Chiral Organometallic Reagents, V[1]

A Test on the Configurational Stability of Chiral Organolithium Compounds Based on Kinetic Resolution; Scope and Limitations

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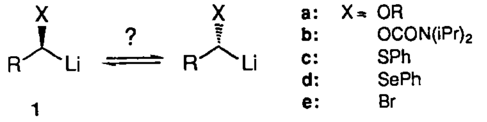
The test on the configurational stability of chiral organolithium compounds is based on the kinetic resolution of the racemic organolithium compound on reaction with an enantiomerically pure electrophile. The limits of this test have been evaluated by model calculations. The factors that have been considered are: Optimum values for the kinetic resolution; effects of < 100% enantiomeric purity of the chiral electrophile; parallel side reactions of the organolithium compounds with the electrophile.

Chiral α-substituted organolithium compounds **1** could be valuable reagents in stereoselective synthesis, provided they are configurationally stable on the time scale defined by their generation and subsequent reactions (Scheme 1).

Scheme 1



This holds e.g. for the alkoxy derivatives **1a**[2], or the carbamoyloxy derivatives **1b**[3]. The corresponding sulfur derivatives **1c**[4] or seleno derivatives **1d**[5,6] have a high tendency to racemize. In contrast, the bromo derivatives **1e** can be handled at low temperatures without racemization[7]. Little information is available regarding the configurational stability of other organometallic species related to **1**, e.g. the Grignard, zinc or titanium[8] species. In this situation it would be handy to have a test to evaluate the configurational stability of such organometallic reagents preferably under conditions similar to their ultimate usage, e.g. addition to carbonyl groups or alkylation by electrophiles.

In a study on deoxyhexoses[9] we observed that a racemic organometallic reagent gave different product compositions on reaction with a chiral electrophile, depending on whether the electrophile was racemic or enantiomerically pure. Specifically, the reaction between the racemate and the enantiomerically pure compound gave the diastereomeric products in a 1:1 ratio. Similar observations were made by Hoppe's group[8b,10,12], e.g. Scheme 2[10].

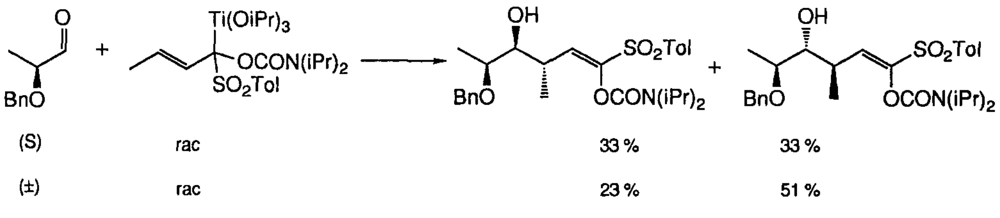
From these observations it may be inferred that the organometallic reagent involved is configurationally stable on the time scale defined by the rate of reaction with the electrophile. The same conclusion could have been drawn from the related observations[11] that a racemic organometallic reagent on reaction with a chiral ketone gave a 1:1 diastereomer ratio when applied in equivalent amounts, but an 8:1 ratio when an excess of the racemic reagent was used.

The Test Reactions

Based on these observations, a test for the configurational stability of organometallic reagents can be devised[12], a test[13] that can be carried out on the racemic organometallic reagent. The situation is illustrated by reactions with the aldehyde **2**[14] as a representative chiral electrophile (Scheme 3).

