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Amplification of the enantiomeric excess of a compound in kinetic resolution by a racemic reagent

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Dedicated to the memory of Pierre Potier

Abstract—The possibility of amplifying the small ee of a enantioimpure substance using a *racemic reagent* in kinetic resolution is discussed. A kinetic treatment of this problem along with some experimental proofs of the concept is presented. Simulation on kinetic resolution of small ee substrate by a *racemic reagent* showed an important enantioenrichment in the substrate ee, sometimes reaching close to absolute ee. Experiments of kinetic resolution of an amine of a small ee by a *racemic acylating reagent* gave a substantial amplification in ee of the amine. The possible transformation of an undetectable low ee in substrate to a detectable higher ee by using a suitable *racemic reagent* is also briefly discussed with help of calculations. The usefulness of asymmetric amplification by a racemic reagent is considered in the context of the biomolecular homochirality on earth.

1. Introduction

The amplification of enantiomeric excesses (ees) has generated a lot of interest for practical reasons and also in relation with the problem of molecular homochirality in living systems.[1–5] The current theories are based on the generation of compounds of small enantiomeric excesses followed by an asymmetric amplification. There are various hypotheses for the initial formation of optical activity, for example, the photolysis by circularly polarized light,[6,7] a spontaneous resolution,[8] or arising as a consequence of parity violation.[2,9] In a racemic prebiotic world, the subsequent asymmetric amplification of ee must be envisaged by processes avoiding the use of chiral auxiliaries. Asymmetric autocatalytic reactions have been proposed to be of prebiotic significancy,[10,11] but it is only recently that a unique chemical model has been discovered by Soai et al. in the organozinc addition on some pyrimidyl aldehydes.[12,13] Amongst the various processes of asymmetric amplification without the help of chiral auxiliaries one can notice the duplication method of Horeau–Langenbeck,[14,15] the crystallization,[8] or chromatography in achiral conditions.[16–18] Another class of asymmetric amplification is the use of a compound of low ee as catalyst to produce large amounts of product with an ee higher than the catalyst, involving a positive nonlinear effect.[19–22] We recently explored an additional possibility of asymmetric amplification by establishing experimentally that a *racemic reagent* can increase substantially the weak ee of a substrate.[23] We wish to report here a full account of this approach.

2. The usefulness of a racemic reagent

There are several facets for the reactions involving either a racemic substrate, a racemic reagent or a racemic catalyst. Usually in the kinetic resolution of a racemic or enantioenriched mixture, the chiral reagent or catalyst is enantiopure.[24–26] The use of enantioimpure reagents or catalysts[27–31] in kinetic resolution has been discussed. *Stereoselectivity factor* $s=k_{rel}$ is the crucial parameter in deciding the ee of the recovered starting material (ee_{sm}) for a given conversion.[24–26] A high s will allow to recover quite large amount of the initial compound with an excellent ee_{sm}. If s is small then the substrate conversion has to be increased in order to get a good ee_{sm}. Mutual kinetic resolution between an alcohol and an anhydride, each one of small ee, led to substantial asymmetric amplifications.[32] The racemic catalysts have been used in some special cases of enantioselective reactions, such as asymmetric activation or asymmetric deactivation (both in the presence of chiral additives)[33] or in the kinetic resolution of nonracemic mixtures.[34]

In the kinetic resolution, the racemic reagent, like an achiral reagent, will not be able to resolve a racemic mixture. But, a *racemic reagent* may modify the initial $ee_{sm(0)}$ of *scalemic substrate* (Scheme 1). There will be an increase of the ee of the recovered starting material [$ee_{sm}>ee_{sm(0)}$] if each of the

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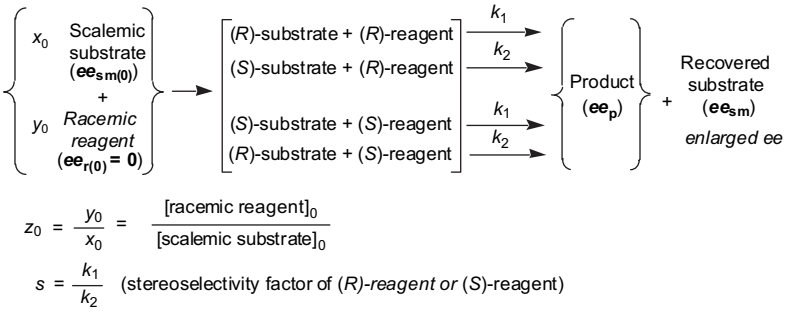


Scheme 1.

enantiomers of the *racemic reagent* displays a high enantiodifferentiation (large stereoselectivity factor $s=k_{rel}$) (Scheme 1). Ugi et al. have performed calculations on reactions between two chiral reactants of various initial enantiomeric excesses.[35] With the assumption of a first-order reaction in each reactant, the kinetic treatment on an equimolar mixture of reactants allowed the authors to set tables of data for various k_{rel} and conversions. The special case of a racemic compound versus a partially resolved reagent (1:1) has been presented, clearly showing an increase of ee_{sm} with conversion. The influence of the initial ee of a reagent on the kinetic resolution of a racemic mixture has been briefly revisited by us in 1999.[28] We recently published an experimental demonstration of this phenomenon.[23] Herein, we present a complete treatment of the enantioenrichment of partially resolved compound by a *racemic reagent*.

