WILEY-VCH

A catalytic reactor for organocatalyzed enantioselective continuous flow alkylation of aldehydes

Riccardo Porta,[a] Maurizio Benaglia,[a]* Alessandra Puglisi,[a] Alessandro Mandoli,[b] Andrea Gualandi,[c] and Pier Giorgio Cozzi[c]*

Abstract: The use of immobilized metal-free catalysts offers the unique possibility to develop sustainable processes in flow mode. A challenging transformation like the intermolecular organocatalyzed aldehyde enantioselective alkylation was performed for the first time under continuous flow conditions. By using a packed-bed catalytic reactor filled with readily available and relatively inexpensive solid-supported enantiomerically pure imidazolidinone, different aldehydes were reacted with three distinct cationic electrophiles. In the organocatalyzed α-alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate excellent enantioselectivities, in some cases even better than in the flask process (up to 95% e.e. at 25 °C) and high productivity (more than 3800 h^{-1}) were obtained, thus showing that the catalytic reactor may efficiently work and continuously produce enantiomerically enriched compounds. The treatment of the alkylated products with Raney Nickel allows to obtain enantiomerically enriched α-methyl derivatives, key intermediates for the production of APIs and natural products.

Introduction

Chiral, non-racemic, α-alkyl-substituted aldehydes are considerably important key substrates for the synthesis of more complex molecules.[1] Consequently there has been substantial interest in the development of a methodology to access these valuable compounds[2] in enantiomerically pure form.[3-5] Breakthrough studies on iminium[6] and enamine[7] organocatalysis have opened the door to address–what was termed the 'Holy Grail' of organocatalysis,[8] the α-alkylation of aldehydes, by different and affordable strategies. In 2004, List reported the first aminocatalytic intramolecular α-alkylation of aldehydes, and more recently, he has extended this chemistry to an intermolecular version.[9]

On the other hand, stereoselective intermolecular α-alkylation of carbonyl derivatives, has been successfully developed by MacMillan and co-workers by exploiting innovative concepts where traditional aminocatalysis is combined with the generation of radical intermediates, by the so called SOMO catalysis[10] or by photoredox catalysis.[11] Additionally, novel synthetic α-alkylation methodologies have been developed by S_N1-type reactions,[12] in which carbocations of sufficient stability generated in situ from alcohols, or stable carbenium ions are employed to perform enantioselective α-alkylation of aldehydes, catalyzed by MacMillan-type catalysts.[13]

However, one of the major problems in organocatalyzed alkylation is the high loading of the catalyst, and the difficulties in recovering the chiral promoter. An organocatalytic α-alkylation strategy for possible large scale applications need to be implemented focusing on these drawbacks. Continuous flow synthetic methodologies offer several advantages over traditional batch procedures:[14] the scale-up of reactions is straightforward, and high reaction reproducibility may be accomplished through accurate parameters control. Furthermore, the transformation of a batch production into a continuous process may be economically convenient, limits the storing of potentially hazardous intermediates, and, in general, offers the opportunity to develop greener productive processes.[15] However, despite the impressive progress of the last years, the application of continuous flow methodologies to the stereoselective synthesis of chiral molecules is still underdeveloped.[16]

In this context, organocatalysis is likely to play a crucial role in the near future; the use of supported metal-free catalysts offers the unique possibility to develop sustainable processes in flow mode. So far a limited number of chiral organocatalysts employed under continuous flow conditions have been studied.[17] Here we describe the design of a catalytic reactor to perform for the first time a challenging transformation like the enantioselective α-alkylation of aldehydes under continuous flow conditions.[18]

Following our previous studies on the heterogenization of chiral imidazolidinones,[19] we have decided to explore the use of solid-supported MacMillan catalysts in this challenging transformation,[20] and perform an organocatalytic enantioselective alkylation under continuous flow conditions.[21] High enantioselectivities (up to 95% e.e.) and productivity much higher than those observed in the flask reaction were obtained.

Results and Discussion

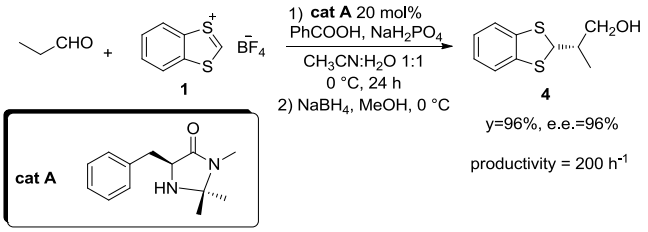
For preliminary experiments we selected the reaction between propionaldehyde and the commercially available 1,3-benzodithiolylium tetrafluoroborate **1** (Scheme 1). In the presence of 20 mol% of the non-supported catalyst **A** the product was isolated, after reduction of the carbonyl group to the

[a] Dr. R. Porta, Prof. Dr. M. Benaglia, Dr. Alessandra Puglisi
Dipartimento di Chimica,
Università degli Studi di Milano
Via Golgi 19, I-20133 Milano, Italy
E-mail: maurizio.benaglia@unimi.it
[b] Dr. A. Mandoli
Dipartimento di Chimica e Chimica Industriale
Università di Pisa
Via Risorgimento, 35, 56126 Pisa, Italy
[c] Dr. A. Gualandi, Prof. Pier Giorgio Cozzi
Dipartimento di Chimica "G. Ciamician",
ALMA MATER STUDIORUM Università di Bologna
Via Selmi, 2, 40126, Bologna, Italy.

Supporting Information for this article is given via a link at the end of the document.

corresponding alcohol, in almost quantitative yield and 96% e.e. after 24 hours of reaction at 0 °C.[20d]

Based on our experience in the field, we decided to synthesize both silica-supported and polymer-supported enantiomerically pure imidazolidinones, prepared starting from the commercially available, relatively inexpensive (*S*)-tyrosine (Figure 1).[19] Silica-supported catalyst **B** was synthesized by grafting a trimethoxysilyl imidazolidinone derivative onto commercially available mesoporous silica nanoparticles.[21b] Polystyrene-supported catalyst **C** was obtained by radical copolymerization between the imidazolidinone vinyl monomer derivative and divinylbenzene[21c] (see Supporting Information for experimental details).



