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A Catalytic Reactor for the Organocatalyzed Enantioselective Continuous Flow Alkylation of Aldehydes

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

The use of immobilized metal-free catalysts offers the unique possibility to develop sustainable processes in flow mode. The challenging intermolecular organocatalyzed enantioselective alkylation of aldehydes was performed for the first time under continuous flow conditions. By using a packed-bed reactor filled with readily available supported enantiopure imidazolidinone, different aldehydes were treated 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 those obtained in the flask process (up to 95% *ee* at 25 °C), and high productivity (more than 3800 h^{-1}) were obtained, which thus shows that a catalytic reactor may continuously produce enantiomerically enriched compounds. Treatment of the alkylated products with Raney-nickel furnished enantiomerically enriched α-methyl derivatives, key intermediates for active pharmaceutical ingredients and natural products.

Introduction

Chiral, nonracemic, 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 method 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 has been 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 extended this chemistry to an intermolecular version.[9]

On the other hand, stereoselective intermolecular α-alkylation of carbonyl derivatives was successfully developed by MacMillan and co-workers by exploiting innovative concepts in which traditional aminocatalysis is combined with the generation of radical intermediates by so-called SOMO catalysis[10] and photoredox catalysis.[11] Additionally, novel synthetic α-alkylation methodologies have been developed by using S_N1-type reactions,[12] in which carbocations of sufficient stability generated in situ from alcohols or stable carbenium ions are employed to perform the 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 difficulties associated with recovering the chiral promoter. An organocatalytic α-alkylation strategy for possible large-scale applications needs to be implemented by 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 parameter 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] Herein, we describe the design of a catalytic reactor to perform a challenging transformation such as the enantioselective α-alkylation of aldehydes under continuous flow conditions for the first time.[18]

Following our previous studies on the heterogenization of chiral imidazolidinones,[19] we decided to explore the use of solid-supported MacMillan catalysts in this challenging transformation[20] and to perform the organocatalytic enantioselec-

[a] *Dr. R. Porta, Prof. Dr. M. Benaglia, Dr. A. Puglisi*
Dipartimento di Chimica, Università degli Studi di Milano
Via Golgi 19, 20133 Milano (Italy)
E-mail: maurizio.benaglia@unimi.it

[b] *Dr. A. Gualandi, Prof. P. G. Cozzi*
Dipartimento di Chimica "G. Ciamician",
ALMA MATER STUDIORUM Università di Bologna
Via Selmi, 2, 40126 Bologna (Italy)
E-mail: piergiorgio.cozzi@unibo.it

[c] *Dr. A. Mandoli*
Dipartimento di Chimica e Chimica Industriale
Università di Pisa
Via Risorgimento, 35, 56126 Pisa (Italy)

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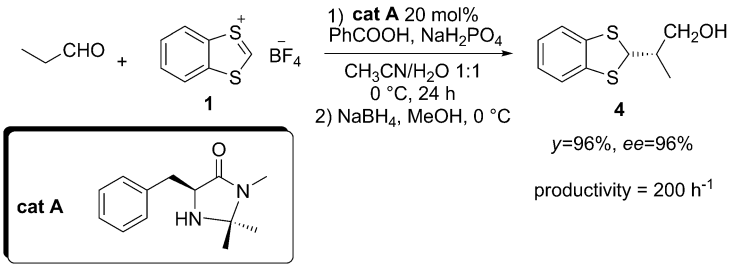
tive alkylation under continuous flow conditions.[21] High enantioselectivities (up to 95% *ee*) and productivity much higher than that observed in the flask reaction were obtained.

