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Diastereoselective Chain-Elongation Reactions Using Microreactors for Applications in Complex Molecule Assembly

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Abstract: Diastereoselective chain-elongation reactions are important transformations for the assembly of complex molecular structures, such as those present in polyketide natural products. Here we report new methods for performing crotylation reactions and homopropargylation reactions by using newly developed low-temperature flow-chemistry technology. In-line purification protocols are described, as well as the application of the crotylation protocol in an automated multi-step sequence.

Keywords: asymmetric synthesis · crotylation · flow chemistry · homopropargylation · microreactors

Introduction

Over the last ten years, our group has made significant advances in the field of machine-assisted synthesis, in particular by using flow-chemistry platforms in combination with polymer-supported reagents.[1] Ultimately, we are aiming to achieve the multi-step synthesis of complex natural products and other significantly functionalised molecules using these methods. We have reported previously on many transformations that benefit from the elevated temperatures and pressures that can be used safely in flow, particularly for the synthesis of aromatic heterocyclic compounds.[2] As flow chemistry and new reactor technology develops, the next step is to adapt stereoselective reactions that require low temperatures and rigorously dry conditions to flow protocols. This would harness the advantage of superior control over temperature, particularly for large-scale applications in which the maintenance of low internal temperatures, that is, below −20 °C, can be a significant issue. Recently, we have reported the use of flow coils immersed in baths containing dry ice to handle organometallics on scale.[3] Herein, we report the development of a series of diastereoselective chain-elongation methods. These reactions have been consistently employed in the synthesis of polyketides. These natural products often display significant biological activity, these compounds are required in significant quantities, rendering stereoselective methods for their preparation an appropriate target for flow-chemistry applications.

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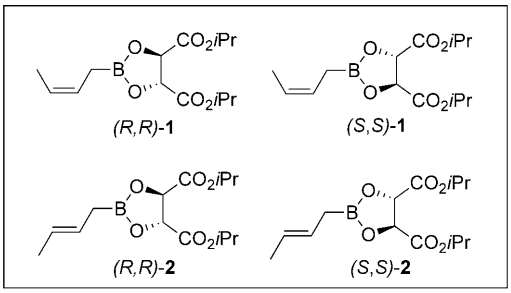
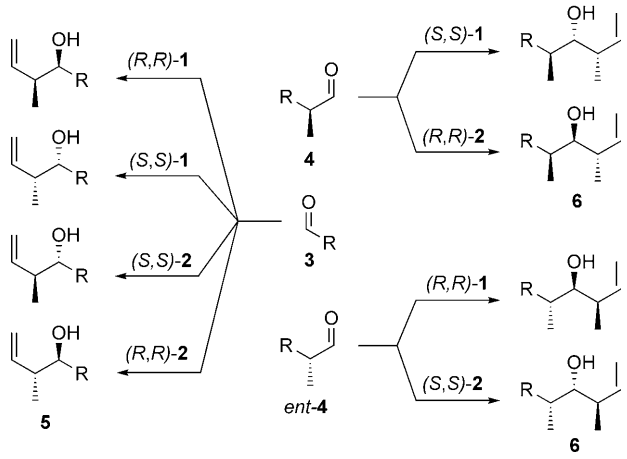
Results and Discussion

Roush crotylation: The Roush crotylation uses a family of enantiopure (*Z*)- or (*E*)-boronates, **1** or **2**, respectively, to give access to *syn* or *anti* propionate relationships (Scheme 1).[4] They are particularly effective in reactions with chiral aldehydes, furnishing complex motifs with high diastereoselectivity through doubly matched asymmetric reactions. Our aim was to convert these reactions into a flow process, whereby the desired diastereoisomer could be formed, the alkene converted to the aldehyde and the chain elongated further with a second crotylation in an iterative sequence.

Technical details: The following reactions were performed on a Vapourtec R2+/R4 flow-chemistry platform.[5] A reliable procedure to establish anhydrous flow conditions was an essential first step in the development of a suitable process. It was found that flushing the pumps, valves and reaction coils with isopropyl alcohol (IPA), followed by acetone and then the dry solvent of choice under an inert atmosphere for at least two hours was needed to eliminate all traces of water from the machine (see general procedure). Currently, there are a number of reactors available to perform low-temperature reactions in flow (Figure 1). A self-made coil can be simply immersed in a dry ice bath. Although this is highly convenient, it can create high backpressures and places a large degree of strain on the tubing and PEEK connectors. Alternatively, a number of low-temperature reactors are becoming available on the market. We made use of the Vapourtec low-temperature coil, which uses a stream of ni-





Scheme 1. Roush crotylation reactions and their stereochemical implications.