Scheme 1. Organocatalytic α-alkylation of propionaldehyde.

In preliminary experiments the supported catalysts **B** and **C** were employed in batch reactions between propionaldehyde and 1,3- benzodithiolylium tetrafluoroborate **1** in order to compare their behavior to that of homogeneous catalyst **A**. Moreover, two different stereoselective alkylations with various electrophiles (**2** and **3**) were performed (Scheme 2).

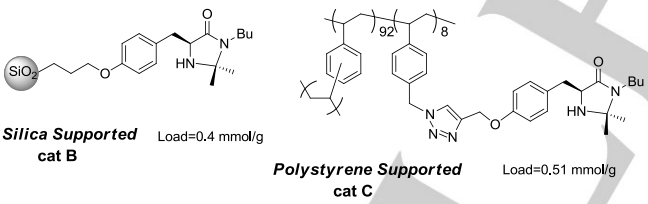
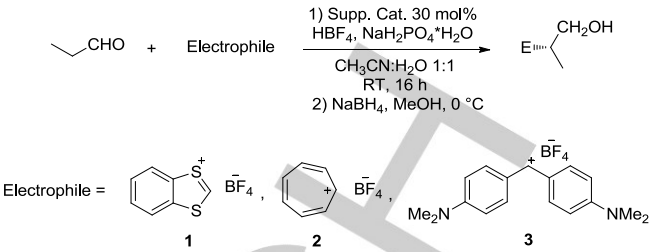


Figure 1. Solid-supported chiral imidazolidinones employed in organocatalytic continuous flow reactors.

The reaction of propionaldehyde with cation **1** was performed at 25 °C for 16 hours in the presence of 30 mol% amount of the tetrafluoroborate salt of silica-supported catalyst **B** (Table 1). The product was obtained in good yield and 90% e.e., with a productivity (160 h^{-1}) comparable to that observed in the literature reaction with homogeneous catalyst **A** (Scheme 1).[20d] Polymer-anchored imidazolidinone **C** behaved similarly; interestingly, both heterogenized chiral catalysts could be easily recovered by centrifugation and offer the possibility to be recycled.[22]



Scheme 2. Batch reactions between propionaldehyde and various electrophiles.

Table 1. Batch reactions with supported catalysts **B** and **C**.

Entry	Cat	Electrophile	Yield (%)[a]	e.e. (%)[b]	Productivity (h^{-1})[c]	TON
1	**B**	**1**	75	90	160	2.5
2	**C**	**1**	67	86	140	2.2
3	**B**	**2**	81	79	170	2.7
4	**C**	**2**	72	90	150	2.4
5	**B**	**3**	84	67	180	2.8
6	**C**	**3**	64	95	130	2.1

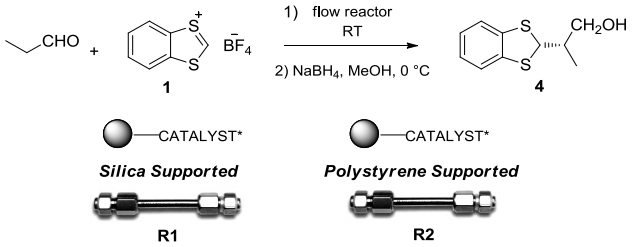
[a] Isolated yields after chromatography. [b] Enantiomeric excess was determined by HPLC on chiral stationary phase. [c] Determined as: mmol product * mmol $catalyst^{-1}$ * $time^{-1}$ *1000; see ref. [17c].

Even more exciting results were obtained in the alkylations with electrophiles **2** and **3**; the reaction at 25 °C with tropylium tetrafluoroborate **2** afforded the expected product in good yield, with 79% and 90% enantioselectivities with catalyst **B** and **C**, respectively. Noteworthy, the reaction performed under homogeneous conditions gave a lower stereoselectivity (for the reaction of butanal with **2** only 22% e.e. was observed, see ref. 13b). That holds true also for the alkylation of propionaldehyde with bis(4-(dimethylamino)phenyl)methylium tetrafluoroborate **3** that afforded the α–alkylated aldehyde in 95% e.e. with supported catalyst **C** (with non-supported MacMillan imidazolidinone the product was isolated with 65% e.e. at 4 °C, see ref [13b]).[23]

Based on these very encouraging results, we then investigated the application of the heterogeneous systems in enantioselective transformations under continuous flow conditions. Two different packed-bed reactors, **R1** and **R2,** were prepared by filling two stainless steel HPLC columns ($ø_i$=0.4 cm, length=6 cm, V=0.75 mL) with catalysts **B** and **C**, respectively (Scheme 3). The continuous flow system was constituted of a syringe pump which fed the reagents continuously into the reactor (See Supporting Information for details relative to the set-up of flow experiments).

The continuous flow stereoselective alkylation of propionaldehye with **1** was performed in both reactors **R1** and **R2** (Table 2). Silica-supported catalyst in reactor **R1** was able to continuously produce compound **4** in 82% e.e., with a productivity of about

1000 h^{-1}. Better results came from the use of the packed-bed reactor **R2**, filled with the polymer-supported catalyst **C**. In this case higher enantioselectivities were observed; indeed with reactor **R2** the asymmetric alkylation of propionaldehyde was performed under continuous flow conditions with enantioselectivities constantly higher than 93% e.e., and up to 95% e.e. at room temperature, with results totally comparable to those obtained under homogeneous conditions, at 0 °C. [24]



Scheme 3. Continuous flow alkylation carried out in packed-bed reactors **R1** and **R2**.