Results and Discussion

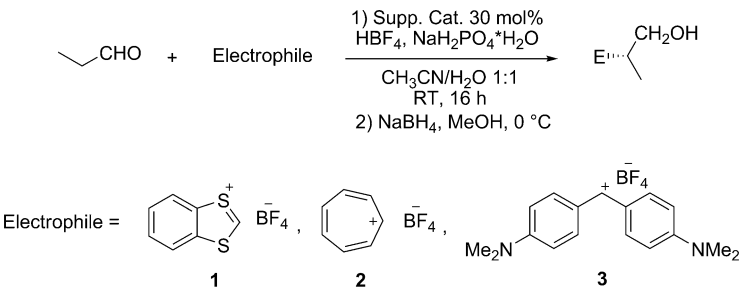
For preliminary experiments, we selected the reaction between propionaldehyde and commercially available 1,3-benzodithiolylium tetrafluoroborate (**1**, Scheme 1). In the presence of unsupported catalyst **A** (20 mol%), the product was isolated after reduction of the carbonyl group to the corresponding alcohol in almost quantitative yield with 96% *ee* after 24 h of reaction at 0 °C.[20d]



Scheme 1. Organocatalytic α-alkylation of propionaldehyde.

On the basis of our experience in the field, we decided to synthesize both silica-supported and polymer-supported enantiomerically pure imidazolidinones, prepared by starting from commercially available, relatively inexpensive (*S*)-tyrosine (Figure 1).[19] Silica-supported catalyst **B** was synthesized by grafting a trimethoxysilylimidazolidinone 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] (for experimental details, see the Supporting Information).

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



Scheme 2. Batch reactions between propionaldehyde and various electrophiles.

The reaction of propionaldehyde with cation **1** was performed at 25 °C for 16 h in the presence of the tetrafluoroborate salt of silica-supported catalyst **B** (30 mol%, Table 1). The product was obtained in good yield with 90% *ee*, and the productivity (160 h^{-1}) was 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]

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

Entry	Catalyst	Electrophile	Yield [%][a]	*ee*[b] [%]	Productivity[c] [h^{-1}]	TON[d]
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 yield after chromatography. [b] Enantiomeric excess was determined by HPLC on a chiral stationary phase (see the Supporting Information). [c] Productivity = (mmol product) × (mmol catalyst)$^{-1}$ × time^{-1} × 1000; see Ref. [18c]. [d] Turnover number (TON) = (mmol product) × (mmol catalyst)$^{-1}$.

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% *ee* with catalysts **B** and **C**, respectively. Noteworthy, the reaction performed under homogeneous conditions gave a lower stereoselectivity (for the reaction of butanal with **2** only 22% *ee* was observed, see Ref. [13b]). That held true also for the alkylation of propionaldehyde with bis[4-(dimethylamino)phenyl]methylium tetrafluoroborate (**3**), which afforded the α-alkylated aldehyde with 95% *ee* by using sup-

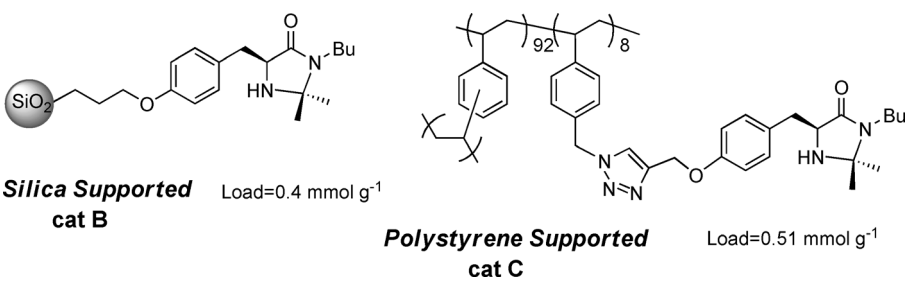
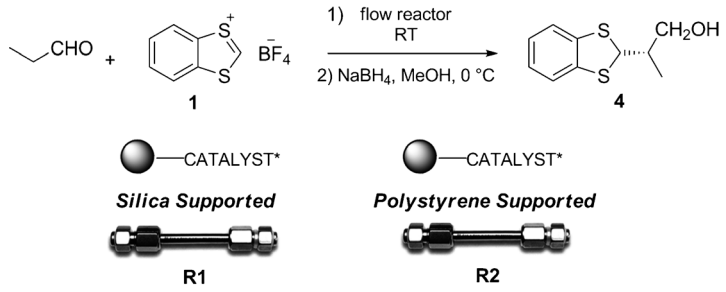


