on the impressive enantioselective trichloromethylation of Morita-Baylis-Hillman (MBH) fluorides (Figure 1).[4] In this work, installment of the trichloromethyl-group occurred through deprotonation of chloroform. Rupperts reagent generated, *in situ,* trifluoromethyl anions that would act as the base towards deprotonation of chloroform. Combined with the organocatalyst, $(DHQD)_2PHAL$, transfer of chiral information during the carbon-carbon bond forming step was secured, leading to the development of an enantioselective trichloromethylation protocol.[5] Although impressive, the approach developed by Shibata utilizes MBH-fluorides in combination with stoichiometric amounts of the Ruppert-Prakash reagent as base, ultimately leading to a protocol somewhat wasteful in fluoride. Additionally, long reaction times (up to 120 hours) under subzero conditions were required. Inspired by the work of Shibata and following our own studies into decarboxylative trihalomethylations, we decided to investigate if an alternative pathway could be devised.

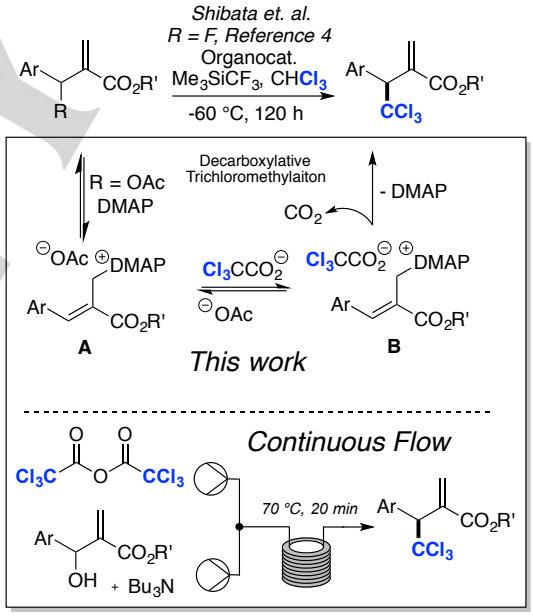

Figure 1. Trichloromethylation of Morita-Baylis-Hillman Derivatives in Batch and Continuous Flow.

The idea was to apply simple acetylation as means of activating the Morita-Baylis-Hillman starting materials (Figure 1). Upon reaction with an organocatalyst, such as DMAP, the known intermediate **A** would be in equilibrium with the starting material. [5a,c],[6] Towards introduction of the nucleophile, it was decided to upgrade trichloroacetate precursors to their corresponding trichloromethyl anions through decarboxylation.[7] This was done in order to avoid the use of stoichiometric amounts of strong base to deprotonate chloroform.[8] Alternatively, one could have considered the application of the chlorinated version of the Ruppert-Prakash reagent, namely

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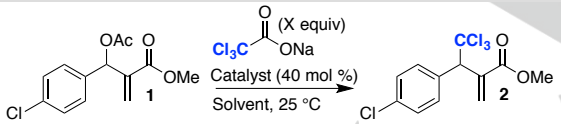
TMS-CCl_3. However, this reagent only has limited commercial availability and along with reports on poor stability it was deemed unsuitable.[9] Hence, exchange of the acetate counter ion with trichloroacetate would lead to intermediate **B**. Substitution of the cation on trichloroacetate from sodium to complex **B** provides a more solvated trihaloacetate ion, a setup previously shown to enhance decarboxylation.[10] Extrusion of carbon dioxide (CO_2) generates the nuchleophilic trichloromethyl anion that upon addition to **B**, forms the product and regenerates the organocatalyst. If successful, this approach would provide straightforward access to trichloromethyl functionalized MBH-derivatives, applying simple trichloroacetate as synthons for trichloromethyl anoins.

In this manuscript we wish to report on the development of the organocatalyzed decarboxylative trichloromethylation of Morita-Baylis-Hillman acetates. The protocol operates under mild conditions and with good functional group tolerance. The method was extended into a two step telescoped continuous flow protocol allowing the direct application of MBH alcohols by an *in situ* activation sequence. When operating in continuous flow, an increase in isolated yields of all trichloromethylated products were observed, and two examples were taken to scale-up isolating more than 10 grams of each product. Finally, substitution of the organocatalyst to $(DHQD)_2PHAL$ provided access to enantioselective trichloromethylation attaining ee´s of 87% at the installed stereo center.