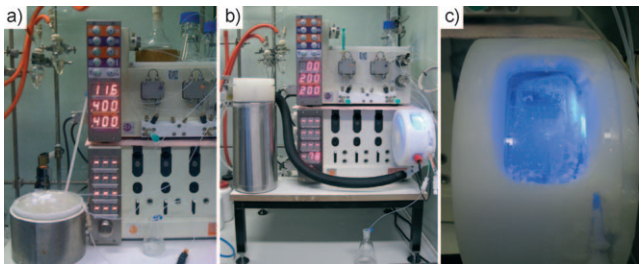
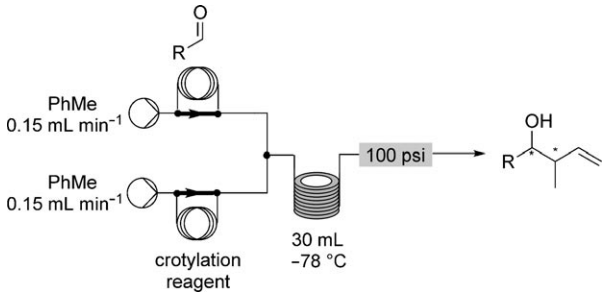


Figure 1. a) PTFE coil and T-piece immersed in a −78 °C bath. b) Vapourtec low-temperature coil. c) Close-up of the low-temperature coil.

trogen flowing over dry ice to establish and maintain low temperatures.

To perform the crotylation reactions on a small scale, one sample loop is loaded with a solution of aldehyde in toluene and the other with a solution of the desired boronate reagent in toluene (Scheme 2). For larger scale reactions, the reagents can be passed directly through the pumps without any damage to the system. The two streams are mixed at low temperature in a T-piece and passed through the reactor coil and a back-pressure regulator, which holds the system under pressure. By using this method, reactions commonly performed in batch mode were easily reproduced under flow conditions, both in terms of yield and diastereomeric ratio (Table 1). We also found that by using the flow conditions, simple substrates (Table 1, entries 1–3 and 11) could



Scheme 2. General set-up for performing Roush crotylation reactions in flow.

be reacted at higher temperatures with no detriment to the diastereomeric ratio.

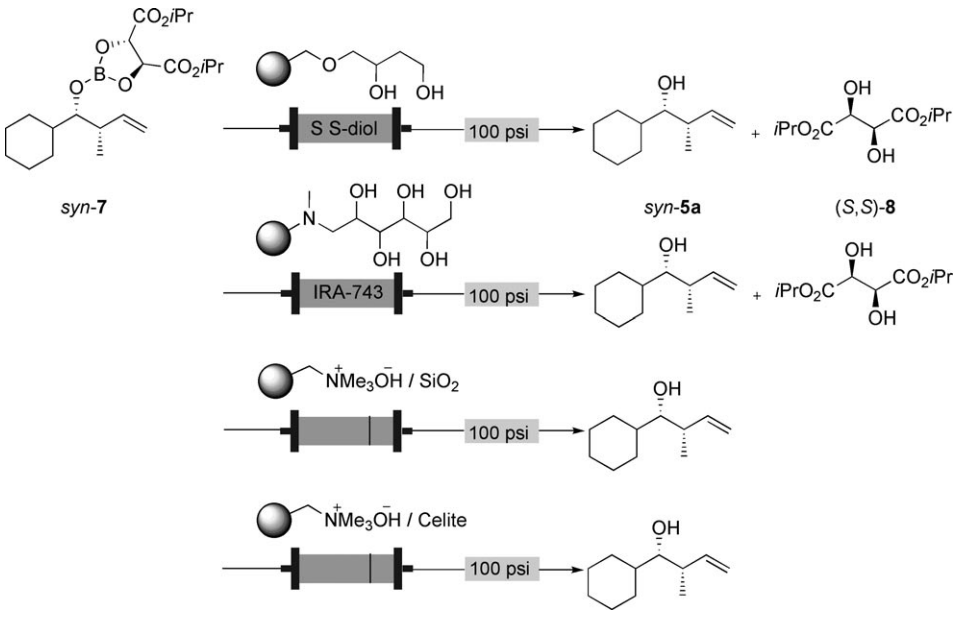
Work-up procedure: There are three alternative work-up procedures that can be employed for this flow-crotylation process. For procedures with an "off-line" work-up, the output stream was directed into a solution of NaOH to hydrolyse the B–O bond present in immediate reaction product **7** (Scheme 3), followed by a typical aqueous extraction. However, in order for a fully continuous flow process to be realised, an in-line work-up was necessary. This would enable the reaction to be telescoped as part of a multi-step sequence with no off-line purification processes being necessary. A number of polymer-supported reagents were screened to effect the in-line clean up (Scheme 3). Solid-supported (SS) diol resin and polyol resin IRA-743 were found to effectively scavenge the boron residues from the reagent stream in sub-stoichiometric amounts. However, the resins bind so strongly to boron that (−)-diisopropyl D-tartrate (**8**) was released as a breakdown product, resulting in product contamination. Nevertheless, this procedure would be useful for the large-scale process, since ester **8** can be readily crystallised at −20 °C and recovered. By comparison, in the off-line work-up, the chiral ester is hydrolysed and removed by filtration over Celite. As an alternative in-line work-up, a column was packed with polymer-supported hydroxide resin followed by a plug of Celite to mimic the hydrolysis process. Taking advantage of a chromatographic effect caused by the scavenging system, we used in-line infrared monitoring[6] to give the product cleanly. A plug of silica gel in place of Celite was also examined, but resulted in a very poor dispersion of the product, whereby a reaction that normally proceeds in 30 min took four hours due to the additional time required for the product to pass through the column. Overall, the work-up procedure chosen depends upon the scale and overall application (i.e., single step versus multi-step) and does not affect the diastereomeric ratio or yield of the reaction under study.