Figure 1. Solid-supported chiral imidazolidinones employed in organocatalytic continuous flow reactors.

ported catalyst **C** (with unsupported MacMillan imidazolidinone, the product was isolated with 65% *ee* at 4 °C, see Ref. [13b]).[23]

On the basis of these very encouraging results, we then investigated the application of the heterogeneous systems to enantioselective transformations under continuous flow conditions. Two different packed-bed reactors, **R1** and **R2**, were prepared by filling two stainless-steel HPLC columns ($\varnothing_i = 0.4$ cm, length = 6 cm, $V = 0.75$ mL) with catalysts **B** and **C**, respectively (Scheme 3). The continuous flow system was constituted of



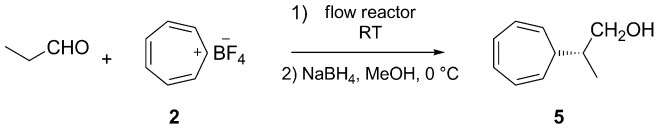
Scheme 3. Continuous flow alkylation performed in packed-bed reactors **R1** and **R2**.

a syringe pump that fed the reagents continuously into the reactor (for details relative to the setup of the flow experiments, see the Supporting Information).

The continuous flow stereoselective alkylation of propionaldehyde with **1** was performed in both reactors **R1** and **R2** (Table 2). The silica-supported catalyst in reactor **R1** was able to continuously produce compound **4** with 82% *ee* and a productivity of approximately 1000 h^{-1}. Better results came from the use of packed-bed reactor **R2**, which was filled with 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 that were constantly higher than 93% *ee* and up to 95% *ee* at room temperature, and the results were totally comparable to those obtained under homogeneous conditions at 0 °C.[24]

Noteworthy, the reactor guarantees high stereoselectivities at different flow rates; the excellent behavior of **R2** also at high flow rates allowed the productivity of the process to be improved to 810 h^{-1} (95% *ee*, four times higher than batch reaction)[25] and up to 1190 h^{-1} (87% *ee*; Table 2, entry 9).[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; **5** was produced with 86% *ee* (Table 3, entry 1 vs. 79% *ee* in batch; Table 1, entry 3). Polymer-anchored catalyst **C** in **R2** in this case was also better performing and afforded product **5** constantly with 94% *ee* and with a remarkable productivity of 3830 h^{-1} (Table 3, entry 5). Notably, the process in flow performed clearly better than in the flask reaction in terms of both productivity and enantioselectivity, which further highlights the unique feature of the present flow reactor system.[27]



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

Table 2. Continuous flow alkylation of propionaldehyde with 1,3-benzodithiolylium tetrafluoroborate (**1**).[a]

Entry	Reactor	Conc. **1** [mol L^{-1}]	Flow rate [mL h^{-1}]	Res. time[b] [min]	Yield[c] [%]	*ee*[d] [%]	Productivity[e] [h^{-1}]
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	0.7	53	41	94	270
5	**R2**	0.11	1.3	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

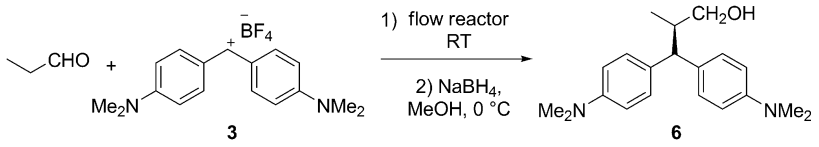
[a] Reaction conditions: **1** (1 equiv.), aldehyde (3 equiv.), NaH_2PO_4 (1 equiv.), CH_3CN/H_2O (7:3). [b] Residence time = (void volume)/(flow rate); void volume was determined experimentally by picnometry: $V_{R1} = 0.59$ mL, $V_{R2} = 0.46$ mL. [c] Yield of isolated product. [d] The *ee* was determined by HPLC on a chiral stationary phase (see the Supporting Information). [e] Productivity = (mmol product) × (mmol catalyst)$^{-1}$ × time^{-1} × 1000; see Ref. [18c].