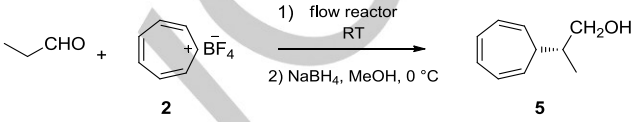
Table 2. Continuous flow alkylation of propionaldehyde with 1,3-benzodithiolylium tetrafluoroborate **1**.

Entry	Reactor[a]	Conc. Electr. **1** (mol/L)	Flow rate (mL/h)	Res. time (min)[b]	Yield (%)[c]	e.e. (%)[d]	Prod. (h^{-1})[e]
1	**R1**	0.15	0.1	276	65	80	70
2	**R1**	0.15	5.4	5	19	82	1030
3	**R2**	0.07	0.1	354	60	80	40
4	**R2**	0.11	0.67	53	41	94	270
5	**R2**	0.11	1.25	28	25	93	310
6	**R2**	0.07	2.0	18	18	95	230
7	**R2**	0.07	4.2	8	14	95	370
8	**R2**	0.11	5.4	7	15	92	810
9	**R2**	0.11	10.8	4	11	87	1190

[a] Reaction conditions: **1** 1 eq., aldehyde 3 eq., NaH_2PO_4 1 eq; solvent CH_3CN:H_2O 7:3. [b] Residence time calculated as void volume/flow rate (void volume determined experimentally by picnometry V_{R1}=0.59 ml, V_{R2}=0.46 ml). [c] Isolated yields. [d] e.e. was determined by HPLC on chiral stationary phase. [e] Determined as: mmol product * mmol $catalyst^{-1}$ * $time^{-1}$ *1000; see ref. [18c].

Noteworthy, the reactor guarantees high stereoselectivities at different flow rates; the excellent behavior of **R2** also at high flow rates allowed to improve the productivity of the process to 810 h^{-1} (95% e.e., four times higher than batch reaction) [25] and up to 1190 h^{-1} (87% e.e., entry 9 Table 2).[26]

Reactors **R1** and **R2** were then employed for the alkylation of propionaldehyde with tropylium tetrafluoroborate **2**. By using the same catalytic columns employed in the reactions of Table 2, the alkylation reported in Scheme 4 was successfully performed. Silica-based reactor **R1** afforded higher enantioselectivity than its batch counterpart, producing **5** in 86% e.e. (entry 1 Table 3 *vs* 79% e.e. in batch, entry 3 Table 1). Polymer-anchored catalyst **C** in **R2** also in this case showed to be better performant, affording in continuo product **5** constantly in 94% e.e. and with a remarkable productivity of 3830 h^{-1} (entry 5 Table 3). It is worth mentioning that the process in flow performed clearly better that in the flask reaction, in terms of both productivity and enantioselectivity, further highlighting the unique feature of the present flow reactor system.[27]



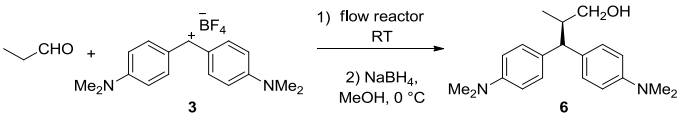
Scheme 4. Continuous flow alkylation carried out in packed-bed reactors **R1** and **R2**.

Table 3. Continuous flow alkylation of propionaldehyde with tropylium tetrafluoroborate.

Entry[a]	Reactor	Flow rate (mL/h)	Res. time (min)[b]	Yield (%)[c]	e.e. (%)[d]	Prod. (h^{-1})[e]
1	**R1**	4.8	6	18	86	1150
2	**R2**	0.67	53	65	94	590
3	**R2**	1.5	24	52	93	1060
4	**R2**	5.4	7	26	94	1910
5	**R2**	10.8	4	26	94	3830

[a] Reaction conditions: **2** 1 eq., aldehyde 3 eq., NaH_2PO_4 1 eq; solvent CH_3CN:H_2O 7:3; **R1** 0.2M, **R2** 0.15M. [b] Residence time calculated as void volume/flow rate (void volume determined experimentally by picnometry V_{R1}=0.59 ml, V_{R2}=0.46 ml). [c] Isolated yields. [d] e.e. was determined by HPLC on chiral stationary phase (see Supporting Information for details). [e] Determined as: mmol product * mmol $catalyst^{-1}$ * $time^{-1}$ *1000; see ref. [18c].

The reaction of propionaldeyhde with benzydryl cation **3** (Scheme 5) performed under continuous flow conditions in reactor **R2** gave the product **6** in 82% e.e. and 1170 h^{-1} productivity.[28]



Scheme 5. Continuous flow alkylation of propionaldehyde with bis(4-(dimethylamino)phenyl)methylium tetrafluoroborate.

Both reductive and oxidative removals of 1,3-benzodithiol moiety are possible;[20a-d] in particular, the treatment of the alkylated products with Raney Nickel allows to obtain enantiomerically enriched α-methyl derivatives, key intermediates for the

production of APIs and natural products (Figure 2). For these reasons, further stereoselective alkylations were performed on selected aldehydes to afford intermediates for important synthetic applications.

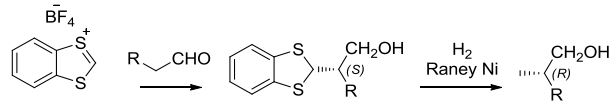
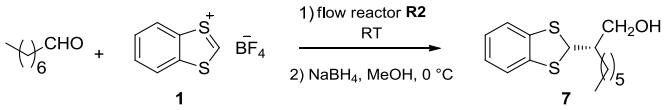


Figure 2. Reductive removal of benzodithiol moiety.

