Unprecedented, fully recyclable, solid-supported reagent for the kinetic resolution of racemic amines through enantioselective *N*-acetylation†

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The high-yielding synthesis and application of the first polymer supported reagent for the kinetic resolution (KR) of amines through enantioselective acetylation is described; this new supported chiral reagent allows the KR of primary amines with excellent selectivities at room temperature; moreover, this supported approach is highly efficient as the Merrifield-supported chiral scaffold can be quantitatively recovered and recycled.

Amines bearing an adjacent enantiomerically pure chiral center are highly valuable in organic chemistry due to their extensive use as chiral auxiliaries,[1] resolving agents[2] and intermediates[3] in the synthesis of biologically important molecules. They are generally accessed by asymmetric transfer hydrogenation, hydrosilylation, hydroboration and enantioselective alkylation of prochiral imines, or by KR using enzymes.[4] In contrast, to the large variety of reagents and catalysts reported for the KR of alcohols over the last decade,[5] non-enzymatic methods designed for amines are in their infancy. In recent years, efforts have therefore been dedicated to designing non-enzymatic alternatives and substantial progress has been made.[6–8]

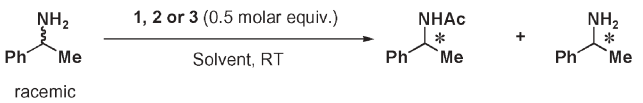
In a recent paper, we described a new and highly efficient enantioselective acetylating agent for the KR of primary amines with a unique solvent-induced reversal of stereoselectivity.[9] Derived from a chiral 1,2-disulfonamide, this new reagent led to the KR of (±)-1-phenylethylamine in an unprecedented 84% ee at room temperature using 0.5 molar equivalents of chiral **(1*S*,2*S*)-1** ($s = 30$), and up to 90% ee using 0.33 molar equivalents at −20 °C. Moreover, the chiral auxiliary could be fully recovered and reused. Further studies led to the discovery of a spectacular salt effect which would increase both the reactivity and the selectivity of **(1*S*,2*S*)-1** while inducing a complete reversal of the stereoselectivity.[10]

For the synthetic organic chemist, supported reagents[11] are highly valuable as they reduce or eliminate the need for difficult labor-intensive purification steps. Herein we wish to report our contribution in the development of the first, fully recyclable, polymer-supported enantioselective acetylating agent for the KR of amines.

In order to establish a straightforward access to a supported reagent and to survey the requisite reaction conditions, preliminary solution-phase experiments were undertaken. The enantioselective *N*-acetylation reactions were performed on (±)-1-phenylethylamine at room temperature using 0.5 molar equivalent of chiral **(1*S*,2*S*)-1** and its *N*-methylated analogue **(1*S*,2*S*)-2**.[12] As shown in Table 1, both the rate and the enantioselectivity of the acetylation were highly solvent-dependent.[13] Thus, for **(1*S*,2*S*)-1**, bearing a free sulfonamide, solvents having a low relative permittivity such as cyclohexane, dioxane, benzene, or $CHCl_3$ (entries 3–6) led to preferential acetylation of the (*R*)-enantiomer, while dipolar-aprotic solvents such as DMPU and DMF (entries 1–2) induced a reversal of the reaction stereochemistry leading to the (*S*)-enantiomer. In contrast, no reversal of stereoselectivity was observed with **(1*S*,2*S*)-2** in any of the solvents used while enantioselection increased in non-dipolar solvents, with up to 70% ee in cyclohexane and benzene (entries 2 and 4). These results combined with the fact that the methyl group was easily introduced using diazomethane, prompted us to attach the chiral reagent to the polymer-support *via* the free sulfonamide using a supported activated diazo linker.[14]

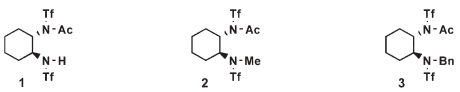
A solution-phase analogue bearing a benzyl group to mimic the resin was therefore prepared. Its synthesis was adapted from the protocol developed by Reese[15] starting from **(1*S*,2*S*)-1**. The benzyl derivative **(1*S*,2*S*)-3** was tested on (±)-1-phenylethylamine using the standard conditions (*e.g.* room temperature/0.5 molar equiv. of reagent). As expected for reagents bearing a *N*-protected sulfonamide, **(1*S*,2*S*)-3** preferentially acetylated the (*R*)-enantiomer. However, the selectivities were slightly lower than the ones observed using **(1*S*,2*S*)-2**, but compared favourably with the selectivities reached using **(1*S*,2*S*)-1**.