Reduction in flow: Prior to the crotylation event the initial aldehyde is often produced from the corresponding ester, either by direct reduction or more commonly by full reduction to the alcohol, necessitating subsequent re-oxidation. Issues with over-reduction have prevented this transforma-

Table 1. Roush crotylation reactions performed in flow using the conditions detailed in Scheme 2.

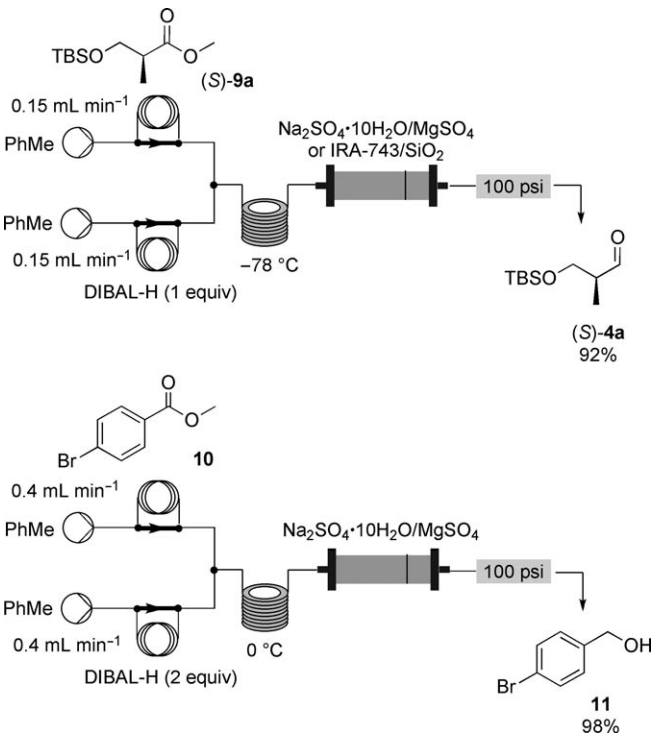
	Aldehyde		Reagent	Product		T [°C]	Work-up	Yield [%]	d.r.[a]
1		**3a**	(*R*,*R*)-**1**		*syn*-**5a**	−78	in-line	89	16:1
2		**3a**	(*R*,*R*)-**1**		*syn*-**5a**	−40	off-line	85	16:1
3		**3a**	(*R*,*R*)-**1**		*syn*-**5a**	−20	off-line	87	14:1
4		**3a**	(*S*,*S*)-**1**		*syn*-**5a**	−78	in-line	90	18:1
5		(*S*)-**4a**	(*S*,*S*)-**1**		*anti*,*syn*-**6a**	−78	in-line	80	8:1
6		(*S*)-**4a**	(*S*,*S*)-**2**		*syn*,*anti*-**6a**	−78	off-line	82	3.6:1
7		(*R*)-**4a**	(*R*,*R*)-**1**		*anti*,*syn*-**6a**	−78	in-line	75	4:1
8		(*S*,*S*)-**4b**	(*S*,*S*)-**1**		*anti*,*syn*-**6b**	−78	in-line	83	11:1
9		(*S*,*R*)-**4b**	(*R*,*R*)-**1**		*anti*,*syn*-**6b**	−78	off-line	70	5:1
10		(*R*)-**4c**	(*R*,*R*)-**1**		*anti*,*syn*-**6c**	−78	off-line	86	16:1
11		**3b**	(*R*,*R*)-**1**		*syn*-**5b**	−40	in-line	94	20:1