For example, the continuous flow alkylation of octanal with 1,3-benzodithiolylium tetrafluoroborate in **R2** afforded, after $NaBH_4$ reduction, the expected alcohol **7** in 94% e.e. The productivity was further improved up to 600 h^{-1} still maintaining a high enantioselectivity (90%, table of Scheme 6). Product **7** can be converted in (*S*)-2-methyl-octanol, a key intermediate for the preparation of natural products[29a-d] and antitumor antibiotic compounds.[29e]

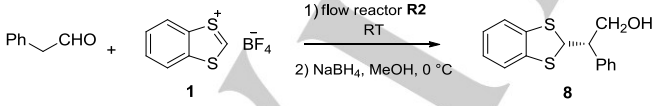


Scheme 6. Continuous flow alkylation of octanal in **R2**.

Flow rate (mL/h)	Residence time (min)[b]	Yield (%)[c]	e.e. (%)[d]	Productivity (h^{-1})[e]
1.5[a]	24	31	94	470
5.4[a]	7	9	90	600

[a] Reaction conditions: **1** 0.11 M, octanal 0.33 M, NaH_2PO_4 0.11 M, in CH_3CN:H_2O 7:3. [b] Residence time calculated as void volume/flow rate. [c] Isolated yields after chromatography. [d] e.e. was determined by HPLC on chiral stationary phase. [e] Determined as: mmol product * mmol catalyst^{-1} * time^{-1} *1000; see ref. [18c].

Similarly, the reaction of phenylacetaldehyde with **1** carried out in reactor **R2** afforded product **8** in 90% e.e. with even higher productivity, up to almost 1000 h^{-1} (Scheme 7).



Scheme 7. Continuous flow alkylation of phenylacetaldehyde in **R2**.

Flow rate (mL/h)	Residence time (min)[b]	Yield (%)[c]	e.e. (%)[d]	Productivity (h^{-1})[e]
1.5[a]	24	29	90	440
5.4[a]	7	18	90	970

[a] Reaction conditions: **1** 0.11 M, phenylacetaldehyde 0.33 M, NaH_2PO_4 0.11 M, in CH_3CN:H_2O 7:3. [b] Residence time calculated as void volume/flow rate. [c] Isolated yields after chromatography. [d] E.e. was determined by HPLC on chiral stationary phase. [e] Determined as: mmol product * mmol catalyst^{-1} * time^{-1} *1000; see ref. [18c].

The reaction product can easily be transformed in (*S*)-2-phenylpropan-1-ol, precursors for Bisabolanes which are anti-inflammatory, anti-viral and anti-mycobacterial agents; they are also key components in essential oils and are employed as additives in perfumes and cosmetics.[30] Furthermore, the enantioselective α-alkylation of phenylacetaldehyde offers a valuable and extremely attractive approach for the preparation of enantiomerically pure α–aryl propionic acids. [31]

Conclusions

In conclusion, a challenging transformation like the intermolecular organocatalyzed aldehyde enantioselective α-alkylation was performed for the first time under continuous flow conditions. By using a packed-bed catalytic reactor filled with readily available and relatively inexpensive solid-supported enantiomerically pure imidazolidinone, different aldehydes were reacted with three distinct cationic electrophiles. High enantioselectivities and productivity clearly higher than those obtained with the *in flask* procedure were observed; in some cases the procedure in flow with the heterogeneous catalyst led to the formation of the product even in higher enantioselectivities than the process in homogeneous conditions with the non-supported catalyst. Noteworthy, the *same* catalytic reactor was used to perform continuously the alkylation of propionaldehyde with three different electrophiles, for a total of more than 100 hours on stream, and always affording the expected products with excellent enantioselectivity, often higher than 90%.
The present methodology paves the road to a more general use of continuous flow conditions for the preparation of key intermediates in the synthesis of a wide class of compounds. The combination of catalytic reactors with other analytical and synthetic devices, recently developed for the automated synthesis of complex molecules,[16] will open new extraordinary possibilities for a successful use of *enabling technologies* in modern organic synthesis.

Experimental Section

General Methods Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F 254 pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300). ^{13}C NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz, with complete proton decoupling. HR-MAS experiments were performed on a Bruker Avance 500 spectrometer, operating at 500.13 MHz (^1H) and at 125.62 MHz (^{13}C). The HR-MAS ^1H,

^{13}C spectra were recorded with a 4-mm Bruker ^{1}H/ ^{13}C HRMAS gradient probe at a temperature of 330 K, using standard Bruker software sequences. The samples were previously swollen in DMF-d_7 as solvent, and packed into a 4-mm HRMAS rotor (50 μl sample volume) and spun at 10 kHz. The 90° pulse widths were 6.0 and 9.0 μs for ^{1}H and ^{13}C, respectively. The ^{13}C spectra were recorded with the inverse gated decoupled methodology. In this case, no polarization transfer from ^{1}H to ^{13}C via NOE takes place because the proton decoupling is only applied during the acquisition period and therefore the resulting ^{1}H-coupled ^{13}C spectrum can be used also for quantitative measurements. After several experiments a 15 s. delay was used, longer delay times did not affect the integral measurements. Enantiomeric excess determinations were performed with Agilent 1200 series HPLC. Solid supported catalysts were isolated by centrifugation using MPW Med. Instruments, Laboratory Centrifuge MPW-260. Reagents mixtures were fed to continuous flow reactors using Syringe Pump SAGE, ThermoOrion model M361 and Syringe Pump KF Technology, New Era Pump system, model NE4000.

Materials Commercial grade reagents and solvents were used without further purifications. 1,3-Benzodithiolylium tetrafluoroborate (technical grade 97%), tropylium tetrafluoroborate (technical grade 97%) were purchased from Sigma-Aldrich 5*S*)-(−)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone monohydrochloride (technical grade 97%), was purchased from Sigma-Aldrich. Propionaldehyde was purified by distillation over calcium chloride under nitrogen atmosphere before use. Octanal and phenylacetaldehyde were purified by distillation over calcium chloride under reduced pressure before use. Apex Prepsil Silica Media 8 μm was purchased from Phenomenex (asymmetry 0.9, pore diameter 120 Å, mean particle size 8.4 μm and surface area 162 m^2/g).