3. The enantioenrichment of partially resolved compound by a racemic reagent

As described in Scheme 1, when a scalemic substrate with $ee_{sm(0)}$ is treated with a racemic reagent, both (*R*)- and (*S*)-reagents will independently start resolving the scalemic substrate. Necessarily, (*R*)- and (*S*)-reagents will convert the opposite enantiomers of scalemic substrate, respectively, into products with the same rate constant ratio $s=k_1/k_2$. Consequently, under conditions of very high *s* value, partial conversion of a substrate of low $ee_{sm(0)}$ allows the recovery of residual substrate with highly enlarged ee_{sm}. The detailed discussion of effects of *s* factor, the initial $[rac\text{-reagent}]_0/[substrate]_0$ ratio ($z_0=y_0/x_0$), and the extent of conversion on the amplification of ee of substrate (ee_{sm}) in kinetic resolution by a racemic reagent is presented below. Henceforth, the expression of stereoselectivity factor *s* of racemic reagent recalls that it is the stereoselectivity factor of both (*R*)- or (*S*)-reagents (Scheme 1). First-order kinetic laws in substrate and in racemic reagent are considered in all the below calculations. The four parallel reactions of Scheme 1 give rise to four differential rate equations. The integration does not lead to an analytical solution to express ee_{sm} or ee_p as function of conversion extent. However, a numerical solution is possible by the fourth-order Runge–Kutta approximation.[28]

3.1. Effect of stereoselectivity factor *s* on the amplification

In Figure 1 are plotted some curves using a *racemic reagent* of various stereoselectivity factors ($s=k_1/k_2$, Scheme 1) with the following initial conditions: equimolar amounts of *rac*-reagent and substrate ($z_0=1$) and $ee_{sm(0)}=20\%$. The curves are computed as described in Ref. 28. Some general trends can be seen from these curves. The initial enantiomeric excess of the substrate is amplified by the racemic reagent (Fig. 1a) with a simultaneous resolution of the racemic reagent by the substrate (Fig. 1b). For a given conversion of substrate, the enantioenrichment depends on the *s* value of racemic reagent (*s* as defined in Scheme 1), higher the *s*

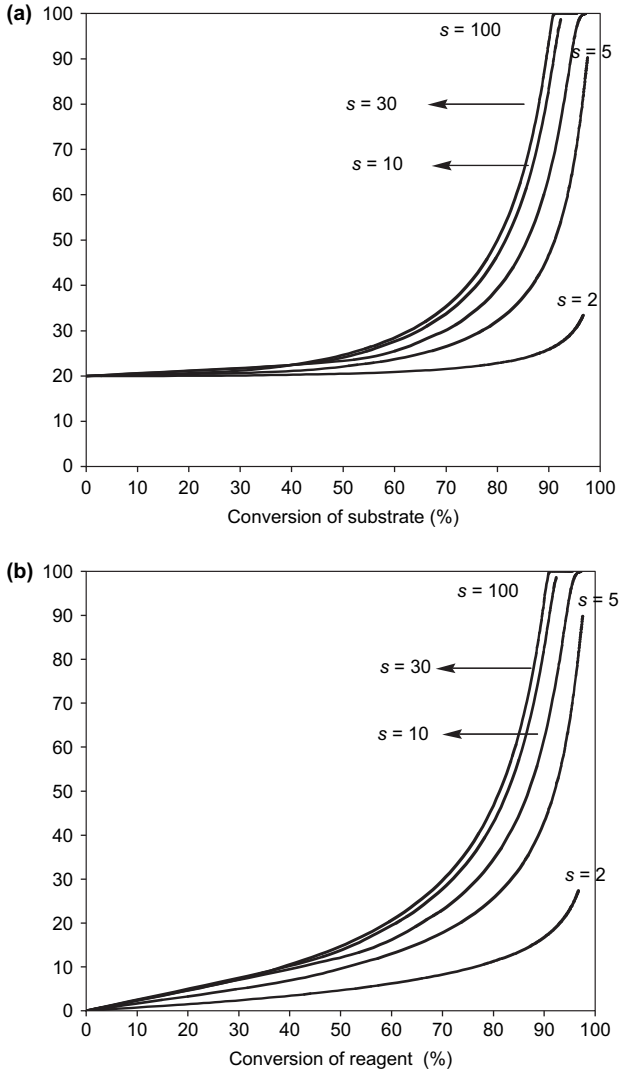


Figure 1. (a) Effect of *s* values on the amplification of ee_{sm}. (b) Simultaneous resolution of the racemic reagent. {computations were done with $ee_{sm(0)}=20\%$, $[racemic\ reagent]_0/[substrate]_0=z_0=1$}.

