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Tuning the Enantioselective N-Acetylation of Racemic Amines: A Spectacular Salt Effect

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Since the pioneering work of Pasteur,[1] kinetic resolution (KR)[2] has become one of the most powerful tools for the preparation of optically active compounds. Hence, during the past decade, a plethora of reagents and catalysts have been designed for the KR of alcohols through enantioselective acylation.[3] In contrast, there have been very few nonenzymatic methods developed for amines,[4,5] and significant progress has only recently been made.[6] Indeed, the design of an enantioselective acyl transfer reagent/catalyst for the resolution of amines is rendered difficult because of the easy nonselective acylation occurring through direct reaction of the amine with the achiral acyl source. Thus, the strong nucleophilicity of the amine compared to that of its corresponding alcohol requires tuning the leaving group ability of the chiral selector in order to enable chiral induction. Whereas prior to 1998, no such reagents had even been described in the literature; since that time, several quite different reagents and one catalyst have been reported that provide useful levels of enantioselection (selectivity factor $s \geq 10$).[6]

In an earlier study, we established that (1*S*,2*S*)-*N*-acetyl-1,2-bistrifluoromethanesulfonamidocyclohexane **1** could serve as a highly enantioselective acetylating agent for the KR of primary amines with a unique solvent-induced reversal of stereoselectivity (Scheme 1).[7,8] Building on these results, we developed the first example of a fully recyclable polymer-supported reagent for the KR of amines.[9] Herein, we wish to report a spectacular salt effect observed while using (1*S*,2*S*)-**1** in the KR of (±)-1-phenylethylamine, which leads to an increase in both reactivity and selectivity, along with a complete reversal of the stereoselectivity.

As salts are well-known to modify certain intrinsic parameters of solvents, such as their viscosity, their permittivity, and, more interestingly, their empirical constant of polarity, we decided to carry out a first series of experiments using the standard acetylation conditions[10] while only varying the nature of the salts (1 M solution in THF). As revealed in Table 1, an increase of the reaction rate by 3−6 times was observed with every salt examined, along with a complete reversal of stereoselectivity. LiBr (entry 2), $LiClO_4$ (entry 3), lithium trifluoromethane sulfonimide (TFSI−Li; entry 4), pyridinium salts (entry 5), ammonium salts (entries 6−11 and 14), and phosphonium salts (entries 12 and 13) all lead to preferential acetylation of the *S* enantiomer, while the *R* enantiomer was favored in neat THF (entry 1). Finally, we observed a tremendous increase in the selectivity from 42% ee ($s = 3.6$ at 50% conversion;[11] entry 1) up to 90% ee ($s = 58$ at 50% conversion; entry 14) using *n*-Oct_3NMeCl (1 M solution in THF).

This remarkable result obtained at room temperature with only 2 equiv of amine relative to the amount of chiral (1*S*,2*S*)-**1** is, to the best of our knowledge, the highest level of selectivity ever observed in this field.

Scheme 1. Kinetic Resolution of Racemic Amines using (1*S*,2*S*)-**1**

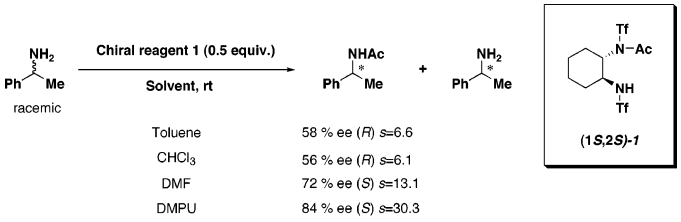
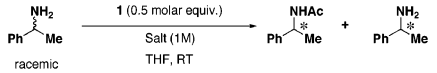


Table 1. Salt Effect on the Enantioselectivity using (1*S*,2*S*)-**1**



entry	time[a] (min)	salt (1 M)	solvent	ee[b] (%)
1	60	−	THF	42 (*R*)[c]
2	20	LiBr	THF	42 (*S*)
3	10	$LiClO_4$	THF	68 (*S*)
4	10	TFSI−Li	THF	54 (*S*)
5	10	*n*-BuPyBr	THF	68 (*S*)
6	20	*n*-Et_4NBr	THF	22 (*S*)
7	10	n-Et_4NCl	THF	74 (*S*)
8	20	*n*-Bu_4NCl	THF	82 (*S*)
9	20	*n*-Bu_4NBr	THF	88 (*S*)
10	20	*n*-Bu_4NI	THF	54 (*S*)
11	10	*n*-Bu_4NBF_4	THF	76 (*S*)
12	20	*n*-Bu_4PCl	THF	44 (*S*)
13	20	*n*-Bu_4PBr	THF	70 (*S*)
14	10	*n*-Oct_3NMeCl	THF	90 (*S*)

[a] The reaction was run until **1** disappeared, unless otherwise stated. [b] Enantiomeric excess of the acetamide determined by HPLC analysis using a chiral phase column. [c] Absolute configuration of the major enantiomer.

Interestingly, variations in the selectivity were observed depending on the nature of both the cation and the anion species. As a general trend, phosphonium and lithium salts induced selectivities lower than those of ammonium salts, whereas for a given anion (e.g., Cl^-), the selectivity appeared to increase with the lipophilicity of the cation species (entries 7, 8, and 14).

These results are in agreement with those observed previously while screening the effect of the solvents on the selectivity. In dipolar solvents, it is suggested that the attack of the amine is guided by the strong hydrogen bonding with the acidic free sulfonamide, as no reversal of stereoselectivity is observed when using the N-methylated analogue of (1*S*,2*S*)-**1**.