Synthesis of Supported Catalysts
Catalysts **B** and **C** are known catalysts. For the synthesis and additional details see Supporting Information.

General Procedure for Batch Reactions Heterogeneous catalyst **B** or **C** (0.042 mmol) was charged in a vial and suspended in 2 mL of solvent mixture (CH_3CN/H_2O = 1/1 *v/v*); tetrafluoroboric acid (0.042 mmol) was added and the mixture was stirred for 10 minutes. Then the electrophile (0.14 mmol), $NaH_2PO_4*H_2O$ (0.14 mmol), and propanal (0.42 mmol) were added and the mixture was stirred for 16 hours at room temperature. After reaction time the crude mixture was diluted with 3 mL of Et_2O, the solid catalyst was filtered and washed with 2 mL of Et_2O. The organic layer was separated and the aqueous phase was extracted twice with 1 mL of Et_2O. The combined organic layers were dried with Na_2SO_4 and diluted with 3 mL of methanol. At the crude mixture was slowly added $NaBH_4$ (0.6 mmol) at 0 °C and it was stirred for 1 hour at 0 °C. The reaction was quenched with 3 mL of H_2O and 5 mL of AcOEt were added. The organic layer was separated and the aqueous phase was extracted twice with 5 mL of AcOEt. The organic layers were recovered, washed with 5 mL of brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure and dried under high vacuum. The crude product was purified by flash column chromatography on silica gel.

General Procedure for Continuous Flow Reactions

Reactor **R1** was prepared by filling a stainless steel HPLC column (ø$_i$ = 0.4 cm, length = 6 cm, V = 0.75 mL) with catalyst **B** (375 mg, 0.15 mmol, 0.2 M) and it was wet through a syringe pump with 4 ml of CH_3CN/H_2O (7/3 *v/v*) mixture at a flow rate of 2 mL/h. Subsequently the reactor was fed with 3 mL of a 0.2 M solution of tetrafluoroboric acid in CH_3CN/H_2O (7/3 *v/v*) at a flow rate of 2 mL/h, then it was washed with 3 mL of CH_3CN/H_2O (7/3 *v/v*) at the same flow rate. Void Volume V_{R1} of **R1** was measured experimentally by picnometry:[4] V_{R1}=046 mL.

Reactor **R2** was prepared by filling a stainless steel HPLC column (ø$_i$ = 0.4 cm, length = 6 cm, V = 0.75 mL) with catalyst **C** (215 mg, 0.11 mmol, 0.146 M) and it was wet through a syringe pump with 4 ml of CH_3CN/H_2O (7/3 *v/v*) mixture at a flow rate of 2 mL/h. Subsequently the reactor was fed with 3 ml of a 0.146 M solution of tetrafluoroboric acid in CH_3CN/H_2O (7/3 *v/v*) at a flow rate of 2 mL/h, then it was washed with 3 mL of CH_3CN/H_2O (7/3 *v/v*) at the same flow rate. Void Volume V_{R1} of **R2** was measured experimentally by picnometry:[4] V_{R2}=0.59 mL.

Alkylation of Aldehydes with 1,3-Benzodithiolylium Tetrafluoroborate A syringe pump was charged with 2 mL of a CH_3CN/H_2O (7/3 *v/v*) solution of reagents (**R1**: 0.15 M 1,3-benzodithiolylium tetrafluoroborate, 0.45 M aldehyde, 0.15 M $NaH_2PO_4*H_2O$; **R2**: 0.11 M 1,3-benzodithiolylium tetrafluoroborate, 0.33 M aldehyde, 0.11 M $NaH_2PO_4*H_2O$) and was fed to the reactor at the indicated flow rate (mL/h) at room temperature. Subsequently the flow reactor was washed with 2 mL of eluent mixture (CH_3CN/H_2O = 7/3 *v/v*) at the same flow rate. The product at the way-out of the reactor was collected at 0 °C in an ice bath and diluted with 3 mL of Et_2O. The organic layer was separated and the aqueous phase was extracted twice with 1 mL of Et_2O. The combined organic layers were dried with Na_2SO_4 and diluted with 3 mL of methanol. The crude mixture was cooled to 0 °C and $NaBH_4$ (1 mmol) was slowly added. After 1 hour stirring at 0 °C the reaction was quenched with 3 mL of H_2O and 5 mL of AcOEt were added. The organic layer was separated and the aqueous phase was extracted twice with 5 mL of AcOEt. The organic layers were recovered, washed with 5 mL of brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure and dried under high vacuum. The crude product was purified by flash column chromatography on silica gel.

Alkylation of Propionaldehyde with Various Electrophiles A syringe pump was charged with 2 mL of a CH_3CN/H_2O (7/3 *v/v*) solution of reagents (**R1**: 0.2 M electrophile, 0.6 M aldehyde, 0.2 M $NaH_2PO_4*H_2O$; **R2**: 0.15 M electrophile, 0.45 M aldehyde, 0.15 M $NaH_2PO_4*H_2O$) and was fed to the reactor at the indicated flow rate (mL/h) at room temperature. Subsequently the flow reactor was washed with 2 mL of eluent mixture (CH_3CN/H_2O = 7/3 *v/v*) at the same flow rate. The product at the way-out of the reactor was collected at 0 °C in an ice bath and diluted with 3 mL of Et_2O. The organic layer was separated and the aqueous phase was extracted twice with 1 mL of Et_2O. The combined organic layers were dried with Na_2SO_4 and diluted with 3 mL of methanol. The crude mixture was cooled to 0 °C and $NaBH_4$ (1 mmol) was slowly added. After 1 hour stirring at 0 °C the reaction was quenched with 3 mL of H_2O and 5 mL of AcOEt were added. The organic layer was separated and the aqueous phase was extracted twice with 5 mL of AcOEt. The organic layers were recovered, washed with 5 mL of brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure and dried under high vacuum. The crude product was purified by flash column chromatography on silica gel

Products of Aldehydes Alkylation

Compound **4-8** are known (see supporting Information for details).