Results and Discussion

In order to test the hypothesis in Figure 1, acetylated MBH-derivative **1** was mixed with two equivalents of sodium trichloroacetate (NaTCA) and DMAP (40 mol %) in NMP (2 mL) as the solvent.

Table 1. Decarboxylative Trichloromethylation Optimization Studies[a]



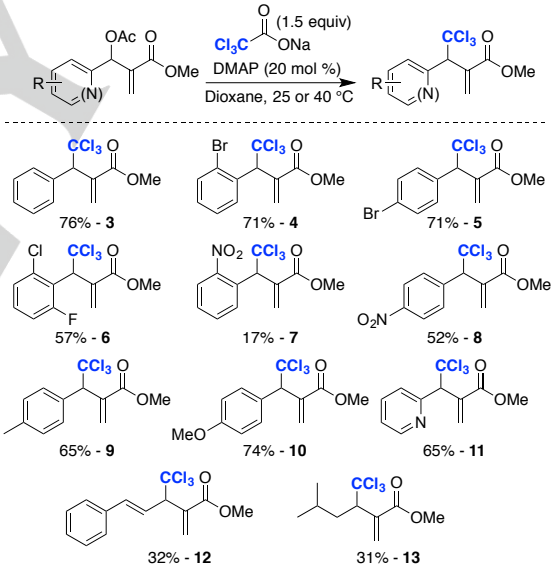
Entry	Catalyst	Solvent	NaTCA (equiv)	Conversion (Yield)[b]/%
1	DMAP	DMF	2	53
2	DMAP	MeCN	2	52
3	DMAP	Dioxane	2	88 (78)
4	DMAP	THF	2	83
5	DBU	Dioxane	2	11
6	DABCO	Dioxane	2	60
7	Pyridine	Dioxane	2	0
8	TEA	Dioxane	2	0
9	DMAP	Dioxane	1.5	78 (78)
10[c]	DMAP	Dioxane	1.5	80 (79)
11[d]	DMAP	Dioxane	1.5	42

[a] General reaction conditions. **1** (0.5 mmol), catalyst (40 mol %), NaTCA (2 equiv), solvent (2 mL), 25 °C, 20 hours. [b] Conversion was determined by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as internal standard. Yields in brackets are isolated yields after column chromatography. [c] DMAP (20 mol %). [d] DMAP (10 mol %), 40% of **1** remained.

Performing the reaction at 50 °C afforded a complex reaction mixture with no detection of the desired trichloromethylated product (**2**). Decreasing the temperature to 25 °C still provided a complex product mixture, but with roughly 15% conversion into **2**. With this lead in hand the reaction conditions were optimized, the results of which is shown in Table 1.

The low degree of product selectivity, when using NMP as the solvent, was attributed to the high polarity of this solvent. Decarboxylation of NaTCA occurs more readily in solvents of increasing polarity with potentially uncontrolled formation of its basic trichloromethyl anion, dichlorocarbenes and byproducts thereof.[11] Lower polarity solvents such as DMF, acetonitrile, dioxane and THF provided a significant increase in the formation of **2** attaining 88% (78% isolated) for dioxane (entries 1-4).[12]

Next, the nature of the organocatalyst was investigated. The standard organocatalysts DBU, DABCO and pyridine all proved inferior with 11%, 60% and 0% conversion, respectively (entries 5-7). Triethylamine was also tested and failed to afford any conversion into product, presumable due to low nucleophilicity of this amine base (entry 8). The loading of NaTCA could be reduced to 1.5 equivalents without loss in isolated yield (entry 9). Finally, the amount of required DMAP was tested. Applying 20 mol % of DMAP proved possible without deterioration of yield, whereas 10 mol % of DMAP only provided 42% conversion to **2** (entries 10 and 11). With optimal reaction conditions in hand the scope of the decarboxylative trichloromethylation was studied and the results are shown in Scheme 1.