Table 1. Some computed data showing the effect of s value on the amplification of ee_{sm} and on simultaneous resolution of *rac*-reagent

S	ee_{sm}[a] (%)	ee_r[a] (%)
2	24	13.5
5	37	32
10	48.5	45
30	59.7	58.1
100	65	63

[a] ee_{sm} and ee_r correspond to the data points of curves of Figure 1 at 85% conversion, respectively, of substrate (Fig. 1a) and *rac*-reagent (Fig. 1b) [initial conditions: $ee_{sm(0)}$=20%, $ee_{r(0)}$=0%, and z_0=1].

value the greater is the ee_{sm} (Fig. 1a). For example (Table 1), at 85% conversion of substrate, an initial 20% ee is amplified to 24% if s=2, while if s=100 it is amplified to 65% ee. It is possible to evaluate the s factor using only a racemic reagent by fitting the experimental curve $ee_{sm}=f$(conversion) with one computed curve such as in Figure 1a. The racemic reagent simultaneously gets resolved by substrate as shown in Figure 1b and Table 1, also depending on the s value. ee of the reagent (ee_r) at the same 85% conversion equal to

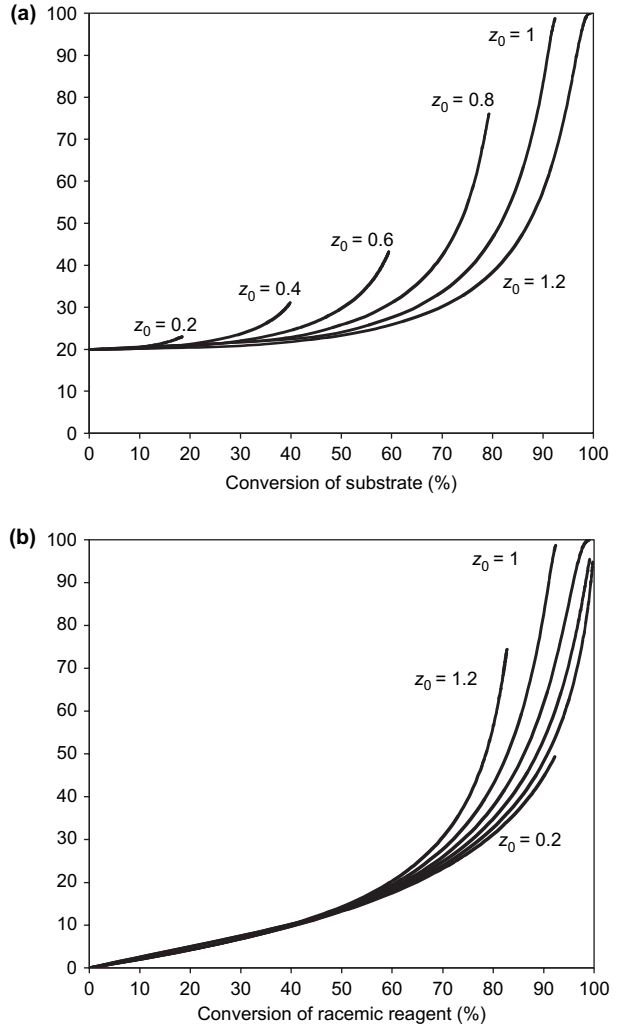


Figure 2. (a) Effect of initial z_0 values on the amplification of ee_{sm}. (b) Simultaneous resolution of the racemic reagent [computations done with $ee_{sm(0)}$=20%, s=30].

Table 2. Computation data showing the greater amplification of ee_{sm} for higher z_0 at a given conversion[a]

Substrate conversion (%)	ee_{sm} (%), z_0<1 (full consumption of *rac*-reagent)	ee_{sm} (%), z_0=1 (partial consumption of *rac*-reagent)
20	24.3, z_0=0.2	20.4
40	31.35, z_0=0.4	22.26
60	44.92, z_0=0.6	27.65
80	81.0, z_0=0.8	46.6

[a] Initial conditions: $ee_{sm(0)}$=20%, $ee_{r(0)}$=0%, s=30 [data of ee_{sm} are located on the curves of Fig. 2a].

13.5% or 63%, when s=2 or 100, respectively. One can notice that at any given conversion, always $ee_{sm}>ee_r$ (Table 1).