Compound **4** was purified by flash column chromatography on silica gel (eluent: Hexane/AcOEt = 9/1) to afford a colorless oil.
TLC R_f = 0.27 (Hexane/AcOEt = 9/1, stained blue with phosphomolibdic acid)
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.21 (dd, 2H), 7.02 (dd, 2H), 5.13 (d, 1H), 3.70 (d, 2H), 2.17-2.09 (m, 1H), 1.06 (d, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ 137.7 (2C), 125.4 (2C), 122.0, 121.9, 64.8, 56.5, 43.6, 13.2.
The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OD-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.8 mL/min, λ=230 nm, τ_{minor}=8.9 min, τ_{major}=10.5 min.

Compound **5** was purified by flash column chromatography on silica gel (eluent: Hexane/AcOEt = 8/2) to afford a colorless oil.
TLC R_f = 0.36 (Hexane/AcOEt = 8/2, stained blue with phosphomolibdic acid)
^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.69 (m, 2H), 6.25 (m, 2H), 5.33 (m, 2H), 3.81 (dd, 1H), 3.64 (dd, 1H), 2.05 (m, 1H), 1.55 (m, 1H), 1.41 (bs, 1H), 1.11 (d, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ 130.8 (2C), 125.0, 124.9, 124.0, 123.2, 66.5, 41.4, 37.3, 14.5.
The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OJ-H column: eluent Hexane/*i*PrOH = 95/5, flow rate 0.8 mL/min, λ=254 nm, τ_{minor}=9.8 min, τ_{major}=11.0 min.

Compound **6** was purified by flash column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 98/2) to afford a colorless oil.
TLC R_f = 0.48(CH_2Cl_2/MeOH = 98/2)
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.18 (m, 4H), 6.69 (m, 4H), 3.92 (d, 1H), 3.61 (dd, 1H), 3.58 (d, 1H), 3.51 (dd, 1H), 2.91 (s, 6H), 2.90 (s, 6H), 2.48 (m, 1H) 0.97 (d, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ 149.0, 149.9 133.0 (2C), 128.6 (2C), 128.3 (2C), 113.1 (2C), 113.0 (2C), 67.2, 53.7, 40.8 (4C), 39.6, 16.4.
The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OD-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.8 mL/min, λ=254 nm, τ_{major}=18.4 min, τ_{minor}=31.7 min.

Compound **7** was purified by flash column chromatography on silica gel (eluent: Hexane/AcOEt = 9/1) to afford a colorless oil.
TLC R_f = 0.28 (Hexane/AcOEt = 9/1, stained blue with phosphomolibdic acid)
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.23 (dd, 2H), 7.02 (dd, 2H), 5.20 (d, 1H), 3.85 (dd, 1H), 3.79 (dd, 2H), 1.94 (m, 1H), 1.30 (m, 10H), 0.89 (t, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ 137.7, 137.6, 125.4, 125.3, 122.0 (2C), 62.4, 56.6, 47.6, 31.6, 29.3, 28.1, 27.1, 22.5, 14.0.
The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OD-H column: eluent Hexane/*i*PrOH = 95/5, flow rate 0.8 mL/min, λ=230 nm, τ_{minor}=10.7 min, τ_{major}=15.1 min.

Compound **8** was purified by flash column chromatography on silica gel (eluent: Hexane/AcOEt = 9/1) to afford a colorless oil.
TLC R_f = 0.40 (Hexane/AcOEt = 8/2, stained blue with phosphomolibdic acid)
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.34-7.27 (m, 5H), 7.20 (m, 1H), 7.13 (m, 1H), 7.02 (m, 2H), 5.34 (d, 1H), 4.05 (m, 2H), 3.37-3.30 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$): 139.1, 137.2, 128.8 (2C), 128.6, 128.4, 127.7 (2C), 125.6, 125.4, 122.3, 122.2, 64.4, 56.2, 54.9.
The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OD-H column: eluent Hexane/*i*PrOH = 9/1, flow rate 0.8 mL/min, λ=230 nm, τ_{minor}=19.0 min, τ_{major}=23.5 min.

Acknowledgements

A. P. thanks FIRB National Project "Multifunctional hybrid materials for the development of sustainable catalytic processes" M. B. thanks COST action CM9505 "ORCA" Organocatalysis. P.G. C. thanks Bologna University, Fondazione Del Monte, and the European Commission through the project FP7-201431 (CATAFLU.OR) for financial support.

Keywords: continuous flow • stereoselective synthesis • organocatalysis • alkylation • catalytic reactor

