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# Fast and Enantioselective Production of 1-Aryl-1-propanols through a Single Pass, Continuous Flow Process

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Abstract: A functional polymer 4, obtained by reaction of (R)-2-(1-piperazinyl)-1,1,2-triphenylethanol with a Merrifield resin, has been loaded in a packed bed reactor and used as catalyst for the continuous enantioselective production of 1-arylpropanols by ethylation of aromatic aldehydes. The high catalytic activity depicted by 4 allows the complete conversion of the substrates with the use of stoichiometric reagent ratios and unprecedently short residence times (down to 2.8 min). In practice, a single-pass operation can be used for all the studied aldehydes, and productions of up to 13.0 mol/gh are recorded. The sequential operation of the flow system for the uninterrupted synthesis of a small library of enantiopure 1-arylpropanols is also reported.

**Keywords:** amino alcohols; asymmetric catalysis; continuous flow process; diethylzinc additions; heterogeneous catalysis; ligand immobilization

# Introduction

Increasing concerns on feedstocks and energy supply, and on the sustainable management of the environment, have led in recent years to a great interest in the development of chemical processes involving a rational use of raw materials, the minimization of energy consumption, and the avoidance of residue generation for the sake of more sustainable production schemes. In this framework, catalysis represents a very attractive approach. In particular, enantioselective catalysis with heterogeneized chiral ligands has contributed to these goals due to its inherent advantages over comparable homogeneous catalysts: workup avoidance and easy recovery and reuse of the catalytic species.<sup>[1]</sup> Moreover, an additional interest in this type of catalysis is the possibility of performing the chemical reactions in a continuous mode in a flow reactor.<sup>[2]</sup> In this manner, reaction and catalyst separation are carried out simultaneously.

In spite of these potential advantages, flow-through processes have in general been restricted to the production scale, and this can be probably ascribed to the need for *engineering* effort for the optimization of the different parameters controlling conversion and enantioselectivity in this kind of processes.

The amino alcohol-promoted, catalytic enantioselective alkylation of aldehydes with diethylzinc is a mechanistically well understood process that, for its experimental simplicity, has been considered as a suitable benchmark for this approach. Thus, since the pioneering work by Itsuno and Fréchet,<sup>[3]</sup> some additional polymer-supported amino alcohols have been introduced for the enantioselective ethylation of aldehydes.<sup>[4]</sup> Although very high enantioselectivities have been achieved in some instances, the primary goal of developing a reasonably fast process has remained elusive, and the reported catalysts and experimental set-ups involve very long residence times and multiple pass operation for the achievement of reasonable conversion levels.<sup>[5]</sup>

In recent years, we have been engaged in the design of functional amino alcohols that could be immobilized onto organic or inorganic supports with minimal perturbation of the molecular regions where the catalytic activity resides.<sup>[6]</sup> As a fruit of this effort, we have been able to develop polymer-supported amino alcohol ligands **1–4** that control the enantioselective alkylation and arylation of aldehydes without any significant decrease in reaction rate or in enantio-selectivity with respect to their homogeneous counterparts.<sup>[6a-e]</sup>

Polymer-supported amino alcohol **4**, derived from easily accessible enantiopure triphenylethylene oxide through a ring-opening strategy,<sup>[7]</sup> stands out as the





Scheme 1. Synthesis of polystyrene-supported ligand 4.

most readily available (Scheme 1), catalytically active and enantioselective among these functional resins.<sup>[8]</sup>

In this paper, we describe the design of a new continuous flow system based on functional resin **4**, and its optimization for the fast, single-pass ethylation of a diverse family of aromatic aldehydes with very high conversion and enantioselectivity.



The continuous flow system used for the present study (Figure 1) consists of a vertical, fritted and jacketed Omnifit glass column which contains the supported catalyst. This column is a low pressure liquid chromatography column with a 10 mm bore size and a 70 mm maximal bed height (5.5 mL), completely filled with the swollen resin. During operation, the reagents are pumped in through the bottom end of the column using two different piston pumps (one for aldehyde substrate/toluene and one for diethylzinc/toluene) in order to minimize the amount of background, non-enantioselective addition reaction before contact with the supported catalyst. A supply of dry toluene allows for swelling of the resin at the beginning of the process and washing of the channel system at the end of the reaction. Isothermal operation is secured by circulation of a cooling fluid at the desired operation temperature through the column jacket.