Table 3. Continuous flow alkylation of propionaldehyde with tropylium tetrafluoroborate.[a]

Entry	Reactor	Flow rate [mL h^{-1}]	Res. time[b] [min]	Yield[c] [%]	*ee*[d] [%]	Productivity[e] [h^{-1}]
1	**R1**	4.8	6	18	86	1150
2	**R2**	0.7	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 equiv.), aldehyde (3 equiv.), NaH_2PO_4 (1 equiv.), CH_3CN/H_2O (7:3), **R1** (0.2 M), **R2** (0.15 M). [b] Residence time = (void volume)/(flow rate); void volume was determined experimentally by picnometry: $V_{R1} = 0.59$ mL, $V_{R2} = 0.46$ mL. [c] Yield of isolated product. [d] The *ee* was determined by HPLC on a chiral stationary phase (see the Supporting Information). [e] Productivity = (mmol product) × (mmol catalyst)$^{-1}$ × time^{-1} × 1000; see Ref. [18c].

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



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

Both reductive and oxidative removal of the 1,3-benzodithiol moiety was possible;[20a–d] in particular, treatment of the alkylated products with Raney-nickel furnished enantiomerically enriched α-methyl derivatives, which are key intermediates for the production of active pharmaceutical ingredients and natural products (Figure 2). For these reasons, further stereoselective alkylations were performed on selected aldehydes to afford intermediates for important synthetic applications.

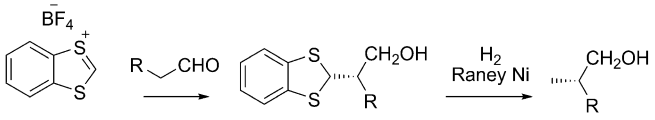
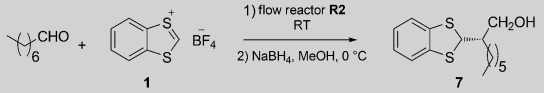


Figure 2. Reductive removal of the benzodithiol moiety.

For example, the continuous flow alkylation of octanal with 1,3-benzodithiolylium tetrafluoroborate in **R2** afforded, after $NaBH_4$ reduction, expected alcohol **7** with 94% *ee* (Table 4, entry 1). The productivity was further improved up to 600 h^{-1} while maintaining high enantioselectivity (90%; Table 4, entry 2). Product **7** could be converted into (*S*)-2-methyloctanol, a key intermediate for the preparation of natural products[29a–d] and antitumor antibiotic compounds.[29e]

Table 4. Continuous flow alkylation of octanal in **R2**.[a]



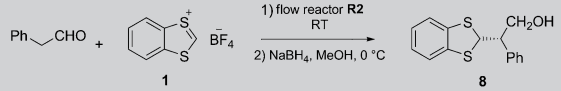
Entry	Flow rate [mL h^{-1}]	Res. time[b] [min]	Yieldv [%]	*ee*[d] [%]	Productivity[e] [h^{-1}]
1	1.5	24	31	94	470
2	5.4	7	9	90	600

[a] Reaction conditions: **1** (0.11 M), octanal (0.33 M), NaH_2PO_4 (0.11 M), CH_3CN/H_2O (7:3). [b] Residence time = (void volume)/(flow rate). [c] Yield of isolated product after chromatography. [d] The *ee* was determined by HPLC on a chiral stationary phase (see the Supporting Information). [e] Productivity = (mmol product) × (mmol catalyst)$^{-1}$ × time^{-1} × 1000; see Ref. [18c].

Similarly, the reaction of phenylacetaldehyde with **1** performed in reactor **R2** afforded product **8** with 90% *ee* with even higher productivity, up to almost 1000 h^{-1} (Table 5).