[a] Determined by GC-MS and ^{1}H NMR spectroscopy.



Scheme 3. Different possible polymer-supported reagents for in-line work-up of the Roush crotylation reactions.

tion from being used to its full effect in industrial processes.[7] When the aldehyde contains a chiral centre in the α-position, as is common with precursors for crotylation reactions, these can be sensitive to racemisation. To circumvent these issues we have developed a procedure for performing reduction reactions in flow directly from the ester to the corresponding aldehyde, with the aim of further reacting the product in flow with a third stream containing a crotylation reagent, and thereby minimising handling of the sensitive intermediates. Following drying of the pumping system, as described earlier, a solution of ester (*S*)-**9a** and a solution of DIBAL-H in toluene were loaded into sample loops and passed through the low-temperature coil (Scheme 4). For optimum results, it is recommended to work at dilutions of 0.5 M or lower, to avoid inorganic precipitates blocking the channels within the valves. The yields of the resulting aldehydes were consistently high (typically over 90%). Performing similar reactions in batch led to significant over-reduction and irreproducibility. The greater reproducibility in the flow process may be a result of the precise control over stoichiometry and temperature compared with adding DIBAL-H dropwise into a batch vessel. There are also options for the in-line work-up of these reactions, which simplify and eliminate manual downstream processing. For example, a column packed with sodium sulfate decahydrate and $MgSO_4$ removes aluminium salts in-line. However, due to the void volume in a column containing sodium sulfate decahydrate, a large dispersion of the product results, which is insignificant for single step operations but problematic for multi-step sequences. Consequently, a column packed with IRA-743 and silica gel gives the same clean product but a much better dispersion profile. Although the main advantage of this method is



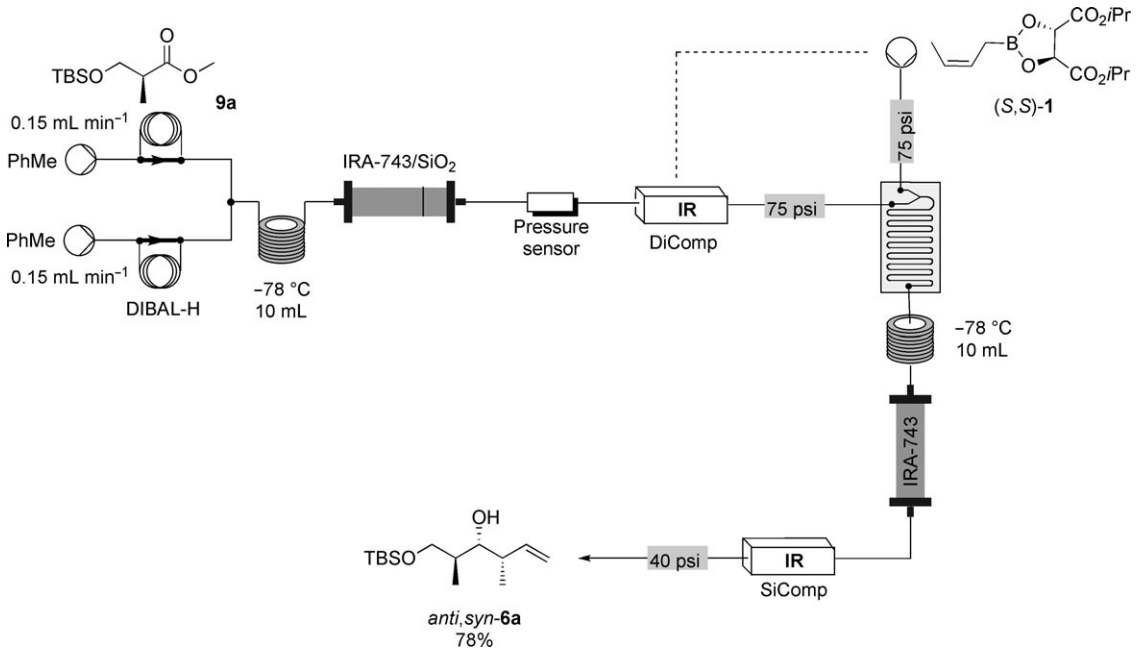
Scheme 4. DIBAL-H reduction reactions in flow.