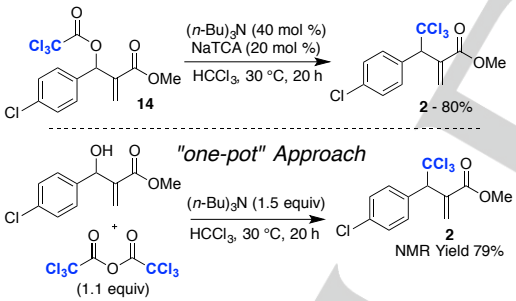


Scheme 1. Decarboxylative Trichloromethylation of MBH-Acetates. Reaction conditions: MBH-Acetate (4 mmol), NaTCA (6 mmol), DMAP (0.8 mmol) in dioxane (10 mL) stirred at 25 or 40 °C for 20 hours, see Supporting Information for each entry.

The non-substituted MBH-acetate resulted in isolation of **3** in 76% yield. Next, different substitution patterns on the aromatic moiety were investigated. Bromide substitution in 2- or 4-position reacted similar to **1** providing **4** and **5**, both in 71% isolated yield. The MBH-acetate derivative carrying 2-fluoro-6-chloro substitution afforded **6** in a 57% isolated yield. Decomposition occurred with nitro-group substitution leading to a low 17% and 52% isolated yields of **7** and **8**, respectively. Turning to electron donating substituents restored the reactivity with **9** and **10** being isolated in 65% and 74% isolated yields. One pyridine derived

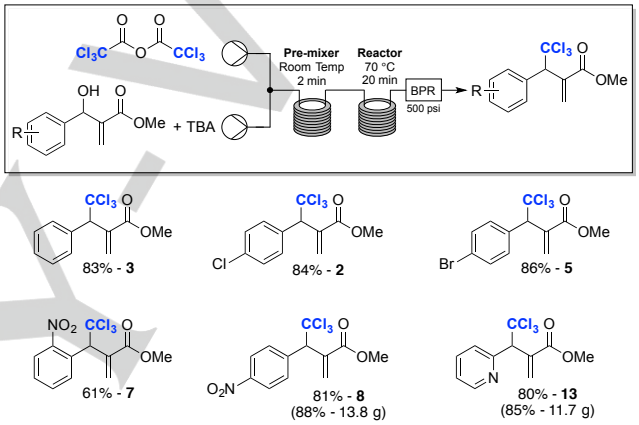
MBH-substrate was also tested and **11** was obtained in a reasonable 65% isolated yield. Replacement of the aromatic moiety with the vinylic MBH-acetate, derived from cinnamyl aldehyde, caused a drop in yield to 32% of **12**. Finally, an aliphatic MBH-acetate was tested, but due to severe decomposition of either the starting material or the product only a mere 31% yield was secured upon column chromatography.

Although most of the compounds **3** – **13** were obtained in reasonable yields, all reactions suffered from decomposition events leading to dark brown slurries upon completion. It was suspected that decomposition pathways could be the result of slow and nonselective formation of intermediates **A** and **B** (Figure 1).[5a],[13] Furthermore, if the intermediate **B** salt precipitated from solution, the result would be an additional slowing factor towards product formation. A possible solution to this scenario would be the direct formation of **B** from the more reactive MBH-trichloroacetates. However, subjecting **14**, seen in scheme 2, to the developed conditions only provided a low 18% NMR-yield of **2** (See supporting information). Instead another round of optimization was undertaken to develop suitable reaction conditions for the decarboxylative trichloromethylation of **14** to form **2**, the result of which is shown in Scheme 2 (see supporting information for full optimization). A few things are worth mentioning in relation to the optimization of the reaction conditions seen in Scheme 2. Tributylamine proved to be the superior organocatalyst, which could be explained by better solubility of the formed intermediate with this base. Also, addition of 20 mol % of NaTCA increased the NMR-yield of **2** from 71% to 87% (80% isolated yield, see Supporting Information). Higher loadings of NaTCA did not have any further impact on the yield of the reaction.[14]



Scheme 2. Redefined Conditions for the Decarboxylative Trichloromethylation of MBH-Adducts.