3.2. Effect of the initial stoichiometry on amplification

Computations were also carried out by varying z_0 values (stoichiometry) while s factor was kept fixed at 30 (Fig. 2). Initial ee of substrate was taken as 20%. Computations were done for z_0=1 (stoichiometric condition: $x_0=y_0$), $z_0<1$ (sub-stoichiometric: $x_0>y_0$), and $z_0>1$ (over-stoichiometric: $x_0<y_0$) (x_0 and y_0 as defined in Scheme 1). With the sub-stoichiometric condition, z_0=0.2, 0.4, 0.6, and 0.8, the complete consumption of racemic resolving reagent will provide substrate conversions of, respectively, 20%, 40%, 60%, and 80% and the ee of the recovered substrate is amplified, respectively, to ee_{sm}=24.3%, 31.35%, 44.92%, and 81% (Fig. 2a). In the stoichiometric (z_0=1) and over-stoichiometric conditions (z_0=1.2), the amplified ees are, respectively, of 99.99% (at 94.25% conversion) and 76.39% (at 94.39% conversion) (Fig. 2a). Interestingly, *at any given conversion, ee_{sm} is greater for lower z_0 value* as seen in Figure 2a. For example (Table 2), at 40% conversion ee_{sm}=22.26% when z_0=1, while when z_0=0.4 ee_{sm}=31.35%. In Figure 2b the simultaneous resolution of racemic reagent is depicted. In the case of $z_0<1$, the racemic reagent is consumed completely in the reaction. One can notice, from the curves (s=30) of Figure 3 (as in Fig. 2a and b), that the trace amounts of racemic reagent

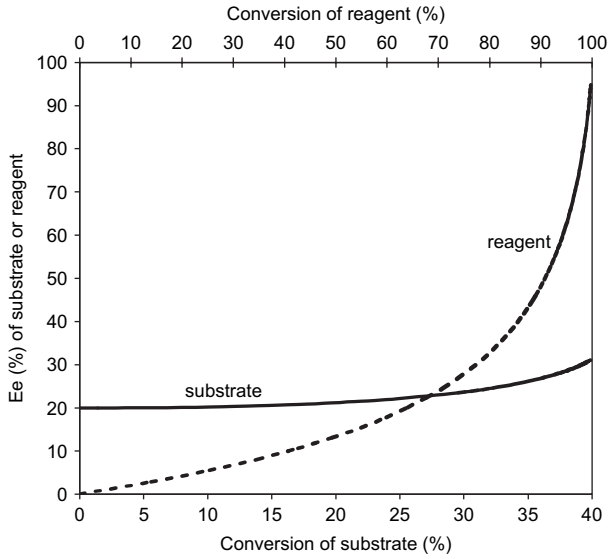


Figure 3. Simultaneous amplification of ee of a substrate and resolution of *rac*-reagent [conditions: $ee_{sm(0)}$=20%, s=30, z_0=0.4].

left at close to complete consumption is highly enantio-enriched (ee_r=86.9% and 94.5%, respectively, at 99.0% and 99.7% of reagent conversions) and $ee_{r(final)}>ee_{sm(final)}$. Unlike the substrate, the resolution of the racemic reagent is improved for higher z_0 value (Fig. 2a and b).

4. Possibility of reaching close to absolute ee by the help of racemic reagent

An extremely enantiopure compound is useful for the study of its physiological properties. Kinetic resolution is one of the ways to achieve very high ees. Horeau[36] described that an enantioimpure compound of ee in the range of 90–95% can be brought to ee >99.9% via the kinetic resolution by enantiopure reagent of high *s* value. The extent of substrate conversion required for achieving ees >99.9% for given *s* was nicely discussed with help of some experiments. Sharpless et al.[37] showed and discussed the possibility of obtaining almost enantiopure allylic alcohols by the kinetic resolution of the corresponding racemic substrates by the DIPT (100% ee)/TBHP/Ti(O*i*-Pr)$_4$ reagent system, which is characterized by some very high *s* values.

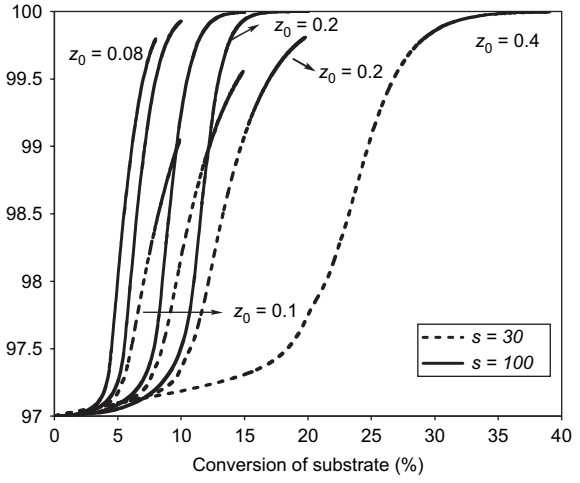


Figure 4. Computed plots showing the dependence of amplification of ee_{sm} ($ee_{sm(0)}$=97%) of recovered substrate on the *s* and z_0 values [solid lines: z_0=0.08, 0.1, 0.15, 0.2; broken lines: z_0=0.1, 0.15, 0.2, 0.4].