the controlled formation of aldehydes from esters, it can also be used to great effect for reduction to the alcohol oxidation level. Starting from ester **10**, *para*-bromobenzyl alcohol (**11**) was produced in 98% yield in 30 min for the complete reduction process, while in batch-mode a lengthy Rochelle's salt work-up is required.

Applications in consecutive multistep sequences: Having established a convenient in-line work-up for the reduction of esters to aldehydes, we are now in a position to perform the reduction–crotylation joint reaction sequence as a single flow process (Scheme 5). This was achieved by timing the addition of a third stream of the crotylation reagent through infra-red monitoring.[8] This whole sequence takes around 4 h to complete, which should be compared to at least one day of work using conventional batch techniques and purifications.

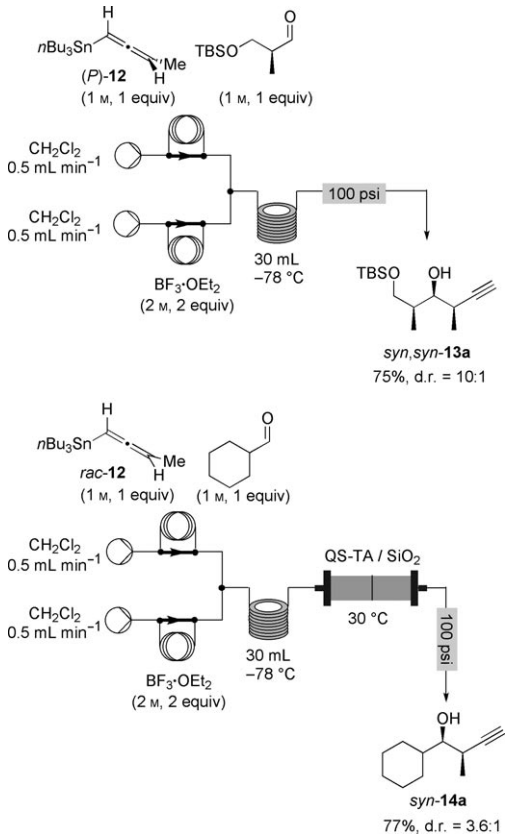
Marshall homopropargylation: A disadvantage of the Roush crotylation procedures adapted for the flow transformation is the fact that a *syn*,*syn* relationship is not easy to establish. Furthermore, depending on the desired application, a terminal triple bond in the product might be more useful for diversification than the alkene produced in the crotylation reaction. One way to address these issues would be to use the Marshall procedure, whereby a chain elongation is achieved through the addition of a chiral allene to an aldehyde.[9,10] In order to compliment the crotylation protocol, we have therefore developed a flow process for the boron trifluoride etherate mediated homopropargylation under Marshall conditions.[10]

In a series of optimisation reactions, we found that the flow process allowed for a significant reduction in the amount of toxic stannane needed to obtain comparable yields to the corresponding batch processes. To perform the reaction under flow conditions, allenyltin compound **12**[11] and the aldehyde are mixed as a 1 M solution in CH_2Cl_2 and $BF_3{\cdot}Et_2O$ is dissolved in CH_2Cl_2 as a 2 M solution. These two standard solutions are then injected into the sample loops of a conventional flow-chemistry platform (Uniqsis FlowSyn[12]



Scheme 5. Reduction and crotylation multi-step flow sequence.

or the Vapourtec R2+/R4 unit[5]), followed by mixing in a cooled T-piece. The reaction mixture is then passed through a cooled coil of appropriate length with respect to the flow-rate employed. The desired stereotriads were obtained in yields and selectivities comparable to the previously published batch reactions, in which less favourable stoichiometries of toxic reagents were used (Scheme 6, Table 2).[13] The



Scheme 6. Marshall homopropargylation reactions in flow.

method was found to be applicable to standard aliphatic aldehydes such as cyclohexyl carbaldehyde (**3a**; Table 2, entries 1–5 and 13) and to a range of substrates frequently used in polyketide synthesis (Table 2, entries 6–9). Unfortunately, chiral aldehydes **4b** and (*R*)-**4c** did not react smoothly with the allenyltin species (Table 2, entries 8 and 9). In both cases, the diastereoselectivities dropped significantly. For aromatic substrates, the results show that the substitution pattern and electronics have a substantial influence on the homopropargylation with respect to both yields and selectivities (Table 2, entries 10–12). In the case of α-unbranched substrates, the selectivity was less impressive (Table 2, entry 13), although this result is comparable to results obtained in conventional batch processes.