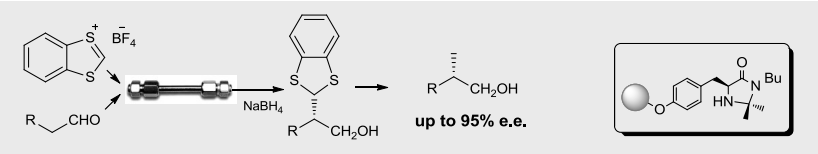
References

[1] For some examples of enantioenriched α-alkyl substituted aldehydes in total synthesis, see: a) K. C. Nicolaou, D. P. Papahatjis, D. A. Claremon, R. L. Magolda, b) R. E. Dolle, *J. Org. Chem.* **1985**, *50*, 1440; c) G. S. Besra, D. E. Minnikin, P. R. Wheeler, C. Ratledge, *Chem. Phys. Lipids* **1993**, *66*, 23; d) T. Wakabayashi, K. Mori, S. Kobayashi, *J. Am. Chem. Soc.* **2001**, *123*, 1372; e) A. Fürstner, M. Bonnekessel, J. T. Blank, K. Radkowski, G. Seidel, F. Lacombe, B. Gabor, R. Mynott, *Chem. Eur. J.* **2007**, *13*, 8762.
[2] D. M. Hodgson, A. Charlton, *Tetrahedron* **2014**, *70*, 2207.
[3] a) *Enantioselective Organocatalysis. Reactions and Experimental procedures.* P. I. Dalko, Ed.; Wiley VCH, Weinheim, **2007**; b) Asymmetric Organocatalysis, in *Topics in Current Chemistry*, B. List, Ed., Springer, **2009**, vol. 291.
[4] a) D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737; b) D. A. Evans, In *Asymmetric Synthesis*; J. D. Morrison, Ed.; Academic: London, UK, **1983**; Vol. 3, p 1.
[5] a) A. G. Myers, B. H. Yang, H. Chen, J. L. Gleason, *J. Am. Chem. Soc.* **1994**, *116*, 9361; b) A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496.
[6] K. A. Ahrendt, J. C. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.
[7] B. List, R. A. Lerner, C. F. III Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[8] a) J. Vesely, R. Rios, *ChemCatChem* **2012**, *4*, 942; b) P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 1360; c) L. Tak-Tak, H. Dhimane, P: Dalko, *Angew. Chem. Int. Ed.* **2011**, *50*, 12146.
[9] a) N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450; b) B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 282.
[10] a) T. D. Beeson, A. Mastracchio, J. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582; b) C. H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**,*129*, 398; c) J. E. Wilson, A. D. Casarez, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11332; d) J. J. III Devery, J. C. Conrad, D. W. C. MacMillan, R. A. II Flowers, *Angew. Chem. Int. Ed.* **2010**, *49*, 6106.
[11] a) D. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77; b) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875; c) H.-W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2010**, *132*, 13600.
[12] a) A. Gualandi, P. G. Cozzi, *Synlett* **2013**, *24*, 281; b) A. Gualandi, D. Petruzziello, E. Emer, P. G. Cozzi, In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; P. I. Dalko, Ed.; Wiley: Weinheim, Germany, **2013**; p 729.
[13] a) P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem. Int. Ed.* **2009**, *48*, 1313; b) F. Benfatti, E. Benedetto, P. G. Cozzi, *Chem. Asian J.* **2010**, *5*, 2047.
[14] For some recent, selected books and reviews: a) *Microreactors in Organic Synthesis and Catalysis*, T. Wirth, Ed.; Wiley-VCH: Weinheim, **2008**; b) V. Hessel, *Chem. Eng. Technol*. **2009**, *32*, 1655; c) K. Geyer, T. Gustafson, P. H. Seeberger, *Synlett* **2009**, 2382; d) C. Wiles P. Watts, *Chem. Commun.* **2011**, 6512; e) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, 4583; f) S. Ceylan, L. Coutable, J. Wegner, A. Kirschning, *Chem. Eur. J.* **2011**, *17*, 1884; g) F. Benaskar, A. Ben-Abdelmoumen, N. Patil, E. Rebrov, J. Meuldijk, L. Hulshof, V. Hessel, U. Krtschil, J. Schouten, *J. Flow Chem.* **2011**, *1*, 74. h) C. Wiles, P. Watts, *Green Chem.* **2012**, *14*, 38; i) T. Tsubogu, T. Ishiwata, S. Kobayashi, *Angew. Chem. Int. Ed.* **2013**, *52*, 659.
[15] For a review discussing the merits of batch and micro flow reactors see a) R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 7502. See also: b) C. Battilocchio, B. J. Deadman, N. Nikbin, M. O. Kitching, I. R. Baxendale, S. V. Ley, *Chem. Eur. J*. **2013**, *19*, 7917 and references cited therein.
[16] For the application of flow chemistry for multistep organic synthesis see: a) S. Newton, C. F. Carter, C. M. Pearson, L. C. Alves, H. Lange, P. Thansandote, S. V. Ley, *Angew. Chem. Int. Ed.* **2014**, *53*, 4915; b) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17; c) M. Baumann, R. I. Baxendale, S. V. Ley, *Mol. Divers.* **2011**, *3*, 613. For other some recent, representative contributions see: d) M. Chen, S. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 4247 and e) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48*, 4017.
[17] Review: A. Puglisi, M. Benaglia, V. Chiroli, *Green Chem.* **2013**, *15*, 1790. For some relevant contributions, see: a) C. Ayats, A. H. Henseler, M. A. Pericàs, *ChemSusChem* **2012**, *5*, 320-325; b) O. Bortolini, L. Caciolli, A. Cavazzini, V. Costa, R. Greco, A. Massi, L. Pasti, *Green Chem.* **2012**, *14*, 992-1000; c) X. Fan, S. Sayalero, M. Pericas, *Adv. Synth. Catal.* **2012**, *354*, 2971-2976; d) O. Bortolini, A. Cavazzini, P. Giovannini, R. Greco, N. Marchetti, A. Massi, L. Pasti, *Chem. Eur. J.* **2013**, *19*, 7802-7808; e) S. B. Otvos, I. M. Mandity, F. Fulop, *ChemSusChem* **2012**, *5*, 266-269; f) Y. Arakawa, H. Wennemers, *ChemSusChem* **2013**, *6*, 242-245.
[18] For very recent contributions with chiral organocatalysts not included in the review see: a) R. Martín-Rapún, S. Sayaleroa, M. A. Pericàs, *Green Chem.* **2013**, *15*, 3295; b) L. Osorio-Planes, C. Rodriguez-Escrich, M. A. Pericas, *Chem. Eur. J.* **2014**, *20*, 2367; c) for a recent monolithic achiral organocatalytic system see: O. Bortolini, A. Cavazzini, P. Dambruoso, P. P. Giovannini, L. Caciolli, A. Massi, S. Pacifico, D. Ragno, *Green Chem.* **2013**, *15*, 2981. For a pioneer work in the field see: A. M. Hafez, A. E. Taggi, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 10853.

