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Polystyrene-Supported (2*S*)-(−)-3-*exo*-Piperazinoisoborneol: An Efficient Catalyst for the Batch and Continuous Flow Production of Enantiopure Alcohols

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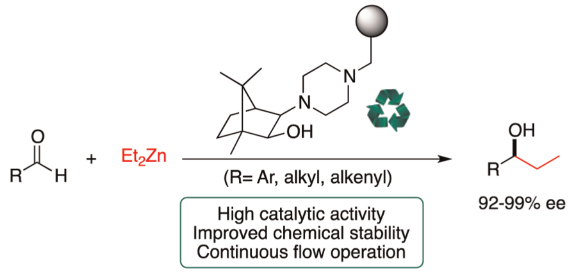
ABSTRACT



A polystyrene-supported analog (PS-PIB) of 3-*exo*-morpholinoisoborneol (MIB), designed for increased chemical stability, has been synthesized and used as a ligand in the asymmetric alkylation of aldehydes with Et_2Zn. The supported ligand turned out to be highly active and enantioselective for a broad scope of substrates (92−99% ee), allowing repeated recycling. A single-pass, continuous flow process implemented with PS-PIB shows only a marginal decrease in conversion after 30 h of operation.

The ligand-accelerated, catalytic enantioselective addition of diorganozinc reagents to aldehydes represents one of the most powerful methods for the production of enantiopure secondary alcohols with a highly predictable configuration.[1] Ligands for these reactions belonging to very different structural types have been synthesized over the past two decades; among them, β-amino alcohols have gained the most widespread use and acceptance. In recent times, as sustainability issues have gained importance in the practice of organic synthesis, the interest in homogeneous ligands has progressively shifted toward catalytic species immobilized on a variety of supports (polymers, inorganic solids, hybrid materials, and nanoparticles),[2] which present additional advantages of simple separation, recovery and reuse of the catalyst, and the possibility of use under continuous flow conditions.[3]

One of the major drawbacks associated with the use of polymer-supported catalysts is a decrease in catalytic activity with respect to the homogeneous case. However,

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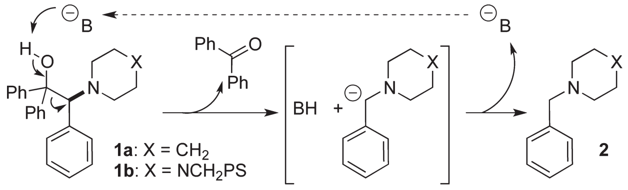
high catalytic activities and enantioselectivities can be achieved if the homogeneous catalyst is supported in such a way that the catalytic site is not perturbed by the polymer backbone.[2d−f,4] In the application of this principle, we reported some years ago an immobilized analog of (*R*)-2-piperidino-1,1,2-triphenylethanol **1a**[5] (resin **1b**), which, to the best of our knowledge, had no precedents in terms of activity and enantioselectivity as an heterogeneous catalyst for the addition of diethylzinc to aldehydes (2 mol %, 4 h at 0 °C, 100% conversion and 95% ee).[3,4b] Despite the impressive results obtained with this immobilized ligand, we realized that it had a limited lifetime that hampered its application in continuous flow devices operating for long periods of time.[3] Gel phase NMR analysis of altered resins showed the presence of 4-benzylpiperazinyl moieties supported on the polymer. These resins (**2b**, X = N−CH_2−PS) proved catalytically active, albeit through a nonenantioselective pathway.[6]

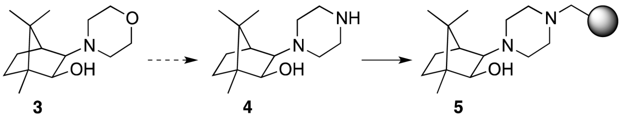
According to previous observations with related amino alcohols[4a,7] and to control experiments with resin **1b**, the amino-substituted resin originates from a base-catalyzed fragmentation of the C−C bond in the *β*-amino alcohol moiety. This largely overlooked fragmentation process (Scheme 1) must be favored by substituents stabilizing the α-amino carbanion primary product, and we reasoned that amino alcohols lacking such substituents in their structures should present greatly enhanced stability in front of bases.

Scheme 1. Base-Catalyzed Fragmentation of **1**



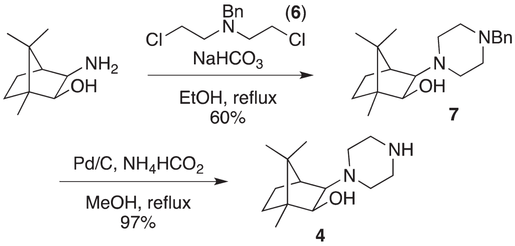
3-*exo*-Morpholinoisoborneol (MIB, **3**), an efficient mediator in diorganylzinc additions to aldehydes,[8] fulfills this requirement, and we accordingly postulated that a supported version of MIB would exhibit an extended lifespan. To allow immobilization without perturbation of the catalytic site, we decided to synthesize the closely related 3-*exo*-piperidinoisoborneol (PIB, **4**) featuring a suitably placed nitrogen atom for anchoring (Scheme 2).