At this stage it was realized that the developed protocol could be converted into a telescoped continuous flow sequence, starting directly from the MBH-alcohols. As seen in Scheme 2, the one-pot approach applying tributylamine, both as base in the initial trichloroacetylation step, but also as the catalyst in the subsequent decarboxylative step afforded **2** in a comparable 79% NMR yield. Trichloroacetic anhydride was chosen as the acetylating reagent, affording tributylammonium trichloroacetate *in situ*, allowing this soluble salt to compensate for otherwise required but poorly soluble NaTCA additive. An enhanced control over reaction parameters, such as temperature, reaction time and pressure is obtained when performing a reaction in continuous flow.[15] Decarboxylative reactions often hold the potential to create run-away scenarios, especially when performed on large scale. However, under continuous flow conditions only a small fraction of the entire reaction mixture is present in the reactor eliminating this potentially dangerous situation.[16],[7b],[10],[17] Two stock solutions were prepared, the first containing the Morita-Baylis-Hillman alcohol (0.2 M) mixed with tributylamine (0.3 M, 1.5 equiv) in chloroform. Stock solution number two would only be the trichloroacetic anhydride (0.24 M, 1.2 equiv) also in chloroform. The two stock solutions were pumped through 1/16" stainless steel tubing at equal flow-rates (0.150 mL/min) through a T-connector and onto a small tubular reactor (0.6 mL) for premixing before entering the second heated tubular reactor (5.98 mL). The flow setup was pressurized using a spring-loaded 500 PSI back-pressure regulator (BPR) to avoid segmented flow by forcing all carbon dioxide, expelled in the decarboxylative step, into solution. A schematic diagram of the flow setup is shown in Scheme 3 (The construction of the flow reactors and the flow system is described in the Supporting Information).



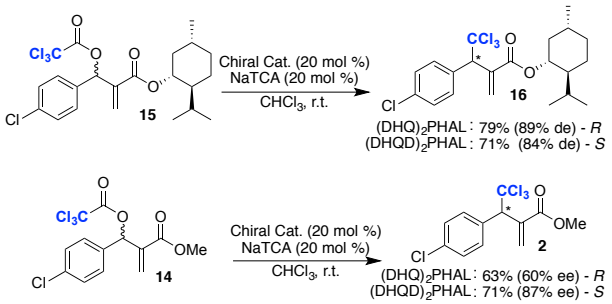
Scheme 3. Telescoped Decarboxylative Trichloromethylation of MBH-Alchohols in Continuous Flow. See Supporting Information for reaction details.

Increasing the reaction temperature to 70 °C allowed the reaction time to be reduced from 20 hours in batch to only 20 minutes on the reactor (22 minutes total retention time including premixing). Collection of reaction mixture was initiated after running the setup for 1.5 times the total retention time thereby ensuring operation under steady state conditions. The results of this study are shown in Scheme 3. Gratifyingly, this two-step continuous flow decarboxylative trichloromethylation outperformed the in Scheme 1 developed batch protocol. Compound **3**, being the simplest and without further functionalization, was isolated in an improved yield of 83%. Model substrate **2** was obtained in a comparative 84% isolated yield whereas **5** was secured in a good 86% yield. Next, substitution with nitro-groups was revisited as these substrates proved problematic in batch mode. Decomposition was diminished in continuous flow leading to the isolation of **7** and **8** in greatly improved 61% and 81% isolated yields, respectively. Compound **13** was also isolated in an enhanced 80% yield.

As the last part of the continuous flow approach, compounds **8** and **13** were selected for scale-up. Towards this purpose the volume of the tubular reactor was increased three-fold to 18.5 mL, keeping the same premixing unit, and the flow-rates were adjusted to maintain a 20 minute reactor retention time (0.463 mL/min). Collection of material under steady state conditions for

501 minutes afforded and excellent 13.8 grams (88% yield) of **8** after silica plug filtration. Repeating this setup for **13** resulted in a similar 11.7 grams (85% yield) isolated material (Scheme 3, results in brackets).