A survey of various solvents having a low relative permittivity, such as dioxane, CH_2Cl_2, and toluene in the presence of *n*-Oct_3-NMeCl (1 M solution in THF), revealed the same phenomenon of

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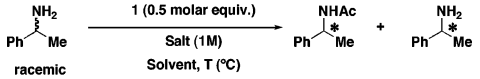
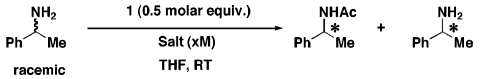
Table 2. Effect of the Solvent on the Enantioselectivity



entry	temperature (°C)	salt (1 M)	solvent	ee[a]/ee[b] (%)
1	25	*n*-Oct_3NMeCl	THF	90 (*S*)[c]/42(*R*)
2	25	*n*-Oct_3NMeCl	dioxane	72 (*S*)/50 (*R*)
3	25	*n*-Oct_3NMeCl	CH_2Cl_2	76 (*S*)/40 (*R*)
4	25	*n*-Oct_2NMeCl	Toluene	78 (*S*)/58 (*R*)
5	−20(0.5 equiv of 1)	*n*-Oct_3NMeCl	THF	94 (*S*)
6	−20(0.33 equiv of 1)	*n*-Oct_3NMeCl	THF	95 (*S*)

[a] Enantiomeric excess of the acetamide determined by HPLC analysis using a chiral phase column. [b] Enantiomeric excess observed without using a salt. [c] Absolute configuration of the major enantiomer.

Table 3. Effect of the Concentration of the Salt on the Enantioselectivity



entry	salt	concentration	salt:**1** ratio	ee[a] (%)
1	*n*-Oct_3NMeCl	1 M	25:1	90 (*S*)[b]
2	*n*-Oct_3NMeCl	0.1 M	2.5:1	80 (*S*)
3	*n*-Oct_3NMeCl	0.01 M	1:4	30 (*S*)
4	*n*-Oct_3NMeCl	0.001 M	1:40	0
5	*n*-Oct_3NMeCl	0.0001 M	1:400	26 (*R*)
6	*n*-Oct_3NMeCl	−	0	42 (*R*)

[a] Enantiomeric excess of the acetamide determined by HPLC analysis using a chiral phase column. [b] Absolute configuration of the major enantiomer.

inversion of the stereoselectivity followed by an increase of the selectivity (entries 2−4, Table 2). Optimizing the reaction conditions produced an additional increase in the enantiomeric excesses, primarily by decreasing the temperature and by increasing the amine/acetylating reagent ratio. Consistent with this expectation, by conducting the reaction at −20 °C under otherwise identical conditions, we were able to isolate the acetamide with 94% ee (s = 115 at 50% conversion; entry 5, Table 2) and up to 95% ee (s = 62 at 33% conversion; entry 6, Table 2) when using 3 instead of 2 equiv of amines versus chiral (1*S*,2*S*)-**1**.

Under these reaction conditions, we could achieve the stereoselective acylation of a family of racemic amines with good to excellent enantioselection. Thus, the KR values of (±)-1-phenylpropylamine, (±)-1-naphthylethylamine, (±)-1,2,3,4-tetrahydro-1-naphthylamine, and (±)-phenylalanine methyl ester were obtained with 90, 84, 70, and 68% ee, respectively.

Table 3 shows the effect of salt concentration on selectivity. Remarkably, concentrations as low as 0.1 M (salt:**1** ratio = 2.5:1) lead to enantiomeric excesses as high as 80% (s = 22 at 50% conversion; entry 2). Comparison with the results of the kinetic study discussed below, which was carried out under overall more dilute conditions, shows that the role of the salt is complex. The same relative salt:**1** ratio gave significantly higher selectivity under overall more dilute conditions.

Figure 1 shows kinetic profiles obtained by reaction calorimetry and relative rate constants calculated from these profiles. The overall concentrations employed in these reactions were much lower in order to keep reaction rates in the range observable by reaction calorimetry. These studies reveal that the influence of the salt on

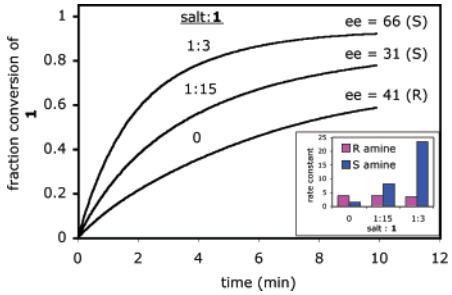


Figure 1. Fraction conversion of acetylating agent versus time for reactions carried out at room temperature using 0.04 M racemic amine, 0.015 M (1*S*,2*S*)-**1**, and *n*-Oct_3NMeCl at 0, 0.001, and 0.005 M.

selectivity may be attributed to a significant promotion of the reactivity of (1*S*,2*S*)-**1** toward the *S* enantiomer, concomitant with only moderate change in its reactivity toward the *R* enantiomer of the amine.

In summary, we have described a spectacular salt effect observed when using (*1S*,*2S*)-**1** in the KR of (±)-1-phenylethylamine, which leads to an increase in reactivity, high levels of selectivity, and a complete reversal of the stereoselectivity. Thus, by modifying the reaction conditions, we were able to isolate the acetamide with an unprecedented 94% ee at −20 °C and 50% conversion (s = 115).

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Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) With chiral **1** in hand, KR of (±)-1-phenylethylamine was achieved with unprecedented levels of enantioselectivity. Up to 84% ee (s = 30) was obtained at room temperature using 0.5 equiv of reagent and up to 90% ee using 0.33 equiv of reagent at −20 °C.
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(11) Conversion percent determined by GC analysis using an internal standard and by quantifying the isolated acetylated product after flash chromatography.

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