Racemic reagent could be an additional and simple tool to obtain almost enantiopure substance starting from a sample of reasonably high ee. As already pointed out above, the degree of amplification is higher for lower z_0 (as indicated by the computed curves in Fig. 2a) and for higher *s* values (as indicated by the computed curves in Fig. 1a). In Figure 4 and Table 3 are presented curves and data, highlighting the criticality of selecting appropriate z_0, for a given *s* value, for transforming an initial high $ee_{sm(0)}$ close to absolute ee while minimizing the loss of substrate. For example, to modify a substrate of 97% ee up to 99.8% ee, by the use of racemic reagent, it is sufficient to choose z_0=0.08 (y_0/x_0=0.08:1.0) if *s*=100 (solid lines in Fig. 4), i.e., 92% of substrate can be recovered with the amplified ee_{sm} of 99.8%. If z_0 is taken higher, say 0.1 (y_0/x_0=0.1:1.0), one has to convert approximately 14% of the substrate, i.e., only 86% of substrate will be recovered with 99.8% ee_{sm}. In the case of *s*=30 (broken lines in Fig. 4), higher substrate conversions are needed for obtaining the same value of ee_{sm} of 99.8%, for example, only 80% of substrate if z_0=0.2 or 71% of substrate if z_0=0.4, can be recovered with ee_{sm} of 99.8%. If *s* is very high, it is possible even to selectively transform almost all the racemic content of the enantioimpure substrate, leaving behind the substrate with close to absolute ee. Some computational data explaining such possibility, with various *s* values, are presented in Table 3. For better appreciation of the very high amplification, enantiomeric ratios (er) are also introduced. Starting from a 97% ee substrate (er=65.6), one can reach up to er as high as 2.178×10^6 (ee_{sm}>99.9999) for a *s* value of 1000 after 5% of substrate conversion.[38] The loss of substrate is merely 5%, a little more than the racemic content (3%) of the initial sample.

5. Use of a racemic acyl transfer agent for amplifying the ee of an amine

Mioskowski et al.[39] recently described the acylation of racemic amine **3** by the monoacetyl bistriflamide **2** (100% ee) (Eq. 1). The authors obtained α-phenylethyl amine **3** with 84% ee for 50% conversion starting from *rac*-**3** (Eq. 1). Stereoselectivity factor ($s=k_{rel}$) was estimated to be 30 for reagent **2**. We have reproduced this experiment. We then took this system as a model to study the usefulness of a racemic reagent.[23] We give here a full account of our results.

Table 3. Computed data showing the possibility of reaching close to absolute ee by the help of racemic reagent ($ee_{sm(0)}$=97% ee)[a]

s=100, z_0=0.2			*s*=1000, z_0=0.05		
Conversion (%)	Recovered substrate		Conversion (%)	Recovered substrate	
	ee[b] (%)	er[c]		ee (%)	er[c]
0	97	65.6667	0	97	65.6667
6.36321	97.0994	67.9516	2.83316	97.5527	80.7222
10.0047	97.5079	79.2543	3.25255	98.3318	118.891
11.1069	98.0796	103.142	3.67567	99.0829	217.082
13.0973	99.5500	443.42	4.43151	99.9702	6708.88
17.1312	99.9949	38,959.9	4.78745	99.9992	2,52,597
19.1579	99.9996	4,60,673.0	4.93543	99.9998	1.2177×10^6
19.8620	99.9998	1.06982×10^6	4.99244	99.9999	2.178×10^6

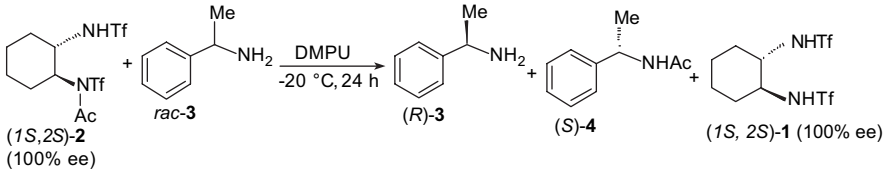
[a] The data were obtained by the mathematical simulations using fourth-order Runge–Kutta approximation on Mathematica program of the four first-order kinetic equations from the four parallel reactions depicted in Scheme 1.[28]
[b] Data located on the solid curve of Figure 4 with *s*=100, z_0=0.2.
[c] Enantiomeric ratio.