Finally, we turned our focus towards the enantioselective installment of the trichloromethyl group onto the Morita-Baylis-Hillman substrates. In the manuscript published by the group of Shibata they found that the chiral pool derived catalysts $(DHQ)_2PHAL$ and its pseudo-enantiomer $(DHQD)_2PHAL$ performed with the highest selectivity.[4] As test substrate the *L*-menthyl-ester **15** was prepared, allowing direct determination of diastereomeric excess of the formed products by ^{1}H-NMR analysis (Scheme 4).



Scheme 4. Enatioselective Decarboxylative Trichloromethylation of Trichloroacetylated-MBH Derivatives. See Supporting Information for reaction details.

Subjecting **15** to the in Scheme 2 developed conditions, using $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ as the organocatalysts, afforded **16** in 78% and 71% isolated yield, respectively.[18] Recrystallization of the product obtained from the $(DHQ)_2PHAL$ allowed determination of the *R*-configuration at the installed stereocenter by X-ray crystallography, which is in accordance with the findings made by the group of Shibata (see Supporting Information).[4] Stereo-inversion was obtained in *S*-**16** using $(DHQD)_2PHAL$ with a good 84% de. Next, the same series of experiments were repeated for methyl ester derivative **14**. This afforded **2** in isolated yields of 63% and 71% for the two catalysts. Application of $(DHQ)_2PHAL$ only revealed a 60% ee of the *R*-enantiomer upon UPC analysis.[19] However, selectivity was restored when the reaction was performed using $(DHQD)_2PHAL$ as the chiral catalyst with a high 87% ee favoring the *S*-configuration as determined by UPCC.

Conclusions

In conclusion, a simple protocol for the organocatalyzed decarboxylative trichloromethylation of Morita-Baylis-Hillman derivatives has been developed. The reaction was, initially, studied in batch applying sodium trichloroacetate as the trichloromehyl anion equivalent leading to moderate yields of the tested substrates. To ensure efficient formation of a key intermediate, the reaction was further developed into a two-step continuous flow protocol starting directly from the Morita-Baylis-Hillman alcohols. Trichloroacetylation of the alcohol functionality and subsequent telescoped decarboxylative trichloromethylation was achieved using simple tributylamine both as base and organocatalyst. Improved yield were obtained for all entries tested under continuous flow. Finally, the enantioselective trichloromethylation was investigated under the novel conditions leading to ee´s as high as 87% favoring a *S*-configuration.

Experimental Section

A detailed description of all general methods, the continuous flow setup, experimental details including ^{1}H-NMR, ^{19}F-NMR and ^{13}C-NMR for all reported compounds.

The following files are available free of charge. Experimental details and spectroscopic data (PDF) X-ray structure of *R* - **16** (CIF)

Acknowledgements

The authors are deeply appreciative of generous financial support from the Danish Counsel of Independent Research – Technology and Production (Grant No. 4148-00031), Danish National Research Foundation (Grants No. DNRF118 and DNRF-93), and Aarhus University.

Keywords: Trichloromethylation • decarboxylation • Continuous flow • organocatalysis • Morita-Baylis-Hillman

[1] (a) G. W. Gribble, *Mar. Drugs.* **2015**, *13*, 4044. (b) M. T. Cabrita, C. Vale, A. P. Rauter, *Mar. Drugs,* **2010**, *8*, 2301. (c) G. W. Gribble, *J. Chem. Educ.* **2004**, *10*, 1441. (d) G. W. Gribble, *Acc. Chem. Res.* **1998**, *31*, 141. (e) G. W. Gribble, *Prog. Chem. Org. Nat.* **1996**, *68*, 1.

