Enantiomeric Synthesis

Kinetic Resolution of Amines: A Highly Enantioselective and Chemoselective Acetylating Agent with a Unique Solvent-Induced Reversal of Stereoselectivity**

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Despite the development of some effective enzymatic processes,[1] racemate resolution through a nonenzymatic, enantioselective acylation pathway has become the focus of tremendous work over the past few years and remains a valuable alternative for the preparation of optically active compounds.[2] In addition, the development of new reagents capable of reacting specifically with either enantiomer by simply modifying the experimental conditions introduces a new challenge.[3]

In the early 1990s, Evans et al.[4] and Vedejs and Chen[5] reported the first examples of nonenzymatic kinetic resolution of secondary alcohols using stoichiometric amounts of chiral acylating agents that allowed the resolution of a broad family of racemic substrates with useful levels of enantioselection (selectivity factor, $s \geq 10$).[6] Soon after, Vedejs et al.,[7] Oriyama et al.,[8] Fuji and co-workers,[9] Miller et al.,[10] Ruble and Fu,[11] and Spivey et al.[12] described some of the first effective chiral acylation catalysts for the kinetic resolution of alcohols.

Amines are another important family of substrates.[13] While their kinetic resolution by enzymatic processes has been studied intensively, little attention has been given to nonenzymatic kinetic resolution. Therefore, over recent years, the design of nonenzymatic alternatives has been the focus of many research efforts, and substantial progress has been made.

In 1998, Murakami and co-workers[14] were the first to report an example of kinetic enantioselective N-acetylation using chiral 2-acetylamino-2′-diacetylamino-1,1′-binaphthyl. However, the levels of selectivity were moderate. Hence, by variation of the reaction conditions, the kinetic resolution of various amines to give products with up to 48% *ee* was achieved using 0.25 equivalents of chiral reagent at room temperature.[15]

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Atkinson and co-workers[16] also contributed to the development of a nonenzymatic process for the kinetic resolution of amines by developing an enantioselective acylating agent derived from 3-(*N*,*N*-diacylamino)quinazolin-4(3*H*)-ones (DAQs).

Recently, Ie and Fu reported the first effective nonenzymatic kinetic resolution of amines using planar-chiral 4-dimethylaminopyridine (DMAP) derivatives.[17] The stereoselective acylation of a family of racemic amines to give products with up to 91% *ee* at −78 °C (at 12.5% conversion) was achieved using 0.125 equivalents of pre-formed acylpyridinium salts derived from the chiral catalyst.[18] Building on these results, Fu and co-workers developed a catalytic system[19] that allowed the kinetic resolution of various benzylic amines with moderate to good selectivities ($11 \leq s \leq 27$). For example, the kinetic resolution of (±)-1-phenylethylamine was described to give products with 79% *ee* using 10 mol% of the chiral catalyst at −50 °C but with only 35% conversion (3.5 turnovers).[20]

Herein, we describe a new and highly enantioselective acetylating agent for the kinetic resolution of primary amines. This reagent allows, to our knowledge, the highest levels of selectivity at room temperature and 50% conversion. Moreover, it exhibits a unique solvent-induced reversal of stereoselectivity that enables us to selectively acetylate one or the other stereoisomer with the same reagent by simply changing the reaction conditions.

For the construction of our new reagent we used *trans*-1,2-diaminocyclohexane as a chiral scaffold, as it has been a very efficient core structure in many reagents and catalysts.[21] Both amino groups were converted into their corresponding trifluoromethanesulfonamide derivatives to confer good leaving-group ability to the nitrogen atoms. Monoacetylation of the bissulfonamide was then readily performed by addition of one equivalent of acetyl chloride in a 76% overall yield from commercially available (1*S*,2*S*)-diaminocyclohexane. The molecular structure was confirmed by single-crystal X-ray determination (Scheme 1).