With respect to larger scale applications, we were interested in the overall performance of the flow Marshall reaction in comparison with a corresponding batch reaction at higher temperatures. As can be seen in Table 2, entries 1–5, the flow process was generally superior to the batch process employing the same conditions. Further application of the Marshall protocols using other Lewis acids, such as magnesium bromide,[14] indium triiodide[15] or indium iodide,[16] to effect *syn*,*anti* or *anti*,*anti* stereochemical relationships within the stereotriad are inherently more complicated due to solubility issues encountered in flow. These extensions are currently being investigated in more detail.[17]

Work-up procedure and in-line purification: The development of an in-line scavenging system for the Marshall reaction was very challenging since a successful chain elongation will result initially in a stannylated alcohol functionality. This tin–oxygen bond is difficult to cleave and, following the release of the free alcohol group, the toxic tin waste has to be separately scavenged.[18,19] Extensive screening of polymer supported reagents showed that numerous systems could affect the cleavage of the Sn–O bond, but that the scavenging of the resulting tin waste was more problematic. Some of the standard scavenging systems resulted in the formation of by-products (elimination products) or further decomposition. The scavenging protocol displayed in Scheme 6b, employing QuadraSil TA (QS-TA; a silica-supported trisamine) and conventional silica gel, proved to be the most reliable combination, yielding the standard testing product **14a** in >95% purity and 77% yield (Scheme 6, Table 2, entry 1). Although this in-line work-up and purification protocol has an effect on the overall yield, the approach is valuable as handling of the toxic tin waste can be circumvented and the overall amount of time required to produce clean material was significantly reduced compared with running the full batch sequence with its associated work up difficulties.

Reduction of the Marshall homopropargylation products in flow: In the challenging case in which both a *syn*,*syn* relationship of stereocentres and a terminal double bond are required for the synthesis programme, the product of the Marshall flow process can be immediately injected into the H-Cube to effect a partial reduction of the triple bond (Scheme 7).[20] The isolated immediate product *syn*-**14a** was re-dissolved in ethyl acetate (0.1 M), and the solution subjected to hydrogenation conditions (25 °C, 10 bar) employing the Lindlar catalyst ($Pd/BaCO_3/PbO$), yielding *syn*-**5a** in 95% yield without compromising the diastereomeric ratio (determined by ^1H NMR spectroscopy). In order to telescope steps in future applications,[21] we were able to perform the hydrogenation in CH_2Cl_2, a solvent which is scarcely used in this kind of transformation, by simply increasing the pressure to 30 bar (Scheme 7).

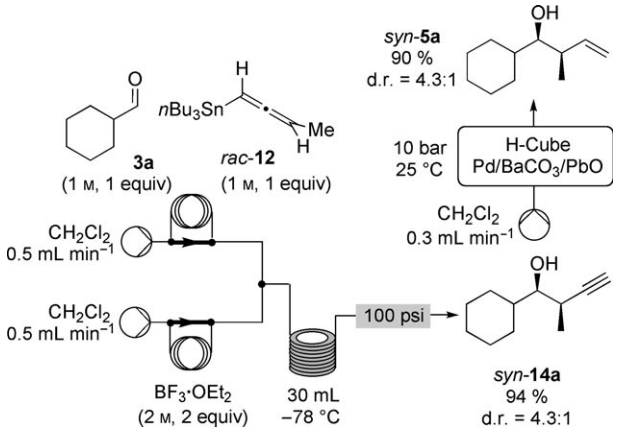
Conclusion

In summary, we have extended the applications of flow-chemistry technology to stereoselective organic transformations that require inert conditions and low temperatures. By

Table 2. Marshall homopropargylation reactions performed in flow using the conditions detailed in Scheme 6.