[2] For selected examples on biologically relevant structures carrying the trichloromethyl group, see: (a) W. Schmidt, T. M. Schulze, G. Brasse, E. Nagrodzka, M. Maczka, J. Zettel, P. G. Jones, J. Grunenberg, M. Hilker, U. Trauer-Kizilelma, U. Braun, S. Schulz, *Angew. Chem. Int. Ed.* **2015**, *54*, 7698. (b) Q. Xioa, K. Young, A. Zakarian, *J. Am. Chem. Soc.* **2015**, *137*, 5907. (c) S. E. Brantley,T. F. Molinski, *Org. Lett.* **1999**, *1*, 2165. (d) G. Helmchen, G. Wegner, *Tetrahedron Lett.* **1985**, *26*, 6047. (e) W. A. Cook, K. H. Cook, W. H. Rueggeberg, *Ind. Eng. Chem.* **1947**, *39*, 868.

[3] (a) A. A. Dudinov, D. V. Kozhinov, M. M. Krayushkin, *Russ. Chem. Bull.* **2001**, *50*, 1259. (b) H. Yu, Y. Xia, J. Wu, *Synth. Commun.* **2006**, *36*, 2421. (c) F. G. Menezes, H. Gallardo, C. Zucco, *Quim. Nova* **2010**, *33*, 2233. (d) T. S. Snowden, *ARKIVOC* **2012**, *2*, 24.

[4] T. Nishimine, H. Taira, E. Tokunaga, M. Shiro, N.Shibata, *Angew. Chem. Int. Ed.* **2016**, *55*, 359.

[5] For a few selected articles on enantioselective transformations starting with achiral MBH-analogues, see: (a) R. Rios, *Catal. Sci. Technol.* **2012**, *2*, 267. b) T. Furukawa, T. Nishimine, E. Tokunaga, K. Hasegawa, M. Shiro, N. Shibata, N. *Org. Lett.* **2011**, *13*, 3972. (c) Y. Wei, M. Shi, *Chem. Rev.* **2013**, *113*, 6659.

[6] (a) S. Nag, S. Bhowmik, H. M. Gauniyal, S. Batra, *Eur. J. Org. Chem.* **2010**, 4705. (b) D. Majee, S. Biswas, S. M. Mobin, S. Samanta, *Org. Biomol. Chem.* **2017**, *15*, 3286. (c) J. Peng, X. Huang, P.-F. Zheng, Y.-C. Chen, *Org. Lett.* **2013**, *15*, 5534. (d) M. Baidya, G. Y. Remennikov, P. Mayer, H. Mayr, *Chem. Eur. J.* **2010**, *16*, 1365.

[7] For a few examples on decarboxylative transformations using trichloroacetates, see: (a) E. P. Ávila, I. F. Souza, A. V. B. Oliveira, V. Kartnaller, J. Cajaiba, R. O. M. A. Souza, C. C. Corrêa, G. W. Amarante, *RSC Adv.* **2016**, *6*, 108530. (b) A. B. Jensen, A. T. Lindhardt, *J. Org. Chem.* **2014**, *79*, 1174. (c) N. R. Ram, V. K. Soni, *J. Org. Chem.* **2015**, *80*, 8922. (d) E. J. Corey, J. O. Link, Y. Shao. *Tetrahedron Lett.* **1992**, *33*, 3435.

[8] (a) V. K. Aggerwal, A. Mereu, *J. Org. Chem.* **2000**, *65*, 7211. (b) J. M. Wyvratt, G. G Hazen, L. M. Weinstock, *J. Org. Chem.* **1987**, *52*, 944. (c) H. Wynberg, *Chem. Rev.* **1960**, *60*, 169.

[9] (a) Y. Li, T. Zheng, W. Wang, W. Xu, Y. Ma, S. Zhang, H. Wang, Z. Sun, *Adv. Synth. Catal.* **2012**, *354*, 308. (b) N. Wu, B. Wahl, S. Woodward, W. Lewis, *Chem. Eur. J.* **2014**, *20*, 7718.

[10] M. Therkelsen, M. T. Rasmussen, A. T. Lindhardt, *Chem. Commun.* **2015**, *51*, 9651.

[11] (a) D. P. Valencia, P. D. Astudillo, A. Galano, F. J. González, *Org. Biomol. Chem.* **2013**, *11*, 318. (b) Z. Pawlak, M. F. Fox, *J. Chem. Soc., Faraday Trans.* **1983**, *79*, 1987. (c) W. M. Wagner, H. Kloosterziel, A. F. Bickel, *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 925. (d) W. M. Wagner, H. Kloosterziel, A. F. Bickel, *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 933. (e) W. M. Wagner, H. Kloosterziel, S. Van der Ven, A. F. Bickel, *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 947.