The *N*-acetylsulfonamide can be classified as an "active ester". As expected, the *N*-acetyl-1,2-bis(trifluoromethanesulfonamide, (1*S*,2*S*)-**1**, reacted at room temperature with benzylamine to yield *N*-acetylbenzylamine in a quantitative yield.

It is noteworthy that while this product reacts with amines, it proved to be stable when dissolved in ethanol. This chemoselectivity was further demonstrated by the quantitative exclusive N-acetylation of 5-amino-1-pentanol. Moreover, this reagent proved to be insensitive to hydrolysis and could be kept on the bench top for several months without any noticeable loss of activity.

We chose to initiate our study with the reaction of reagent (1*S*,2*S*)-**1** on (±)-1-phenylethylamine. The enantioselective N-acetylations were performed using 0.5 mol equivalent of chiral (1*S*,2*S*)-**1** (unless otherwise specified). In a preliminary experiment, a good chemical yield and a promising level of selectivity were observed. Indeed, complete conversion of the starting material into the *N*-acetylated product with 58% *ee* ($s = 7$) was obtained in toluene at room temperature, as determined by high-performance liquid chromatography

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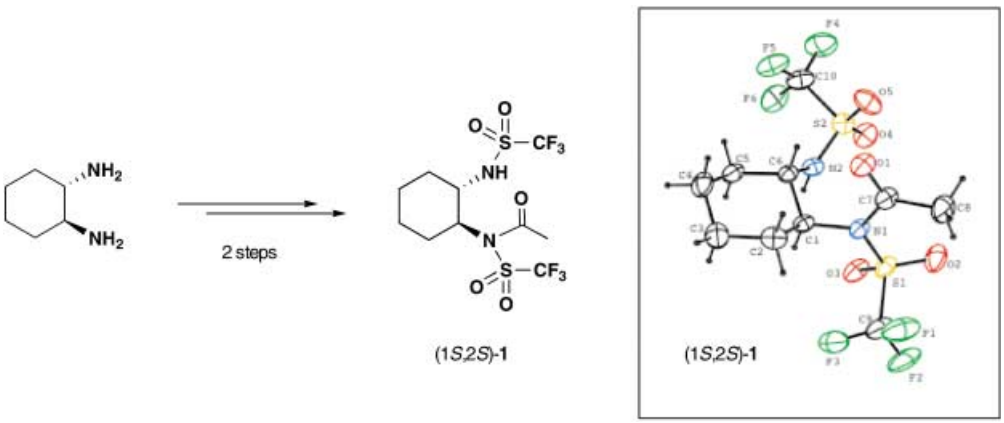
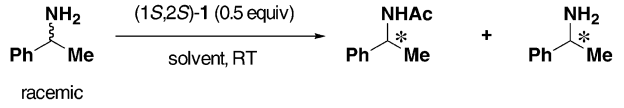


Scheme 1. Synthesis of (1*S*,2*S*)-**1** and its structure as determined by X-ray crystallographic analysis.

(HPLC) analysis using a column with a chiral stationary phase (Chiracel OD, *n*-pentane/ethanol 98/2). In addition, the chiral auxiliary was recovered in a yield of over 90% and could be reused. This result compares favorably with those described by Fu and Murakami.