The reaction product could easily be transformed into (*S*)-2-phenylpropan-1-ol, a precursor for bisabolanes, which are anti-inflammatory, antiviral, and antimycobacterial 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]

Table 5. Continuous flow alkylation of phenylacetaldehyde in **R2**.[a]



Entry	Flow rate [mL h^{-1}]	Res. time[b] [min]	Yield[c] [%]	*ee*[d] [%]	Productivity[e] [h^{-1}]
1	1.5	24	29	90	440
2	5.4	7	18	90	970

[a] Reaction conditions: **1** (0.11 M), phenylacetaldehyde (0.33 M), NaH_2PO_4 (0.11 M), CH_3CN/H_2O (7:3). [b] Residence time = (void volume)/(flow rate). [c] Yield of isolated product after chromatography. [d] The *ee* was determined by HPLC on a chiral stationary phase (see the Supporting Information). [e] Productivity = (mmol product) × (mmol catalyst)$^{-1}$ × time^{-1} × 1000; see Ref. [18c].

Conclusions

The challenging intermolecular organocatalyzed enantioselective α-alkylation of aldehydes 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 treated with three distinct cationic electrophiles. High enantioselectivities and productivities 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 with enantioselectivities that were higher than those obtained for procedures performed under homogeneous conditions with an unsupported catalyst. Noteworthy, the same catalytic reactor was used to perform the continuous alkylation of propionaldehyde with three different electrophiles, for a total of more than 100 h on stream, and the expected products were always afforded with excellent enantioselectivities, often higher than 90%.

The present methodology paves the road to the 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 the successful use of enabling technologies in modern organic synthesis.

Experimental Section

General methods

Dry solvents were purchased and stored under an atmosphere of nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) by using silica gel 60 F 254 precoated glass plates (0.25 mm thickness) and visualized by using UV light. Flash chromatography was performed on silica gel (230–400 mesh). ^{1}H NMR spectra were recorded with spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300). ^{13}C NMR spectra were recorded with 300 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz with complete proton decoupling. High-resolution magic-angle spinning (HRMAS) experiments were performed with a Bruker Avance 500 spectrometer operating at 500.13 MHz (^{1}H) and at 125.62 MHz (^{13}C). The HRMAS ^{1}H and ^{13}C spectra were recorded with a 4 mm Bruker ^{1}H/^{13}C HRMAS gradient probe at a temperature of 330 K by using standard Bruker software sequences. The samples were previously swollen in [D_7]DMF 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 through NOE takes place because 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 an Agilent 1200 series HPLC. Solid-supported catalysts were isolated by centrifugation by using MPW Med. Instruments, Laboratory Centrifuge MPW-260. Reagents mixtures were fed to continuous flow reactors by 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 purification. 1,3-Benzodithiolylium tetrafluoroborate (technical grade 97%), tropylium tetrafluoroborate (technical grade 97%), and (5*S*)-(−)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone monohydrochloride (technical grade 97%) were purchased from Sigma–Aldrich. Propionaldehyde was purified by distillation over calcium chloride under a 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, surface area: 162 m^2g^{-1}).

Syntheses

Synthesis of Supported Catalysts

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

General procedure for batch reactions

Heterogeneous catalyst **B** or **C** (0.042 mmol) was charged in a vial and suspended in CH_3CN/H_2O (1:1 *v/v*, 2 mL); tetrafluoroboric acid (0.042 mmol) was added, and the mixture was stirred for 10 min. Then, the electrophile (0.14 mmol), $NaH_2PO_4{\cdot}H_2O$ (0.14 mmol), and propanal (0.42 mmol) were added, and the mixture was stirred for 16 h at room temperature. After the desired reaction time, the crude mixture was diluted with Et_2O (3 mL), and the solid catalyst was filtered and washed with Et_2O (2 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (2× 1 mL). The combined organic layer was dried with Na_2SO_4 and diluted with MeOH (3 mL). $NaBH_4$ (0.6 mmol) was slowly added at 0 °C to the crude mixture, and the resulting mixture was stirred for 1 h at 0 °C. The reaction was quenched with H_2O (3 mL) and EtOAc (5 mL) was added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (2×5 mL). The organic layers were recovered, washed with brine (5 mL), and dried with Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was 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 CH_3CN/H_2O (7:3 *v/v*, 4 mL) at a flow rate of 2 mL h^{-1}. Subsequently, the reactor was fed with 0.2 M tetrafluoroboric acid in CH_3CN/H_2O (7:3 *v/v*, 3 mL) at a flow rate of 2 mL h^{-1}, and it was then washed with CH_3CN/H_2O (7:3 *v/v*, 3 mL) at the same flow rate. The void volume (V_{R1}) of **R1** was measured experimentally by picnometry: V_{R1} = 0.46 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 CH_3CN/H_2O (7:3 *v/v*, 4 mL) at a flow rate of 2 mL h^{-1}. Subsequently, the reactor was fed with 0.146 M tetrafluoroboric acid in CH_3CN/H_2O (7:3 *v/v*, 3 mL) at a flow rate of 2 mL h^{-1}, and it was then washed with CH_3CN/H_2O (7:3 *v/v*, 3 mL) at the same flow rate. The void volume (V_{R1}) of **R2** was measured experimentally by picnometry: V_{R2} = 0.59 mL.

Alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate

A syringe pump was charged with a CH_3CN/H_2O (7:3 *v/v*, 2 mL) solution of reagents (**R1**: 0.15 M 1,3-benzodithiolylium tetrafluoroborate, 0.45 M aldehyde, 0.15 M $NaH_2PO_4{\cdot}H_2O$; **R2**: 0.11 M 1,3-benzodithiolylium tetrafluoroborate, 0.33 M aldehyde, 0.11 M $NaH_2PO_4{\cdot}H_2O$) and was fed to the reactor at the indicated flow rate at room temperature. Subsequently, the flow reactor was washed with the eluent mixture (CH_3CN/H_2O = 7:3 *v/v*, 2 mL) at the same flow rate. The product at the exit of the reactor was collected at 0 °C in an ice bath and was diluted with Et_2O (3 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (2× 1 mL). The combined organic layer was dried with Na_2SO_4 and diluted with MeOH (3 mL). The crude mixture was cooled to 0 °C and $NaBH_4$ (1 mmol) was slowly added. After 1 h stirring at 0 °C, the reaction was quenched with H_2O (3 mL) and EtOAc (5 mL) was added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (2×5 mL). The organic layers were recovered, washed with brine (5 mL), and dried with Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was 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 a CH_3CN/H_2O (7:3 *v/v*, 2 mL) solution of reagents (**R1**: 0.2 M electrophile, 0.6 M aldehyde, 0.2 M $NaH_2PO_4{\cdot}H_2O$; **R2**: 0.15 M electrophile, 0.45 M aldehyde, 0.15 M $NaH_2PO_4{\cdot}H_2O$) and was fed to the reactor at the indicated flow rate at room temperature. Subsequently, the flow reactor was washed with the eluent mixture (CH_3CN/H_2O = 7:3 *v/v*, 2 mL) at the same flow rate. The product at the exit of the reactor was collected at 0 °C in an ice bath and diluted with Et_2O (3 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (2×1 mL). The combined organic layer was dried with Na_2SO_4 and diluted with MeOH (3 mL). The crude mixture was cooled to 0 °C and $NaBH_4$ (1 mmol) was slowly added. After 1 h stirring at 0 °C, the reaction was quenched with H_2O (3 mL) and EtOAc (5 mL) was added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (2×5 mL). The organic layers were recovered, washed with brine (5 mL), and dried with Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was dried under high vacuum. The crude product was purified by flash column chromatography on silica gel.

Products of aldehydes alkylation

Compounds **4–8** are known (for details see the Supporting Information).

Compound **4** was purified by flash column chromatography (silica gel, hexane/EtOAc = 9:1) to afford a colorless oil. TLC: R_f = 0.27 (hexane/EtOAc = 9:1, stained blue with phosphomolybdic 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 ppm (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 ppm. HPLC (Daicel Chiralcel OD-H column, hexane/*i*PrOH = 9:1, flow rate = 0.8 mL min^{-1}, λ = 230 nm): t_R = 8.9 (minor), 10.5 min (major).