Scheme 2. MIB Structural Modification To Allow Anchoring on a Solid Support through a Remote Position



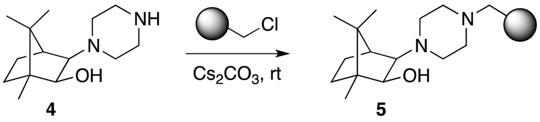
The piperazine ring was built on (2*S*)-(−)-3-*exo*-aminoisoborneol[9] with bis(2-chloroethyl)amine[10] (**6**). After hydrogenolysis of the benzyl group, **4** was obtained in almost quantitative yield (Scheme 3).

Scheme 3. Synthesis of the Ready-to-Anchor Ligand **4**



Immobilization of PIB to Merrifield resins with different levels of functionalization was carried out in a straightforward manner by shaking a mixture of **4**, the Merrifield resin, and cesium carbonate in DMF[2e] (Table 1).

Table 1. Anchoring of Ligand **4** to Merrifield Resins



	f_0[a]	time (h)	f[b]	f_{max}[c]	yield[11] (%)
5a	1.3	24	0.85	1.03	83
5b	0.53	96	0.38	0.48	79

[a] f_0 = mmol of Cl/g of resin (initial substitution level). [b] f = mmol of ligand/g of resin (calculated by elemental analysis of nitrogen). [c] f_{max} = maximum ligand substitution level (mmol of ligand/g of resin).[11]

The functional resins **5** were then tested in the addition of Et_2Zn to benzaldehyde. Amino alcohol **7**, a homogeneous analog, was also tested for comparison purposes (Table 2, entry 1) and exactly replicated the performance of MIB.[8] Interestingly, enantioselectivity was unaffected when

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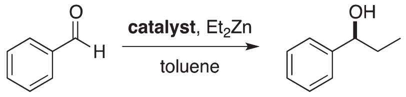
resins **5a**–**b** were used under the same experimental conditions (entries 2, 4, and 6). The catalytic activity of resin **5a** was only marginally lower than that of **7**, and full conversion could be achieved with the resin in an even shorter reaction time (4 h) by increasing the amount of resin (entries 1, 2, and 4). For comparison, an immobilized version of DAIB supported on PS through the amino group required 73 h (5 mol % loading) for 91% conversion.[2a] In the present instance, reactions could be conveniently performed at room temperature with only a minor erosion in ee (entries 3 and 5), and for higher productivity, more densely loaded **5a** worked as well as **5b** (entries 2 and 6).

Table 2. Optimization of Reaction Conditions with Resins **5a**–**b**

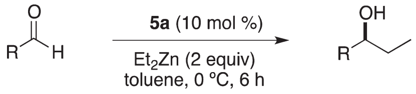


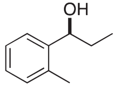
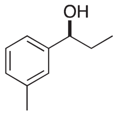
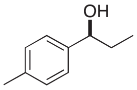
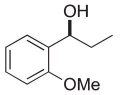
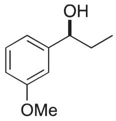
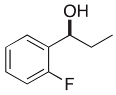
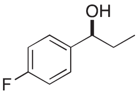
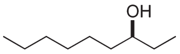
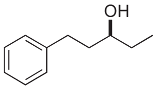
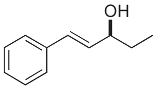
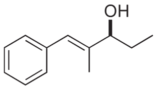
entry	catalyst	Et$_2$Zn [equiv]	catalyst loading	temp	*t* [h]	conv [%][a]	ee [%][a]
1	**7**	1.5	4%	0 °C	4.5	98	98
2	**5a**	2	10%	0 °C	4	>99	98
3	**5a**	2	10%	rt	4[b]	>99	97
4	**5a**	2	5%	0 °C	4[c]	86	98
5	**5a**	2	5%	rt	5.5	98	96
6	**5b**	2	10%	0 °C	6	98	98

[a] By GC on a β-DEX 120 column. [b] After 2.5 h, conversion was 90%. [c] After 1 h, conversion was 55%.

The optimized conditions for the enantioselective addition of diethylzinc to benzaldehyde were next applied to a representative family of aldehydes (Table 3).

Table 3. Scope of Resin **5a**



entry	product	conv (%)[a]	select (%)[a]	yield (%)	ee (%)[a]
1		>99	94	83	98
2		>99	>99	89	99
3		>99	>99	89	98
4		>99	>99	91	98
5		>99	>99	86	99
6		>99	97	91	97
7		>99	99	92	98
8		98	>99	87	92
9		82	98	80	94
10		92	76	65	93
11		64	81	50	99

[a] By GC on a β-DEX 120 column.