Table 4. Amplification of ee of **3** by the use of *racemic reagent* **2**[a,b]

Amine **3** initial ee (%) [$ee_{sm(0)}$ and 1 mol equiv]	Acylating agent *rac* **2** (mol equiv)	Conversion of **3**[c] (%)	Recovered amine **3**[d] ee_{sm} (%)	Calculated ee_{sm}[f] with s=30	Amide **4**[d] ee_p (%)
85.8	0.20	20.0	94.0	96.4 {z_0=0.2}	—
85.8	0.23	23.0	98.0	97.6 {z_0=0.23}	46.3
67.0	0.28	28.0	83.0	85.6 {z_0=0.28}	25.0
67.0	0.53	53.0	95.5	>99[g] {z_0=0.53}	37.0
67.0	0.64	64.0	98.0	>99.9[h] {z_0=0.64}	54.0
67.0	0.83	83.0	>99.5[e]	>99.9 {z_0=0.83}	60.8
4.2	0.40	40.0	6.7	6.6 {z_0=0.40}	—
4.2	0.50	50.0	8.2	7.8 {z_0=0.50}	0.15
4.2	0.90	90	22.6	33.9[i] {z_0=0.90}	1.8

[a] Reactions were performed at −20 °C for 20–48 h in DMPU till the complete consumption of *rac*-**2**.
[b] In the whole table, the data concern **3** and **4** with (*R*)-configuration.
[c] Conversion calculated from ees of **3** and **4** or measured by GC.
[d] Measured by HPLC (OD-H) on the corresponding amide obtained by acetylation.
[e] >99.5% ee means that the minor peak is not detected during HPLC analysis.
[f] The values were obtained by the mathematical simulations using fourth-order Runge–Kutta approximation on Mathematica program.[28]
[g] The computed value was 95.5% at 45.7% conversion.
[h] The computed value was 98% at 54.1% conversion.
[i] The value was 22.6% at 87.9% conversion.

When amine (*R*)-**3** of various ee_0 (initial values) was allowed to react with less than 1 equiv of *racemic reagent* **2**, significant amplification in ee of recovered amine **3** was obtained (Eq. 2, Table 4). For example, 0.28 equiv of *racemic reagent* **2** (i.e., z_0=0.28) was allowed to react completely with 1.0 equiv of (*R*) amine **3** of 67% ee [$ee_{sm(0)}$]. The total consumption of *rac*-**2** means 28% conversion of **3**, the isolated residual amine **3** has an ee_{sm}=83% (*R*, 62% yield). This was in excellent agreement with the value obtained by the calculations with s=30 and z_0=0.28, which indicated 85.6% ee. The corresponding *N*-acetylamine **4** (product) was obtained in 25% ee (ee_p) (*R*). A set of asymmetric amplifications of scalemic amine **3** under various experimental conditions confirmed the good correlation between $ee_{sm(0)}$, ee_{sm}, the size of s, z_0, and extent of conversion (Table 4). One can see from Table 4 that the final amplified ee values estimated by the calculations match reasonably well the experimental data. It was pointed out by Mioskowski et al.[39] that the s value in this reaction is not constant, it increases during the course of the reaction.[40] We have also observed similar phenomenon, however, the various s values for the reaction were always found to be around 30. We have then studied the alternate reaction of *N*-acetyl bistriflamide **2** of small ee with *racemic amine* **3** (Eq. 3, Table 5).[23] When 0.93 equiv of racemic amine **3** was allowed to react completely with 1.0 equiv of acylating agent (1*S*,2*S*)-**2** of 1.5% ee (i.e., 93% conversion of **2**), the remaining 7% unreacted acylating agent (1*S*,2*S*)-**2** was isolated with 15.5% ee. The calculations using similar reaction conditions, i.e., s=30 and z_0=0.93, indicated ee_{sm}=16.9% ee (15.5% ee was shown at 92.8% conversion). With the same z_0=0.93, ee_{sm} equals 6.6% or 11.2% if s=5 or 10, respectively. The experimental results of Tables 4 and 5 and calculations clearly confirm that a racemic reagent can easily enhance the ee of its partner if the stereoselectivity factor is not too small.

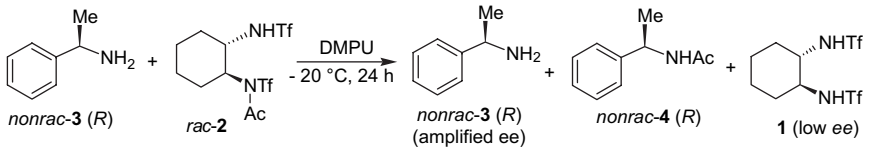


(1)

Table 5. Amplification of ee of the acyl transfer agent **2** by use of *racemic amine* **3**[a,b]

Entry	Initial ee (%) [$ee_{sm(0)}$] of acyl transfer agent **2** (1 mol equiv)	Mol equiv of *rac*-reagent (amine) **3**	Conversion of **2**[c] (%)	ee_{sm} (%) of recovered **2**[d]	Calculated[e] ee_{sm} with s=30
1	15.0	0.50	50.0	25.0	27.7 {z_0=0.5}
2	20.0	0.65	55.0	28.0	33[f] {z_0=0.65}
3	5.0	0.80	80.0	31.0	21.5[g] {z_0=0.8}
4	1.5	0.93	93.0	15.5	16.9[h] {z_0=0.93}

[a] Reactions were performed at −20 °C for 20–48 h in DMPU till the complete consumption of *rac*-**3**.
[b] In the whole table, the data concern **1** and **2** with (1*S*,2*S*)-configuration.
[c] Complete conversion of **3** was assumed, except in entry 2 (calculated from ee of **2** and ee of **4**).
[d] Measured after isolation and hydrolysis into **1**, followed by ^{19}F NMR with quinidine as shift reagent, in entry 4 ee was also measured on recovered **2** by HPLC.
[e] See 'footnote f' of Table 4.
[f] The computed value was 28% ee at 48.9% conversion.
[g] The computed value was 31% ee at 87% conversion (z_0=0.87).
[h] Computed value of 15.5% ee for 92.8% conversion.