	Aldehyde	Reagent	Product	T [°C]	Work-up	Yield [%]	d.r.[a]
1	**3a**	*rac*-**12**	*syn*-**14a**	−78	in-line	77	3.6:1
2	**3a**	*rac*-**12**	*syn*-**14a**	−78	off-line	94	4.3:1
3[b]	**3a**	*rac*-**12**	*syn*-**14a**	−20	off-line	77	3.1:1
4	**3a**	*rac*-**12**	*syn*-**14a**	0	off-line	78	3.2:1
5[b]	**3a**	*rac*-**12**	*syn*-**14a**	RT	off-line	76	3.0:1
6	(*S*)-**4a**	(*P*)-**12**	*syn,syn*-**13a**	−78	off-line	75	10:1
7	(*R*)-**4a**	(*M*)-**12**	*syn,syn*-**13a**	−78	in-line	54	>10:1
8	(*S,S*)-**4b**	(*P*)-**12**	*syn,syn*-**13b**	−78	in-line	53	2:1
9	(*R*)-**4c**	(*M*)-**12**	*syn,syn*-**13c**	−78	in-line	64	2.5:1
10	**3b**	*rac*-**12**	*syn*-**14b**	−78	off-line	75	10:1
11	**3c**	*rac*-**12**	*syn*-**14c**	−78	off-line	49	3.9:1
12	**3d**	*rac*-**12**	*syn*-**14d**	−78	off-line	22	3.6:1
13	**3e**	*rac*-**12**	*syn*-**14e**	−78	in-line	43	1:1

[a] Determined by ^{1}H NMR spectroscopy. [b] Only 1.2 equivalents of Lewis acid were used.



Scheme 7. Marshall homopropargylation reaction and subsequent reduction in flow.

developing reliable flow procedures for both the Roush crotylation reaction and the Marshall homopropargylation reaction, we have significantly increased the repertoire of organic transformations possible in flow, particularly for future polyketide natural-product synthesis. Furthermore, by performing these reactions as a single process together with reductions or subsequent hydrogenations, this machine-assisted approach provides the common starting materials used in complex molecule assembly in a much shorter time period than the corresponding batch reactions.

Experimental Section

General Remarks: Toluene was dried and freshly distilled from sodium wire before use. Dichloromethane was distilled from calcium hydride. All reactions were performed under an atmosphere of argon and carried out using flow-chemistry platforms the pumps, tubing, and so forth of which have been dried by using the protocol outlined below. Unless otherwise specified, reactants and reagents, as well as polymer-supported reagents and scavengers were used as purchased, without further purification. Infrared spectra were recorded as neat samples on a Perkin–Elmer Spectrum One FTIR spectrometer fitted with an ATR sampling accessory. ^{1}H NMR spectra were recorded at 27 °C on a Bruker DPX-400. Residual protic solvent was used as the internal reference ($CHCl_3$ δ_H = 7.27 ppm). ^{13}C NMR spectra were recorded at 125 MHz on a Bruker DPX-400. The resonance of $CDCl_3$ (δ_C = 77.0 ppm, t) was used as the internal reference. GC-MS was performed on a Perkin–Elmer Turbomass Autosystem XL with a Supelco SLB-5 ms column (30 m × 0.25 mm × 0.25 μm film thickness) and positive electron ionisation (EI+). Optical rotation was measured by using a Perkin–Elmer Polarimeter 343 with the sample temperature maintained at 25 °C. $[\alpha]_D^{25}$ is reported in units of 10^{-1} deg g^{-1} cm^2. Concentration is quoted in units of 0.01 g cm^{-3}. HRMS were recorded on a Waters Micromass LCT Premier Q-TOF spectrometer by electrospray ionisation (ESI) or an ABI/MDS Sciex Q-STAR Pulsar. Unless otherwise stated, the mass reported contains the most abundant isotopes. Limit: ±5 ppm. Flash column chromatography for obtaining analytically pure material was carried out by using silica gel [Merck or Breckland (230–400 mesh)] under pressure with DE/PE mixtures (DE = diethyl ether, PE = petroleum ether, b.p. 40–60 °C).