[19] a) A. Puglisi, M. Benaglia, R. Annunziata, V. Chiroli, R. Porta, A. Gervasini, *J. Org. Chem.* **2013**, *78*, 11326; b) S. Guizzettl, M. Benaglia, J. S. Siegel, *Chem. Commun.* **2012,** *48*, 3188; c) M. Benaglia, G. Celentano, M. Cinquini, A. Puglisi, F. Cozzi, *Adv. Synth. Catal.* **2002**, *344*, 149.
[20] a) A. Gualandi, P. Canestrari, E. Emer, P. G. Cozzi, *Adv. Synth. Cat.* **2014**, *342*, 528, b) A. Gualandi, M. Emma, J. Giacoboni, L. Mengozzi, P. G. Cozzi, *Synlett* **2013**, *24*, 449; c) A. Gualandi, D. Petruzziello, E. Emer, P. G. Cozzi, *Chem. Comm.* **2012**, *48*, 3614; d) A. Gualandi, E. Emer, M. G. Capdevila, P. G. Cozzi, *Angew. Chem. Int. Ed.* **2011**, *50*, 7842. For a reaction of **1** on a supported MacMillan Catalyst, see: e) A. M. P. Salvo, F. Giacalone, F. Noto, M. Gruttadauria, *ChemPlusChem* **2014**, DOI: 10.1002/cplu.201400030: in this work lower enantioselectivities were observed with the supported catalyst.
[21] For organocatalyzed reactions via substrate-iminium activation under continuous flow conditions see: a) V. Chiroli, M. Benaglia, F. Cozzi, A. Puglisi, R. Annunziata, G. Celentano, *Org. Lett.* **2013**, *15,* 3590; b) R. Porta, M. Benaglia, V. Chiroli, F. Coccia, A. Puglisi, *Isr. J. Chem.* **2014,** *54*, 381; c) V. Chiroli, M. Benaglia, A. Puglisi, R. Porta, R. P. Jumde, A. Mandoli, *Green Chem.* **2014,** *16*, 2798.
[22] Studies on the recyclability of the immobilized catalysts in batch processes are ongoing in our group.
[23] The higher e.e.'s obtained in some reactions with supported catalysts, compared to the homogenous catalyst, are a not common phenomenon, that requires additional studies. It should be noted that higher enantioselectivities were observed both in batch and in flow (see Table 1). In addition, silica-based catalysts behaved somehow differently from polystyrene-anchored catalysts, thus pointing at an important role played by the nature and the morphology of the solid support.
[24] Concentration of the cation was chosen in order to have approximately a local 1:1 cation:catalyst ratio in the reactor, and to secure a total solubility of the electrophile in the solvent mixture.
[25] Overall TOF was calculated for the reaction of Scheme 3, according the conditions of entry 8, Table 2: after 72 hours operation, reactor **R2** afforded 6 mmol of product, for a TON of 57 (compared to TON of 2.2 after 16 hours of the supported catalyst in batch (Table 1).
[26] Studies are underway to further optimize the experimental protocol, for example by recycling the unreacted electrophilic reagent (**1-3**)**.** For example, after 1h reaction, the product at the way-out of the reactor was collected at 0 °C in an ice bath and extracted with hexanes. To the aqueous acetonitrile phase, containing the unreacted carbocation, fresh aldehyde was added and the mixture was employed in a new reaction, affording the expected alkylated product, although in lower yield, thus demonstrating the possibility to recycle the unreacted alkylating reagent in excess.
[27] The present heterogenized chiral catalyst represents one of the very few cases where the immobilization of the catalyst not only did not lead to any decrease in the ability to stereocontrol the reaction, but it improved the stereochemical efficiency of the catalytic species.
[28] With silica-based reactor **R1** lower enantioselectivities were obtained: with a flow rate of 5.4 mL/h the product was obtained in 75% e.e and 2090 h^{-1} productivity (see Supporting Information for further details).
[29] a) J. E. Bello, J. G. Millar, *Tetrahedron: Asymmetry*, **2013**, *24*, 822; b) S. Li, S. Liang, W. Tan, Z. Xu, T. Ye, T. *Tetrahedron,* **2009,** *65*, 2695; c) D. Enders, T. Schußeler, *Tetrahedron Letters*, **2002**, *43*, 3467; d) Y. Shirai, M. Seki, K. Mori, *Eur. J. Org. Chem.* **1999**, 3139; e) P. Wipf, Y. Kim, P. J. Fritch, *J. Org. Chem*, **1993**, *58*, 7195.
[30] See ref. [19a] and references cited therein.
[31] For a recent application of a stereoselective arylation in an organocatalytic synthesis of anti-inflammatory drugs, see: J. S. Harvey, S. P. Simonovich, C. R. Jamison, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 13782.

Entry for the Table of Contents (Please choose one layout)
Layout 2:

FULL PAPER



Organocatalyzed α–alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate was performed under continuous flow conditions; by optimizing the experimental set-up, excellent enantioselectivities, in some cases even better than in the flask process (up to 95% e.e. at 25 °C) and high productivity (more than 3800 h^{-1}) were obtained, thus showing that a metal-free catalytic reactor may efficiently work and continuously produce enantiomerically enriched compounds.

Riccardo Porta, Maurizio Benaglia Alessandra Puglisi, Alessandro Mandoli, Andrea Gualandi, and Pier Giorgio Cozzi**

Page No.

A catalytic reactor for organocatalyzed enantioselective continuous flow alkylation of aldehydes