A thorough investigation of this reaction was then undertaken. First, we examined the effect of the solvent on the selectivity of the reaction (Table 1). A wide-ranging study of solvents established that both the rate and the enantioselectivity of the acetylation are highly solvent-dependent; however, no correlation could be made between the reaction time and the *ee* value obtained. Hence, while three hours were needed to reach total conversion with 40% *ee* in dichloromethane (entry 6), total conversion was reached in dimethyl sulfoxide (DMSO) after one hour of stirring and the optical yield was considerably higher (60% *ee*; entry 12). It was noted that solvents having low relative permittivity such as toluene, chloroform, 1,4-dioxane, cyclohexane, THF, dichloromethane, and ethyl acetate led to preferential acetylation of the *R* enantiomer (entries 1–7), while dipolar nonprotic solvents such as DMSO, *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc), *N*-methylpyrrolidone (NMP), *N*,*N*,*N*',*N*'-tetramethylurea (TMU), hexamethylphosphoramide (HMPA), and 1,3-dimethyltetrahydro-2-pyrimidinone (DMPU) induced both a reversal of the reaction stereochemistry, thus leading to the *S* enantiomer, and a significant rise in the stereoselectivity (entries 10–18). Finally, dipolar protic solvents such as *N*-methylformamide (NMF) and methanol also induced a reversal of the stereoselectivity; however, the *ee* values were lower (entries 8 and 9).[22]

Table 1: Influence of the solvent on enantioselectivity using (1*S*,2*S*)-**1** as the acylating agent.



Entry	*t* [h][a]	Solvent	ε_t[b]	*ee* [%][c]	*s*
1	2	toluene	2.38	58 (*R*[d])	6.6
2	2	$CHCl_3$	4.81	56 (*R*)	6.1
3	2	1,4-dioxane	2.21	50 (*R*)	4.8
4	2	cyclohexane	2.02	46 (*R*)	4.2
5	3	THF	7.58	42 (*R*)	3.6
6	3	CH_2Cl_2	8.93	40 (*R*)	3.4
7	1	EtOAc	6.02	18 (*R*)	1.7
8	1	NMF	18.24	34 (*S*)	2.8
9	1	MeOH	32.66	38 (*S*)	3.2
10	1	acetone	20.56	30 (*S*)	2.4
11	1	CH_3CN	35.94	35 (*S*)	2.8
12	1	DMSO	46.45	60 (*S*)	7.2
13	3	DMF	36.71	72 (*S*)	13.1
14	3	DMAc	37.78	72 (*S*)	13.1
15	3	NMP	32.2	74 (*S*)	14.6
16	3	TMU	23.6	78 (*S*)	19.0
17	3	HMPA	29.6	84 (*S*)	30.3
18	3	DMPU	36.12	84 (*S*)	30.3

[a] The reaction was run until (1*S*,2*S*)-**1** disappeared, unless otherwise stated. [b] Relative permittivity of the pure liquid at 24°C. [c] The enantiomeric excess was determined by high-performance liquid chromatography (HPLC) analysis using a column with a chiral stationary phase. [d] The absolute configuration of the acetylated enantiomer was assigned by comparison with an authentic standard.

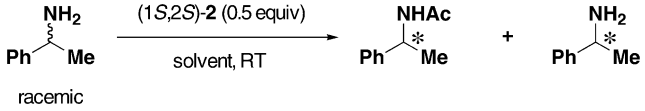
DMPU was the solvent of choice for the kinetic resolution of (±)-1-phenylethylamine, as the product was obtained in 84% *ee* in this solvent system ($s = 30$; entry 18). This is a remarkable result given that it is obtained at room temperature with only two equivalents of amine relative to the amount of chiral (1*S*,2*S*)-**1**. Moreover, to the best of our knowledge, this is the first example of a process in this field that displays a marked solvent-induced reversal of enantioselectivity.

A ^{1}H NMR study of (1*S*,2*S*)-**1** revealed a shift of the free sulfonamide NH resonance according to the nature of the solvent. Hence, in [D_8]toluene this proton signal appeared at $\delta = 4.3$ ppm, whereas in CD_2Cl_2, CD_3CN, and [D_6]DMSO, it appeared at $\delta = 5.0$, 6.7, and 9.7 ppm, respectively. This downfield shift is typical for acidic protons since their acidity is increased because of the effect of solvation in bipolar solvents.