Table 1 Influence of the solvent on the selectivity using **1**, **2** and **3**



		ee[a] (%)		
Entry	Solvent	1	2	3
1	DMF	72 (*S*[b])	20 (*R*)	—
2	DMPU	84 (*S*)	40 (*R*)	—
3	Cyclohexane	46 (*R*)	70 (*R*)	56 (*R*)
4	Dioxane	50 (*R*)	50 (*R*)	—
5	Benzene	52 (*R*)	70 (*R*)	54 (*R*)
6	$CHCl_3$	56 (*R*)	60 (*R*)	50 (*R*)

[a] Enantiomeric excess determined by HPLC analysis using a chiral phase column. [b] Absolute configuration of the acetylated enantiomer assigned by comparison with an authentic standard.



† Electronic supplementary information (ESI) available: details of experimental procedures and characterization of synthesized compounds. See http://www.rsc.org/suppdata/cc/b5/b504200c/

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On the basis of our solution-phase study, we set out to develop a solid-phase version of our chiral acetylating agent with a benzyl-type anchorage. Polymer-supported reagent **(1*S*,2*S*)-4** (Fig. 1) was thus prepared in four steps as shown in Scheme 1; each step being monitored using IR spectroscopy (recorded using a Perkin-Elmer 2000 FT-IR directly on the resin beads). The solid-phase synthesis was initiated by treating commercially available Merrifield resin (chloromethylated polystyrene, 1% cross-linked divinylbenzene, 1.58 mmol g^{-1}) with 4-hydroxybenzaldehyde and sodium hydroxide in DMSO (90 °C),[16] to afford the benzaldehyde resin **5** ($\nu_{C=O}$ = 1695 cm^{-1}) in excellent yield (>95% determined by elemental analysis; loading = 1.39 mmol g^{-1}). Resin **5** was then treated with 1,3,5-triisopropylbenzene sulfonyl hydrazine at room temperature leading to the supported hydrazone **6** which was subsequently treated with potassium hydroxide in a MeOH/THF mixture (90 °C). The resulting supported benzyl diazonium salt **7** reacted at room temperature with (1*S*,2*S*)-*N*-acetyl-1,2-bis-trifluoromethanesulfonamidocyclohexane **(1*S*,2*S*)-1** leading to the desired supported chiral reagent **4** ($\nu_{C=O}$ = 1732 cm^{-1}). The loading of resin **4** was determined as 0.58 mmol g^{-1} by treating it with an excess of (±)-1-phenylethylamine and quantifying the recovered acetylated product. This value, also confirmed by fluorine elemental analysis, represents a 65% overall yield from readily available Merrifield resin.

With chiral-**4** in hand, we investigated its efficiency in the KR of (±)-1-phenylethylamine. The reactions were performed at room temperature in various solvents using 0.2 equivalents of supported reagent under otherwise identical conditions.‡ The results are collected in Table 2.

The first experiment in DMF was consistent with our expectation as no reversal of stereoselectivity was observed along with a very low level of selectivity (4% ee, Table 2, entry 1). In all other solvents however, the selectivities were moderate to good. In addition, except in dioxane (entry 5) where supported-**(1*S*,2*S*)-4** led to a level of selectivity comparable to the one observed when using **(1*S*,2*S*)-3**, the ee's were higher. Hence, $CHCl_3$ and benzene

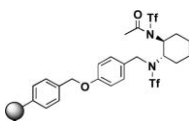
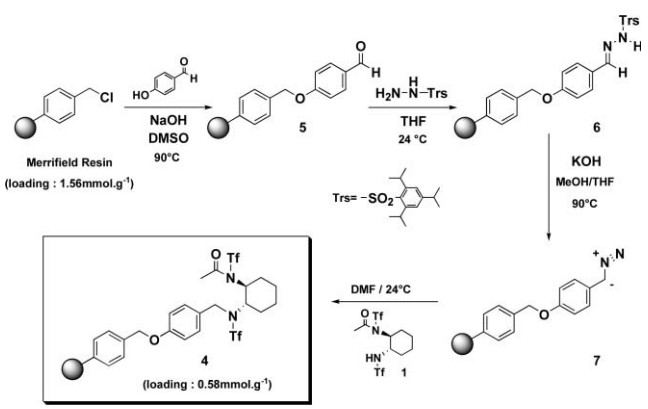
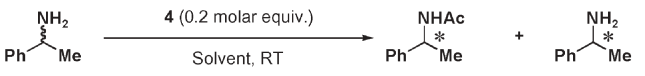


Fig. 1 **(1*S*,2*S*)-4**.