When the reactor is completely filled with the swollen functional resin, isothermal piston flow operates. Under these conditions, conversion is only determined by the feed composition, the reaction temperature, and the mean residence time of the reactants in the reactor. The design equation for an isothermal piston flow reactor in a stationary state is:

$$\frac{W}{F_{A0}} = \int_{0}^{X_A} \frac{dX_A}{-r_A}$$

where W is the volume occupied by the catalyst,  $F_{A0}$  is the flow of the limiting reagent,  $X_A$  is the conversion and  $r_A$  is the rate of the reaction. For a given amount of catalyst (corresponding to a totally filled column), complete conversion can be achieved through the ma-





Figure 1. Continuous flow system used in the addition of Et<sub>2</sub>Zn to aldehydes.

nipulation of two parameters: flow rate and temperature. If enantioselectivity has to be simultaneously optimized, variation in temperature becomes severely limited so that, in practice, only the flow rate allows ample variation. It is thus evident that only a highly active catalyst can allow the simultaneous achievement of high levels of conversion and enantioselectivity in short residence times.

As an initial stage in this study, these parameters were optimized for the addition of diethylzinc to benzaldehyde (Table 1).

In all continuous flow experiments, the catalytic resin was first swollen with dry toluene for one hour. Next, the reactions were carried out by passing through the column equal flows of a 0.9 M solution of benzaldehyde and a 1.1 M solution of diethylzinc, both in toluene. Aliquots of the efluent at different operation times were withdrawn to determine conversion and enantioselectivity. Experiment 1, performed with a catalyst loading of 1.1 g, showed that rather high conversions (*ca.* 90%) could be achieved at 0°C at a flow rate of 0.24 mLmin<sup>-1</sup>. On the other hand, when the reaction temperature was lowered to -10°C, conversion showed a significant decrease. For experiment 2, we loaded the column with 1.5 g of functionalized resin (corresponding to 0.975 mmol of

**Table 1.** Simultaneous optimization of flow rate and reaction temperature for the single-pass, continuous enantioselective ethylation of benzaldehyde with resin **4**.

PhCHO/toluene (0.9 M)		+ Diethylzinc/toluene (1.1 M)			► OH Ph (R)	
Experiment	<i>t</i> [h]	<i>Т</i> [°С]	Resin 4 [g]	Flow rate <sup>[a]</sup> [mLmin <sup>-1</sup> ]	Conv. <sup>[b]</sup> [%]	ee <sup>[b]</sup> [%]
1	1 2 3 4 5 6 7 8	$     \begin{array}{r}       0 \\       0 \\       0 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\       -10 \\ $	1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1	0.24 0.24 0.24 0.24 0.24 0.24 0.24 0.24	- 91 88 85 76 70 66	- 94 95 95 94 95 94
2	1 2 3 4 5	0 0 0 0 0 0	1.5 1.5 1.5 1.5 1.5	0.24 0.24 0.24 0.24 0.24 0.24 0.24	88 97 97 96 95	93 94 94 94 94 94
3	1 2 3 4 5 6	10 10 10 10 10 10	1.5 1.5 1.5 1.5 1.5 1.5	0.24 0.24 0.28 0.288 0.288 0.288	92 98 98 94 95 94	93 93 93 93 93 93 92

<sup>[a]</sup> Total flow rate (0.12 mLmin<sup>-1</sup> for each reagent).