We propose that the acetylation of the amine proceeds through two different mechanisms which depend on the polarity of the solvent. Hence, strong hydrogen bonding with the acidic sulfonamide guides the attack of the amine in bipolar solvents, while only steric interactions govern the selectivity in nonbipolar solvents. To support this hypothesis

we prepared the *N*-methylsulfonyl analogue (1*S*,2*S*)-**2** and treated it with (±)-1-phenylethylamine at room temperature employing exactly the same conditions as used for (1*S*,2*S*)-**1** (Table 2). As expected, no reversal of stereoselectivity was

Table 2: Influence of the solvent on the enantioselectivity with (1*S*,2*S*)-**2** as the acylating agent.



Entry	*t* [h][a]	Solvent	*ee* [%][b]	*ee* [%][c]
1	1	DMPU	40 (*R*[d])	84 (*S*)
2	1	DMF	20 (*R*)	72 (*S*)
3	1	DMSO	12 (*R*)	60 (*S*)
4	1	1,4-dioxane	50 (*R*)	50 (*R*)
5	1	CCl_4	60 (*R*)	50 (*R*)
6	1	toluene	64 (*R*)	58 (*R*)

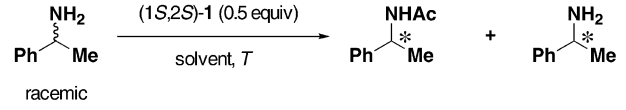
[a] The reaction was run until (1*S*,2*S*)-**2** disappeared, unless otherwise stated. [b] The enantiomeric excess was determined by HPLC analysis on a column with a chiral stationary phase. [c] The enantiomeric excess was obtained using (1S,2S)-**1**. [d] The absolute configuration of the acetylated enantiomer was assigned by comparison with an authentic standard.

observed in bipolar solvents (entries 1–3), while enantioselection increased in nonbipolar solvents (entries 5–6). Hence, we have demonstrated the key role of the free sulfonamide in bipolar–nonprotic solvents.

Next, we examined the possibility of increasing the selectivity by lowering the temperature of the reaction (Table 3). Decreasing the temperature to below 0 °C induced a slight increase in the *ee* values when carrying out the reaction in the four solvents given in Table 3, thus demonstrating that the selectivity of the reaction is also temperature-dependent.

Finally, increasing the amine/acetylating reagent ratio should, in principle, also increase the selectivity. Under otherwise identical conditions, we observed an increase in the enantioselectivity from 86 to 90% when using three equivalents of amines relative to (1*S*,2*S*)-**1** instead of two (entries 4 and 5; Table 3).

Table 3: Influence of the temperature on enantioselectivity using (1*S*,2*S*)-**1** as the acylating agent.

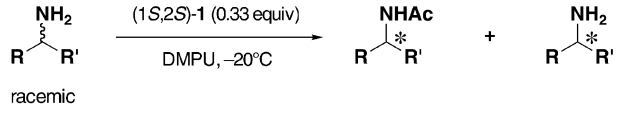


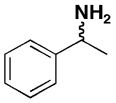
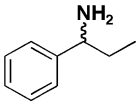
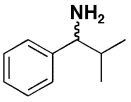
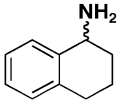
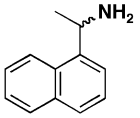
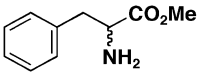
Entry	*T* [°C]	Solvent	*ee* [%][a]	*s*
1	−10	DMAc	74 (*S*[b])	14.6
2	−20	DMF	77 (*S*)	17.7
3	−20	NMP	78 (*S*)	19.0
4	−20	DMPU	86 (*S*)	36.7
5	−20	DMPU	90[c] (*S*)	29.4

[a] The enantiomeric excess was determined by HPLC analysis on a column with a chiral stationary phase. [b] The absolute configuration of the acetylated enantiomer was assigned by comparison with an authentic standard. [c] Using three equivalents of amine versus (1*S*,2*S*)-**1**.

After optimization of the reaction conditions we achieved the stereoselective acetylation of various alkyl amines with good selectivities (Table 4).