We were pleased to observe that both conversion and enantioselectivity were excellent with aromatic aldehydes bearing both electron-donating and -withdrawing groups (Table 3, entries 1–7) and irrespectively of congestion near the carbonyl group (entries 1, 4, and 6). For α-unsubstituted aliphatic aldehydes (entries 8–9) as well as for α,β-unsaturated aldehydes (entries 10–11) excellent results were equally recorded. It is important to remark that, to the best of our knowledge, **5** is the most enantioselective polystyrene-supported ligand for the ethylation of aldehydes reported so far.[2,4]

Once the efficiency and applicability of **5** were demonstrated, the possibility of recovery and reuse of the resin was evaluated (Table 4). For practical reasons, intercycle hydrolytic steps are best omitted, but contact of the *charged* catalytic resin with air needs to be completely avoided[12] due to the high sensitivity to oxygen of the nitrogen-chelated ethylzinc alkoxide.[13] Under these conditions, we managed to run up to five cycles without any decrease in either enantioselectivity or conversion.

With this key aspect affecting the stability of **5**·ZnEt properly clarified, we undertook its implementation in a single-pass, continuous flow process for enantioselective aldehyde ethylation. This ought to be possible in light of the very high catalytic activity exhibited by PIB resins **5**. The employed experimental setup was prepared as in previously described similar processes.[3] To our delight, direct translation of the reaction conditions used in batch mode ([PhCHO]: 0.44 M in toluene; [ZnEt$_2$]: 0.88 M in dry toluene; reaction at 0 °C) with a loading of 0.5 g of **5a** (f = 0.78 mmol·g^{-1}) resulted in very high conversion at a convenient (0.24 mL·min^{-1}) combined flow rate and

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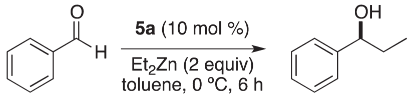
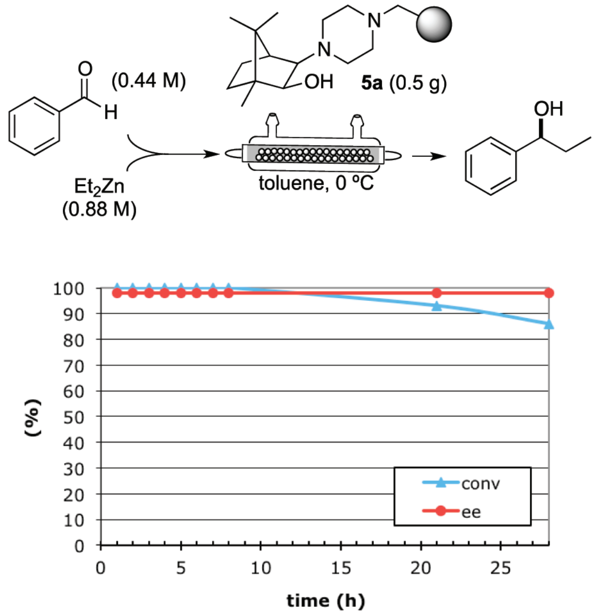
(11) Yield calculated as $100f/f_{\mathrm{max}}$. Details are given in refs 2e and 4c.
(12) See Supporting Information for practical details.
(13) Oxygen could give rise to the gradual decrease of catalytic activity, probably by generation of an inactive zinc peroxide species. See: Sosnovsky, G.; Brown, J. H. *Chem. Rev.* **1966**, *66*, 529.

Table 4. Recycling Experiments with Resin **5a**



run	conv (%)	yield (%)	ee (%)
1	>99	88	98
2	>99	92	98
3	>99	92	98
4	>99	90	98
5	98	91	98

Scheme 4. Continuous Flow Ethylation of Benzaldehyde



showed an excellent robustness of the resin, as illustrated in Scheme 4. The system could be submitted to continuous flow operation for 30 h, and it was not until after 20 h that a small drop in conversion was observed. Even more remarkably, there was no deterioration in enantioselectivity at all in the whole process.

In one single continuous flow operation 13.0 g of enantiopure alcohol were isolated, which represents a TON of 251 (referred to the product) and a productivity of 6.4 $\mathrm{mmol \cdot h^{-1} \cdot g_{resin}{}^{-1}}$. The recorded TON represents a 10-fold increase with respect to the recycling tests and a 30-fold increase compared to batch conditions. Noteworthy, this new supported ligand not only extends the lifetime of its predecessor **1a** by 1 order of magnitude under continuous flow conditions but also has a TON that is 8 times higher. The residence time under these flow conditions was 6 min, in sharp contrast with the required time for full conversion at the same temperature under batch conditions (6 h).

In conclusion, a very robust polystyrene-supported amino alcohol ligand for the highly enantioselective alkylation of aldehydes with diethylzinc has been developed. A continuous flow alkylation reaction relying on this ligand has been operated for over 30 h at consistently high conversion and enantioselectivity. Understanding the nature of chemical processes leading to catalyst decomposition and deactivation has allowed the implementation of corrective actions and paves the way for the development of catalytic systems susceptible to industrial application. In particular, the preservation of enantioselectivity with time during flow operation strongly indicates that the fragmentation of the amino alcohol moiety has been efficiently suppressed.

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Supporting Information Available. Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.