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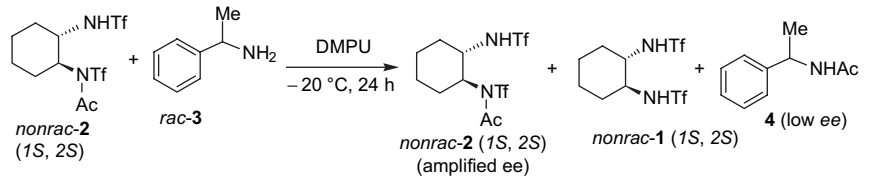

(3)

6. Racemic reagent and molecular homochirality in prebiotic racemic world

The prevalence of racemic reagents in the prebiotic racemic world can be easily envisaged. Some phenomena, as pointed out in Section 1 of this article, may cause a minor enantiomeric imbalance in an initially racemic compound.[6–9] From the previous discussion it is clear that if the stereoselectivity factor *s* is sufficiently high, a racemic reagent should be able to selectively remove the racemic content of an enantioimpure sample, leading to almost absolute ee (Fig. 4 and Table 3). Similarly, one can also envisage to transform a quasi-racemic mixture with very low ee that is undetectable by the usual GC and HPLC techniques, into a detectable high ee through kinetic resolution by a racemic reagent. Ugi et al., in fact, proposed that kinetic resolution of racemic substance by a partially resolved reagent may be of interest in connection with 'origin of pure chiral molecules'.[35] In Table 6 are presented some computations describing the use of racemic reagent for that purpose. Let assume that a substance (12.6 g of molecular weight 420) with an initial ee of 0.0015% [$ee_{sm(0)}$] (undetectable)[41] was allowed to react with *racemic reagent* (s=1000)[38] in an appropriate [*rac*-reagent]$_0$/[substrate]$_0$ ratios (z_0). It is then possible to recover residual substrate with 8.9% ee (1.1 mg), or with 51% ee (260 μg) or with >99.9% ee (186 μg). A still lower $ee_{sm(0)}$=0.00015% (undetectable) can also be brought to as high as 20% ee (52 μg). Of course the recovered weights and the ees are not significant in a synthetic point of view. However, when such kinetic resolution phenomena are subsequently coupled with nonlinear effects (NLE) in asymmetric catalysis or autocatalysis,[42] a large amount of product with very high ee will be obtained from a minor amount of sample of undetectable low ee. In our previous paper,[23] we successfully demonstrated a related possibility by starting from monoacetyl bistriflamide **2** of 1.5% ee [$ee_{sm(0)}$] (instead of an undetectable low ee). Kinetic resolution using the racemic amine **3** and subsequent hydrolysis of recovered **2** provided the bistriflamide **1** with ~15% ee. Diethylzinc addition on aldehydes using the bistriflamide **1** of ~15% ee (ee_{sm}), as catalyst, afforded large quantities of product alcohol with very high ee (>97% ee), thanks to a strong positive nonlinear effect. Therefore, taking into consideration, as said in beginning of this section, the availability of racemic reagents characterized by a large *s* value in the racemic prebiotic world, the amplification of very small ee by a racemic reagent coupled with subsequent asymmetric catalysis involving NLE,[42] may also be considered as one of the possible processes that led to the biomolecular homochirality on earth. Minor amounts of the partially enantioenriched racemic reagent, as a result of simultaneous kinetic resolution (Figs. 1–3), could also lead to biomolecular homochirality. The ability of a racemic reagent to transform *undetectable low ees* to *detectable higher ees* may also find an application as a test to confirm the perfect racemic composition of a sample available in large quantities.[43]

Table 6. Computations showing the change of *undetectable low ee* to a *detectable high ee* using racemic reagent of high selectivity factor (s=1000)[36] in kinetic resolution process[a]

ee of substrate (%)	Conversion (%)	Weight of the recovered substrate[b] (mg)	ee of substrate (%)	Conversion (%)	Weight of the recovered substrate[b] (mg)
0.0015 (initial)	0	12,600.0 (initial)	0.00015 (initial)	0	12,600.0 (initial)
1.83642	99.9593	5.12949	0.0186333	99.6019	50.166
3.63964	99.9792	2.61638	0.037142	99.8005	25.1352
5.41529	99.9859	1.77838	1.01163	99.9927	0.922835
7.18166	99.9892	1.35639	5.00868	99.9985	0.190947
8.91917	99.9912	1.10477	10.0011	99.9992	0.0988381
31.3049	99.9971	0.367381	15.007	99.9995	0.0681326
51.1606	99.9979	0.260415	16.4819	99.9995	0.0626641
75.4037	99.9983	0.213007	18.344	99.9995	0.0570252
86.2866	99.9984	0.200307	20.1879	99.9996	0.0524761
90.1785	99.9984	0.195856			
99.9759	99.9985	0.186859			

[a] The data were obtained by the mathematical simulations using the fourth-order Runge–Kutta approximation on Mathematica program of the four first-order kinetic equations corresponding to four parallel reactions as depicted in Scheme 1 (z_0=1).[28]
[b] A sample of a molecular weight 420 (30 mmol).