Table 4: Kinetic resolution of various amines using (1*S*,2*S*)-**1** as the acylating agent.



Entry	Amine	*ee*[a] [%]
1		90[b]
2		86
3		72
4		69
5		73
6		80

[a] The enantiomeric excess was determined by HPLC analysis using a chiral phase column. [b] All reactions led to 33% yield after 24 h at −20 °C.

Increasing the steric hindrance of the alkyl group of the alkyl amine from a methyl group (entry 1) to an isopropyl group (entry 3) resulted in a decrease in the enantioselectivity from 90 to 72% *ee*. Acetylation of the more rigid (±)-1,2,3,4-tetrahydro-1-naphthylamine gave a product with 69% *ee* (entry 4). Surprisingly, increasing the bulkiness of the aromatic unit did not result in an increase in the selectivity; acetylation of (±)-1-naphthylethylamine afforded a product with 73% *ee* (entry 5). Finally, (±)-phenylalanine methyl ester proved to be a good substrate, with the corresponding acetamide derivative being obtained with 80% *ee* (entry 6).

In summary, we have demonstrated that *N*-acetyl-1,2-bis(trifluoromethanesulfonamide), (1*S*,2*S*)-**1**, can serve as an highly effective reagent for the kinetic resolution of amines to give products with an unprecedented 84% *ee* at room temperature using two equivalents of amine and up to 90% *ee* using three equivalents of amine at −20 °C. In addition, a unique solvent-induced reversal of stereoselectivity was observed, which can be rationalized on the basis of two different mechanistic pathways depending on the polarity of the solvent. Ongoing efforts are focused on both improving the reaction enantioselectivity by tuning chiral reagent (1*S*,2*S*)-**1** and increasing its scope.

Experimental Section

1: Freshly distilled acetyl chloride (1.88 mL, 2.64 mmol) was added dropwise by syringe to a stirred solution of 1,2-bis(trifluoromethanesulfonamido)cyclohexane (Aldrich; 1.00 g, 2.64 mmol), and triethylamine (5.50 mL, 3.96 mmol) in diethyl ether (20 mL) at −20 °C. The mixture was stirred for 3 h at 0 °C, after which time the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (ethyl acetate/*n*-hexane 1/9) to afford the desired product as a white solid in 85 % yield. m.p. 111 °C; $[\alpha]_D^{20} = +17.46°$ ($c = 1.5$; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.10–1.60 (m, 3H), 1.70–2.00 (m, 3H), 2.05–2.35 (m, 1H), 2.35–2.60 (m, 1H), 2.52 (s, 3H), 3.60–4.05 (m, 1H), 4.10–4.60 (m, 1H), 5.04 ppm (d, $J = 10$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.4$, 25.5, 26.8, 29.1, 35.4, 54.5, 66.9, 119.4, 119.5, 170.0 ppm; FT-IR (CsI): $\tilde{\nu} = 3296$, 3221, 2947, 2868, 1737, 1716, 1456, 1385, 1233, 1200, 1131, 1071, 1016, 971, 942, 918, 896, 737, 611, 532 cm^{-1}; MS (IC/NH_3): *m*/*z* 438 $[M+NH_4]^+$.

General procedure for enantioselective acetylation of secondary alkyl amines: The racemic amine (0.36 mmol) was added dropwise by syringe to a stirred solution of chiral acetylating agent (0.12 mmol) in the chosen solvent/temperature system. The mixture was stirred at the same temperature and the reaction was followed by thin layer chromatography analysis (ethyl acetate/*n*-hexane 2/8). Once complete conversion of the reagent was observed, the solvent was removed by distillation under reduced pressure. The resulting residue was then purified by flash chromatography on silica gel (ethyl acetate/*n*-hexane 1/1) and analyzed by high-performance liquid chromatography (HPLC) on a chiral stationary phase.

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