[12] Background NaTCA decarboxylation in dioxane for 24 hours at 25 °C and 40 °C only showed 7% and 29% conversion, respectively.

[13] For rearrangement of MBH-acetates, see (a) Y. Liu, D. Mao, J. Qian, S. Lou, Z. Xu, Y. Zhang, *Synthesis* **2009**, *7*, 1170. (b) M. Kalyva, A. L. Zografos, E. Kapourani, E. Giambazolias, L. Devel, A. Papakyriakou, V. Dive, Y. G. Lazarou, D. Georgiadis, *Chem. Eur. J.* **2015**, *21*, 3278. (c) R. K. Sankar, R. S. Kumbhare, A. T. Dharmaraja, H. Chakrapani, *Chem. Commun.* **2014**, *50*, 15323.

[14] In the event that a formed trichloromethyl anion decomposes prior to addition, this then forms a dichlorocarbene and a non-product forming intermediate of types to **A** or **B** carrying chloride as the counter ion. Trichloroacetate for chloride substitution reforms complex **B**, which could explain the positive effect of the NaTCA additive.

[15] (a) J. Britton, C. L. Raston, *Chem. Soc. Rev.* **2017**, *46*, 1250. (b) T. Wirth, *Angew. Chem. Int. Ed.* **2017**, *56*, 682. (c) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2015**, *11*, 1194. (d) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892. (e) P. Filipponi, A. Gioiello, I. R. Baxendale, *Org. Process. Res. Dev.* **2016**, *20*, 371. (f) C. J. Mallia, I. R. Baxendale, *Org. Process. Res. Dev.* **2016**, *20*, 327. (g) D. R. Snead, T. F. Jamison, *Angew. Chem. Int. Ed.* **2015**, *54*, 983. (h) I. R. Baxendale, *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519.

[16] For references on safety aspects in continuous flow, see: (a) N. Kockmann, P. Thenée, C. Fleischer-Trebes, G. Laudadio, T. Noël, *React. Chem. Eng.* **2017**, *2*, 258. (b) M. Teci, M. Tilley, M. A. McGuire, M. G. Organ, *Org. Process. Res. Dev.* **2016**, *20*, 1967. (c) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688. (d) F. Mastronardi, B. Gutmann, C. O. Kappe, *Org. Lett.* **2013**, *15*, 5590.

[17] P.P Lange, L. J. Goosen, P. Podmore, T. Underwood, N. Sciammetta, *Chem. Commun.* **2011**, *47*, 3628.

[18] Due to poor solubility of $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ in chloroform a decreased loading of 20 mol % organocatalyst was applied.

[19] A portion of the material obtained from the reaction of **14** in the presence of $(DHQ)_2PHAL$ was converted into **16** by acidic hydrolysis followed by DCC coupling with L-menthol. This allowed determination of the major enantiomer *R* by UPC analysis (See supporting information).

10.1002/chem.201704972

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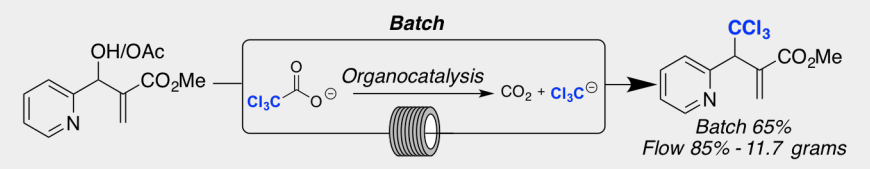

Decarboxylative trichloromethylation of Morita-Baylis-Hillman substrates occurs readily in the presence of an amine-based organocatalyst. Applying simple trichloroacetates, as the trichloromethyl anion precursors, this transformation takes place both in batch and under continuous flow.

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Organocatalyzed Decarboxylative Trichloromethylation of Morita-Baylis-Hillman Adducts in Batch and Continuous Flow