7. Conclusion

We established both computationally and experimentally the usefulness of a *racemic reagent*[44] in amplifying the small ee of a substrate via a kinetic resolution process, in confirmation of the Ugi's pioneering work.[35] The following conclusions can be drawn from the above discussion: (i) a *racemic reagent* can amplify the ee of a scalemic substrate. The amplification depends on both the stereoselectivity factor s and the initial $[rac\text{-reagent}]_0/[substrate]_0$ ratio (z_0 value), which modulates the conversion extent. The loss of substrate can be minimized while obtaining the maximum ee amplification by an appropriate selection of racemic reagent (i.e., s value) and z_0. The process can be quite efficient if the stereoselectivity factor is large enough. (ii) It is possible to evaluate the s factor using only a racemic reagent by looking at the curve $ee_{sm}=f(\text{conversion})$ in order to fit with one computed curve such as in Figure 1a. (iii) One can also envisage to approach a detectable higher ee from an initially undetectable low ee using this process, this may find an application as a test of perfect racemic composition of a sample.[43] (iv) This ee enrichment process coupled with some other amplification phenomenon in asymmetric catalysis (such as NLE) may be useful in the discussion on the origin of biomolecular homochirality on earth, taking into account the prevalence of some stereoselective racemic reagents in a prebiotic racemic world.

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Supplementary data

It includes description of the four parallel kinetic equations used in fourth-order Runge–Kutta approximation, calculation of the application of a racemic reagent to test the perfect racemic composition of a sample, and computations depicting the amplification of an initially small ee by the kinetic resolution under various conditions (scalemic vs scalemic and scalemic vs racemic reactants). This material is available free of charge via the internet at http://sciencedirect.com. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.077.

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40. Conversion-dependent stereoselectivity factors have been reported by Jacobsen et al.[47]
41. With present analytical techniques it is practically difficult to measure accurately an ee<0.1%.[48] Schoofs and Horeau suggested some kinetic resolution methods to determine ees lower than 1%.[49] In contrast, it is easy to measure accurately very high ees (>99.5%).[48,50] It was shown that using some special techniques one can detect trace amounts of enantiomeric impurities (ee>99.99%).[50]
42. Soai's autocatalytic addition of i-Pr_2Zn on pyrimidine aldehyde provides spontaneous random generation of excess of one enantiomer in the addition product in the absence of external chiral influence.[12,13] It was shown that the minor imbalance in the enantiomeric distribution (undetectable low ee) amongst a few number of molecules taken from racemic sample will lead to a controlled asymmetric synthesis in the Soai's autocatalytic system, involving a strong (+)-NLE.[51]
43. An enantiopure reagent cannot be differentiated by kinetic resolution if a substrate is truly racemic or quasi-racemic (for example, $ee_{sm(0)}$~0.1%), since it gives resolution in both cases. In contrast, a true racemic reagent cannot resolve a truly racemic substrate, although, it will be able to enlarge the initially low ee of a quasi-racemic substrate to some final detectable high ee_{sm} (see Supplementary data for some computations on this application). Soai's autocatalytic system[12,13] can also identify trace amounts of enantiomeric excess in various types of chiral substances.[12b,51,52]
44. A racemic catalyst will not modify in principle the initial enantiomeric excess of substrate [$ee_{sm(0)}$]. The catalyst remains of racemic composition through the course of reaction (unless an autoinduction process or kinetic partitioning[30] arising from interaction between catalyst and product). We examined the kinetic resolution of an (*E*)-1-cyclohexylbut-2-en-1-ol of 18% ee by the Sharpless epoxidation[37] with the *rac*-DIPT/TBHP/Ti(O*i*-Pr)$_4$ catalyst system (10 mol % equiv). The ees of the recovered allylic alcohol and the epoxide were found to be 18% ee at any conversion. A catalytic kinetic resolution involving the unusual pseudo zero-order[34,53] kinetics laws with respect to substrate is a special case where a racemic catalyst can modify the initial small $ee_{sm(0)}$ into final large ee_{sm}. Lloyd-Jones et al.[34] have discussed and showed this possibility in Pd-catalyzed kinetic resolution. The authors used this as a simple test to evaluate the selectivity factor from a racemic ligand before the enantiopure ligand is synthesized.
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