<sup>[b]</sup> Determined by GC with a Cyclodex- $\beta$  column; (S)-1phenylpropanol is the major isomer. chiral ligand). This is the maximum amount of dry resin that can be swollen in the employed experimental set-up without provoking a flow collapse. With this increased catalyst amount, and by working at 0°C, very high conversions (95–97%) were achieved with a constant enantioselectivity (94% ee). In order to improve the production of our system and to reach complete conversions, experiment 3 was carried out at 10°C. Gratifyingly enough, the steady state of the system was reached in ca. 1 hour, and (S)-1-phenylpropanol was obtained with essentially complete conversion (98%) and 93% enantioselectivity. As shown in the last three entries in Table 1, an increase in the total flow rate to 0.288 mLmin<sup>-1</sup> did not exhibit any benefit. Therefore, the optimal conditions for the continuous flow addition of diethylzinc to benzaldehyde in the employed experimental set-up were 10°C, 1.5 g of resin **4** and a flow rate of 0.24 mLmin<sup>-1</sup>  $(0.12 \text{ mLmin}^{-1} \text{ of benzaldehyde solution})$ . This flow rate involves a residence time of the reagents within the catalyst bed of only 9.8 min.<sup>[9]</sup> For comparison purposes, the same level of conversion is achieved under stirred, batch conditions in 1.5 h with 4 mol% of the same polymer-supported catalyst.<sup>[6e]</sup>

With the experience gained in the optimization of the system for the case of benzaldehyde, we were interested in examining the behaviour of a diverse family of aromatic aldehydes in the continuous flow process. In order to obtain comparative data, the selected aldehydes were first tested under stirred batch conditions using 6 mol% of resin **4** in toluene (Table 2).

 Table 2. Batch catalytic enantioselective ethylation of aldehydes 5a-f.

		ОН
СН	O Et <sub>2</sub> Zn	
s	<b>4</b> (6 mol%) Toluene, 10 °C, 4 h	s
5a – f	,	6a – f

Substrate	Conv. <sup>[a]</sup> [%]	Select. <sup>[a]</sup> [%]	ee <sup>[a]</sup> [%]
benzaldehyde (5a)	99	>99	93
2-fluorobenzaldehyde ( <b>5b</b> )	99	99	91
4-fluorobenzaldehyde (5c)	87	98	92
2-(trifluoromethyl)benzalde-	71	76	78
hyde ( <b>5d</b> )			
4-(trifluoromethyl)benzalde-	98	99	90
hyde ( <b>5e</b> )			
4-cyanobenzaldehyde ( <b>5f</b> )	>99	>99	89

<sup>[a]</sup> Determined by GC with a Cyclodex- $\beta$  column. The only by-product was the corresponding benzyl alcohol, and the configuration of the major product enantiomer was (*S*).

Table 3. Continuous flow reactions with different substrates.<sup>[a]</sup>



Entry	Substrate	Flow Rate <sup>[b]</sup> [mLmin <sup>-1</sup> ]	Res. Time [min]	Т [°С]	Conv. <sup>[c]</sup> [%]	Select. <sup>[c]</sup> [%]	ee <sup>[c]</sup> [%]
1	benzaldehyde (5a)	0.24	9.8	10	99	98	93
2	2-fluorobenzaldehyde (5b)	0.24	9.8	10	95	>99	87
3	4-fluorobenzaldehyde (5c)	0.24	9.8	10	93	>99	93
4	2-(trifluoromethyl)benzaldehyde (5d)	0.24	9.8	10	87	87	84
5	2-(trifluoromethyl)benzaldehyde (5d)	0.24	9.8	20	95	86	82
6	4-(trifluoromethyl)benzaldehyde (5e)	0.24	9.8	10	99	98	89
7	4-cyanobenzaldehyde (5f)	0.72	2.8	10	>99	>99	87

<sup>[a]</sup> The employed toluene solutions were 0.9 M in aldehyde and 1.1 M in  $Et_2Zn$ . A loading of 1.5 g of the functionalized resin **4** was used in each case.

<sup>[b]</sup> Total flow rate (half from each reagent).

<sup>[c]</sup> Conversion, selectivity and enantiomeric excess were determined by GC with a Cyclodex- $\beta$  column. The only by-product was the corresponding benzyl alcohol, and the configuration of the major product enantiomer was (*S*).