Procedure for the Roush crotylation reaction under flow conditions, employing an in-line work-up: The system manifold [pumps, valves, tubing (0.5 mm id, perfluoroalkoxy (PFA)) and reactor coil] of a Vapourtec R2+/R4 unit were dried with IPA (2 mL min^{-1}, 15 min), acetone (1 mL min^{-1}, 1 h) and anhydrous toluene (0.5 mL min^{-1}, 2 h). A solution of aldehyde in toluene (0.5 M) was then loaded into a PEEK sample loop (2 mL), and the crotylation reagent (1 mmol) in toluene (2 mL) was loaded into the other PEEK sample loop (2 mL). The two solutions were pumped through the apparatus at a combined rate of 0.3 mL min^{-1} and mixed in a Vapourtec low-temperature coil (10 mL plus two premixing coils) held at −78 °C. The output of the coil was directed into an Omnitfit column (10 × 100 mm) containing Amberlyst IRA-700 hydroxide resin (2 g) and a plug of Celite (2 cm). The solution was collected and evaporated in vacuo. By using this procedure, (*S*)-3-*tert*-butyldimethylsilyloxy-

2-methylpropanal ((*S*)-**4a**) was reacted with crotylation reagent (*S,S*)-**1** to yield olefin *anti,syn*-**6a** as a colourless oil (80%, d.r. = 8:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.84 (ddd, J = 7.3, 10.4, 17.5 Hz, 1H), 5.05–5.02 (m, 2H), 3.82 (dd, J = 3.9, 9.9 Hz, 1H), 3.61–3.55 (m, 2H), 3.38 (dt, J = 4.6, 6.7 Hz, 1H), 2.35–2.27 (m, 1H), 1.82–1.73 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 7.1 Hz, 3H), 0.87 (s, 9H), 0.05 ppm (d, J = 2.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 142.47, 113.88, 79.60, 67.98, 41.26, 36.62, 25.85, 18.14, 14.10, 13.40, −5.61, −5.64 ppm; IR (ATR): $\tilde{\nu}$ = 3510, 2929, 2858, 1463, 1253, 1075 cm^{-1}; $[\alpha]_D^{25}$ = +6.4 (c = 2.00, $CHCl_3$). The spectroscopic data correspond to the literature.[4a]

Procedure for the Marshall homopropargylation reaction under flow conditions, employing an in-line work-up: A pre-dried (see above) Vapourtec R2+/R4 unit or Uniqsis FlowSyn was used as the flow-chemistry platform, equipped with two sample loops (2 mL), a T-piece and a self-made PTFE reactor coil (30 mL, inner diameter 0.5 mm). This reactor coil was attached to an Omnifit glass column (6.6×10 mm), which was filled with Quadrasil-TA (300 mg) and silica gel (300 mg), followed by a back pressure regulator (100 psi). The T-piece and reaction coil were immersed in a dry ice/acetone bath and the setup was purged with anhydrous CH_2Cl_2. A solution of aldehyde (2 mL, 0.1 M) and (tri-*n*-butylstannyl)-1,2-butadiene (**12**) in CH_2Cl_2 and a solution of BF_3·OEt_2 in CH_2Cl_2 (2 mL, 0.2 M) were injected into independent sample loops and pumped at a combined rate of 0.5 mL min^{-1}. The solution exiting the system was collected for 3 h and concentrated in vacuo to give the desired homopropargylic alcohol. By using this procedure, (*R*)-3-*tert*-butyldimethylsilyloxy-2-methylpropanal ((*R*)-**4a**) was reacted with (*M*)-(tri-*n*-butylstanyl)-1,2-butadiene ((*M*)-**12**) in the presence of BF_3·OEt_2 to yield diastereomerically pure (2*R*,3*R*,4*S*)-1-*tert*-butyldimethylsilyloxy-2,4-dimethyl-5-butyn-3-ol (*syn,syn*-**13a**, d.r. > 10:1, 54%, 28 mg, 0.11 mmol) as a colourless oil (purity > 95% by ^{1}H NMR spectroscopy). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (dd, J = 3.0, 9.8 Hz, 1H), 3.72 (dd, J = 3.9, 9.8 Hz, 1H), 3.70–3.72 (m, 1H), 3.42 (d, J = 1.5 Hz, 1H), 2.48–2.56 (m, 1H), 2.08–2.18 (m, 1H), 2.05 (d, J = 2.0 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 7.1 Hz, 3H), 0.92 (s, 9H), 0.08 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 86.4, 78.2, 69.9, 69.4, 36.3, 30.2, 25.9, 18.2, 17.7, 9.4, −5.6, −5.7 ppm; IR (ATR): $\tilde{\nu}$ = 3495, 3313, 2956, 2930, 2908, 2884, 2858, 1472, 1463, 1391, 1374, 1362, 1254, 1158, 1139, 1092, 1059, 1018, 1006, 990, 966, 939, 908, 834, 815, 776, 681, 666 cm^{-1}; $[\alpha]_D^{25}$ = −9.3 (c = 0.74, $CDCl_3$). The spectroscopic data correspond to the literature.[13b]

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