Compound **5** was purified by flash column chromatography (silica gel, hexane/EtOAc = 8:2) to afford a colorless oil. TLC: R_f = 0.36 (hexane/EtOAc = 8:2, stained blue with phosphomolybdic 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 (br s, 1H), 1.11 ppm (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 ppm. HPLC (Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 95:5, flow rate = 0.8 mL min^{-1}, λ = 254 nm): t_R = 9.8 (minor), 11.0 min (major).

Compound **6** was purified by flash column chromatography (silica gel, 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 ppm (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 ppm. HPLC (Daicel Chiralcel OD-H column, hexane/*i*PrOH = 9:1, flow rate = 0.8 mL min^{-1}, λ = 254 nm): t_R = 18.4 (major), 31.7 min (minor).

Compound **7** was purified by flash column chromatography (silica gel, hexane/EtOAc = 9:1) to afford a colorless oil. TLC: R_f = 0.28 (hexane/EtOAc = 9:1, stained blue with phosphomolybdic 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 ppm (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 ppm. HPLC (Daicel Chiralcel OD-H column, hexane/*i*PrOH = 95:5, flow rate = 0.8 mL min^{-1}, λ = 230 nm): t_R = 10.7 (minor), 15.1 min (major).

Compound **8** was purified by flash column chromatography (silica gel, hexane/EtOAc = 9:1) to afford a colorless oil. TLC: R_f = 0.40 (hexane/EtOAc = 8:2, stained blue with phosphomolybdic 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 ppm (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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 ppm. HPLC (Daicel Chiralcel OD-H column, hexane/*i*PrOH = 9:1, flow rate = 0.8 mL min^{-1}, λ = 230 nm): t_R = 19.0 (minor), 23.5 min (major).

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Keywords: alkylation · catalytic reactor · continuous flow · organocatalysis · stereoselectivity

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[24] Concentration of the cation was chosen to have approximately a local 1:1 cation/catalyst ratio in the reactor and to secure total solubility of the electrophile in the solvent mixture.
[25] Overall turnover frequency was calculated for the reaction of Scheme 3 according to the conditions of entry 8, Table 2: after 72 h operation, reactor **R2** afforded 6 mmol of product, for a turnover number of 57 [compared to a turnover number of 2.2 after 16 h for 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 (i.e., **1**–**3**). For example, after 1 h reaction, the product at the exit of the reactor was collected at 0 °C in an ice bath and extracted with hexanes. Fresh aldehyde was added to the aqueous acetonitrile phase containing the unreacted carbocation, and the mixture was employed in a new reaction, which afforded the expected alkylated product, although in lower yield; this thus demonstrates the possibility to recycle the unreacted alkylating reagent that is in excess amount.
[27] The present heterogenized chiral catalyst represents one of the very few cases in which immobilization of the catalyst did not lead to any decrease in the ability to control the stereochemical outcome of the reaction, and 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^{-1}, the product was obtained with 75% *ee* and 2090 h^{-1} productivity (see the Supporting Information).
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R. Porta, M. Benaglia, A. Puglisi, A. Mandoli, A. Gualandi, P. G. Cozzi**

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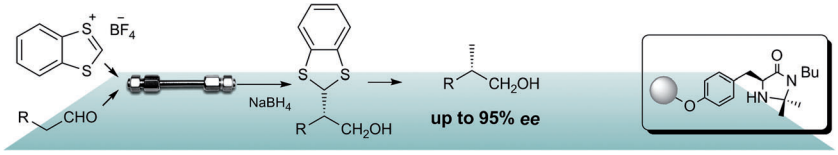
A Catalytic Reactor for the Organocatalyzed Enantioselective Continuous Flow Alkylation of Aldehydes



Flowing enantioselectivity: The organocatalyzed α-alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate is performed under continuous flow conditions; excellent enantioselectivities (up to 95% *ee*) and high productivity ($>3800\ h^{-1}$) are obtained. Thus, a metal-free catalytic reactor can continuously produce enantiomerically enriched compounds.