Next, experiments were performed to determine the optimal flow rate and temperature conditions for each aldehyde in the continuous flow process. These conditions were then used to carry out a preparative experiment for each substrate, the output flow containing the reaction product being collected in every case for 3 h (Table 3). In the case of benzaldehyde (5a), and using a flow rate of  $0.24 \text{ mLmin}^{-1}$ , the system has a production of 4.4 mmol/h per gram of resin 4, allowing the preparation of 2.61 g of pure (S)-1-phenylpropanol in a 3 h run. Especially significant is the result obtained with 2-(trifluoromethyl)benzaldehyde 5d (entries 4 and 5 in Table 3) since we could increase the conversion by more than 20%, the ee by 6% and the selectivity by 10% with respect to the batch process.

It is evident from the comparison of the results in Table 2 and Table 3 that the continuous process and the batch process lead to practically identical results in terms of chemical selectivity (addition *vs.* reduction) and enantioselectivity except for the case of 2-(trifluoromethyl)benzaldehyde, where the continuous process leads to much better results. With respect to reaction times, in turn, the continuous process is much faster, allowing in some cases a 24-fold reduction of the reaction time. Thus, for the highly reactive 4-cyanobenzaldehyde (**5f**), the flow rate could be increased up to  $0.72 \text{ mLmin}^{-1}$ . Under these conditions, the residence time was reduced to only 2.8 min and the production of the system was 13.0 mmol/h per gram of resin **4**. Besides these unprecedented short

reaction times for the considered chemistry, the continuous flow conditions reported here completely suppress the mechanical deterioration of the resin beads that unavoidably takes place under stirring in batch conditions, thus shortening the useful life-time of the polymer-supported catalyst.

It is worth noting that, since the exploratory study in Table 1 was carried out with toluene solutions 0.9M in benzaldehyde and 1.1M in Et<sub>2</sub>Zn, the substrates in Table 3 were also tested using solutions of the same concentrations for homogeneity reasons. However, it is evident that the use of a larger excess of Et<sub>2</sub>Zn would lead to increased conversions or, conversely, could allow increased flow rates. To test this hypothesis, we repeated the ethylation of the less reactive 2-fluorobenzaldehyde (5b) by using a 0.5 M solution of the aldehyde and a 1.1 M solution of diethylzinc at the same flow rate and temperature as in Table 3. Gratifyingly, we observed a complete conversion (>99%), alcohol **6b** being obtained with an *ee* of 89%. In the same manner, we were also able to increase the flow up to 0.72 mLmin<sup>-1</sup> without any drop in the results. Thus, even for less reactive aldehydes the residence time can be decreased to 2.8 min (i.e.; the production increased to 7.4 mmol/gh) at the cost of a higher diethylzinc consumption.

Finally, we also wanted to test the possibility of using the developed flow system for the consecutive alkylation of different substrates, since this could be particularly important for the automatic synthesis of small or medium sized libraries of enantiopure 1-aryl-

Table 4. Consecutive additions of  $Et_2Zn$  to several aldehydes  $s^{[a]}$ 

Substrate	<i>t</i> [h]	Conv. <sup>[b]</sup> [%]	Select <sup>[b]</sup> [%]	ee <sup>[b]</sup> [%]
benzaldehyde (5a)	1	>99	>99	92
• • • /	2	>99	>99	92
2-fluorobenzaldehyde (5b)	3	>99	>99	87
	4	>99	99	86
4-fluorobenzaldehyde (5c)	5	88	>99	93
	6	85	>99	92

<sup>[a]</sup> The employed toluene solutions were 0.9M in aldehyde and 1.1M in Et<sub>2</sub>Zn. A loading of 1.5 g of the functionalized resin 4 was used. The combined flow rate was 0.24 mLmin<sup>-1</sup>, and the reaction temperature 10°C. The resin was washed with toluene before adding the next aldehyde.