Scheme 1 Synthesis of **(1*S*,2*S*)-4**.

Table 2 Influence of the solvent on the selectivity using **4**



Entry	Chiral reagent	Solvent	ee[a] (%)
1		DMF	4 (*R*[b])
2		Cyclohexane	32 (*R*)
3		CH_2Cl_2	40 (*R*)
4		THF	46 (*R*)
5		Dioxane	48 (*R*)
6		$CHCl_3$	62 (*R*)
7		Benzene	82 (*R*) 82 (*R*[c])

4 (0.2 mol equiv. / RT)

[a] Enantiomeric excess determined by HPLC analysis using a chiral phase column. [b] Absolute configuration of the acetylated enantiomer assigned by comparison with an authentic standard. [c] Enantiomeric excess after 4 consecutive cycles.

respectively led to 62 and 82% ee (entries 6–7) while they respectively led to 50 and 54% when using **(1*S*,2*S*)-3**. Benzene was found to be the solvent of choice for the KR of (±)-1-phenylethylamine as, in this solvent system, the product was obtained in 82% ee at room temperature (s = 12.3; entry 7).[17] Moreover, these results appeared to compare favourably with those described in the literature by Fu[8] and Murakami.[6]

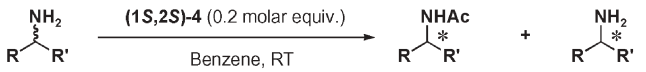
This phenomenon where the cross-linked polymer-supported version of a chiral auxiliary gives higher ee values than its solution-phase counterpart is not unique.[18] However at this stage, it is difficult to say how much of this is due to conformational constraints imposed by the cross-link environment, how much arises from other effects of the microenvironment such as modification in solvation in the polymer interior, or how much is due to the ratio between the racemic amine and the supported chiral reagent. However, we can probably rule out the latter as only 4% variation of the selectivity was previously observed when using 2 equivalents of amines instead of 3 (amine/reagent ratio of 2 vs 3 led to 86 *vs* 90% ee).[9]

Under these reaction conditions, we could achieve the stereoselective acylation of a family of racemic amines with moderate to good enantioselection. Thus, the KR of (±)-α-ethylbenzylamine (Table 3, entry 2), (±)-1-naphthylethyl amine (entry 3) and (±)-phenylalanine methylester (entry 4) were obtained with respectively 69, 78 and 70% ee.

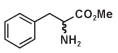
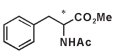
In order to investigate how many times **(1*S*,2*S*)-4** could be reused, we carried out multiple acetylation–regeneration sequences. Thus, it was observed that chiral-**4** could be reused repeatedly at least up to 4 times without any noticeable loss of selectivity (entry 7; Table 2).

In summary, we have developed the first, fully recyclable solid-supported reagent for the non-enzymatic KR of amines. The best selectivity was observed in benzene, in which **(1*S*,2*S*)-4** led to the KR of (±)-1-phenylethylamine with 82% ee using 0.2 equivalents of solid-supported chiral reagent (s = 12.3). This is a remarkable result given the fact it is obtained at room temperature. In addition, this work demonstrates that cross-linked polymer-supported chiral reagents can lead to higher ee values then their solution-phase counterparts. Ongoing efforts are focused on both enlarging the scope of **(1*S*,2*S*)-4** and developing a rational for its stereoselectivity.

Table 3 Kinetic resolution of various amines using **4**



racemic

Entry	Amine	Product	ee[a]
1			82 (s = 12.3)
2			69 (s = 6.4)
3			78 (s = 9.8)
4			70 (s = 6.7)

[a] Enantiomeric excess determined by HPLC analysis using a chiral phase column.

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Notes and references

‡ **General Procedure:** (±)-1-phenylethylamine (65 μL, 0.50 mmol) was added to an agitated solution of **(1*S*,2*S*)-4** (172 mg; 0.10 mmol) in the chosen solvent at room temperature. The mixture was agitated at the same temperature for 3 hours. The resin was then filtered, washed with MeOH and CH_2Cl_2, and the solvent removed under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (EtOAc/Hexane: 1/1) and analyzed by chiral HPLC.

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