<sup>[b]</sup> Conversion, selectivity and enantiomeric excess were determined by GC with a Cyclodex-β column. The only byproduct was the corresponding benzyl alcohol, and the configuration of the major product enantiomer was (S).

propanols (6). In practice, we used the experimental set-up in three consecutive reactions using three different substrates. The results of this experiment have been collected in Table 4. As can readily be seen, by simply washing the functional resin with toluene after the desired amount of a particular aldehyde has been passed through, the next aldehyde can be converted to the corresponding 1-arylpropanol with complete chemical selectivity and levels of enantiocontrol identical to those observed for the individual experiments in Table 3.

# Conclusions

In summary, the use of resin **4** has allowed the development of a most practical continuous flow system for the fast, enantioselective alkylation of aldehydes. Due to the simple design and the very reduced set of parameters parameters controlling conversion and enantioselectivity it can be easily optimized for any individual substrate.

In spite of the drawbacks usually ascribed to polymeric beads with respect to monolithic resins because of uncontrolled fluid dynamics,<sup>[2a]</sup> resin **4** has led to the (by far) fastest continuous process ever reported for the enantioselective ethylation of aldehydes under flow conditions. This very high catalytic activity, which allows complete conversion under single pass operation at reasonably high flow rates has permitted the sequential operation of the flow system for the uninterrupted synthesis of a small library of enantiopure 1-arylpropanols. Studies on the integration of the flow reactor with more advanced robotic systems and application of resin **4** to different enantioselective processes are now underway in our laboratories.

# **Experimental Section**

# **Continuous Flow System Description and Details of the Reaction Procedure**

The continuous flow system (see Figure 1) was set up around a vertical fritted and jacket-thermostated Omnifit glass column (10 mm of bore size and 70 mm of maximum bed height) with a volume of 5.5 mL, which was loaded with the functional resin 4. HPLC connectors allowed the column to be connected to two Ismatec piston pumps using 1/16 in hard wall PTFE tubing. The two reagents and dry toluene were kept in three independent bottles with connector caps with valves for an easy and inert connection to the tubing. Two additional connectors, also with valves, allow for washing of the channels with toluene and swelling of the resin at the beginning of the process. All the solutions were prepared under a dry inert atmosphere in a glove-box using bottles with valves. During operation, nitrogen balloons were used to equalize pressure through the whole system. The reagent solutions (0.9M or 0.5M in aldehyde and 1.1M in  $Et_2Zn$ ) were pumped through the column with identical flows and the crude was collected through the upper end of the reactor in a round-bottom flask under N<sub>2</sub>. Aliquots or the crude were quenched by addition of saturated aqueous NH<sub>4</sub>Cl. The aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the organic phases combined, dried and concentrated under vacuum. The results were determined by gas chromatography (see Supporting Information).

#### General Procedure for the Addition of Diethylzinc to Aldehydes under Batch Conditions using Resin 4 as Catalyst

A suspension of the polymer bound catalyst **4** (6 mol%) in toluene (0.13 mL) was smoothly stirred 30 min under N<sub>2</sub> at room temperature to swell the polymer. The corresponding swollen resin was cooled to 10 °C and a solution of diethylzinc (0.25 mL, 0.27 mmol) was added. After 20 min, the aldehyde (**5a-f**) (0.125 mmol) was added dropwise, and the resulting mixture was kept under smooth stirring for 4 h. The reaction was then quenched by the addition of saturated NH<sub>4</sub>Cl solution (2 mL). The resin was removed by filtration, the aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×2 mL) and the combined organic phases were dried and concentrated under vacuum. Conversion, selectivity and enantiomeric excesses were determined from the crude mixture by GC. Conditions of analyses and retention times of the (*R*)and (*S*)- isomers are given in the Supporting Information.

### **Supporting Information**

General experimental details. Characterization of 6a-6f, copies of <sup>13</sup>C and <sup>1</sup>H NMR spectra of 6a-6f are given in the Supporting Information.

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- [9] Residence time of the reaction was estimated by pumping a fluorescent solution of "Coumarin 6" through the column loaded with previously swollen resin 4, and using a standard UV lamp as detector ( $\lambda = 365$  nm).

932