On reaction of the racemic organolithium compound **1** with the aldehyde **2** the two combinations (*S*)-**1** with (*S*)-**2**, and (*R*)-**1** with (*S*)-**2** may react at unequal rates. Neverthe-

Scheme 2



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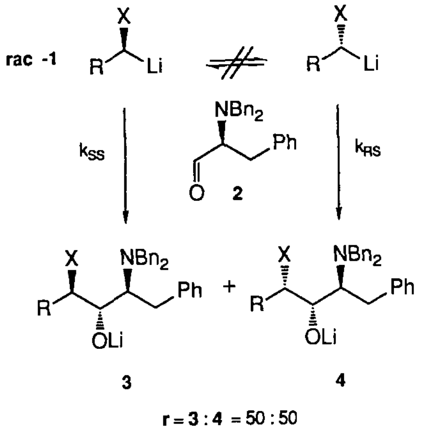
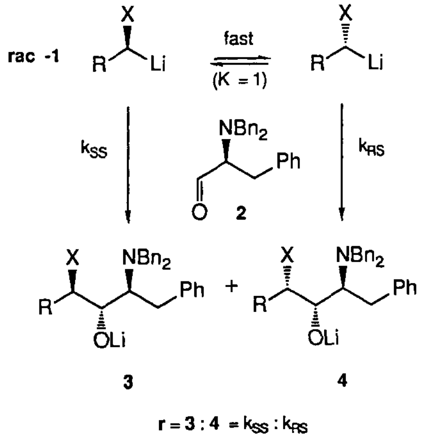
Scheme 3



less, if the reaction is allowed to go to completion, the two diastereomeric products **3** and **4** should be obtained in a 1:1 ratio, as long as the organolithium compound **1** is configurationally stable, i.e. the enantiomer ratio of racemic **1** (50:50) is directly translated into the diastereomer ratio of the products **3** and **4** (Scheme 3).

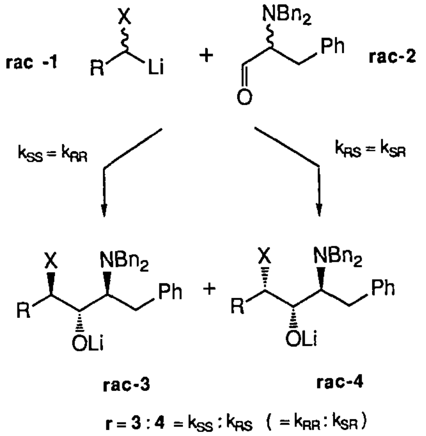
If, on the other hand, the organometallic reagent **1** is configurationally labile, the diastereomer ratio of the products is expected to deviate from a 50:50 ratio, provided that k_{SS} is sufficiently different from k_{RS} (Scheme 4). The prevalence of the latter condition has to be established in a separate experiment. The ratio of k_{SS}/k_{RS} is revealed by the reaction of the racemic organolithium compound **1** with the same aldehyde (electrophile), this time as racemate. The ratio of the diastereomeric (racemic) products **3** and **4** obtained in this experiment directly reflects the k_{SS}/k_{RS} ratio (which has to be equal to k_{RR}/k_{SR}) (Scheme 5).

Scheme 4



The test is based on the kinetic resolution (k_{SS}/k_{RS}) that occurs on reaction of a racemate with a chiral reagent. In a first experiment (*Experiment 1*), racemic **1** is allowed to react with the racemic electrophile **2**. The product ratio reveals the degree of kinetic resolution k_{SS}/k_{RS}, the value of which has to be sufficiently different from 50:50.

Scheme 5

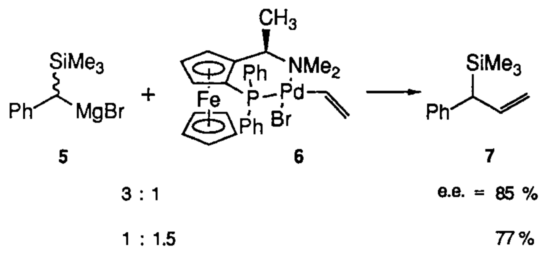


Provided, the electrophile is not available as a racemate, but only in enantiomerically pure form, *Experiment 1* can also be carried out by allowing one equivalent of the racemic organometallic reagent to react with 0.1 – 0.2 equivalents of the enantiomerically pure electrophile. As Figure 1 shows, at low conversion the product ratio **3**/**4** does not deviate significantly from k_{SS}/k_{RS}. In a second experiment (*Experiment 2*) the racemic organometallic compound **1** is allowed to react with the enantiomerically pure electrophile. If the same diastereomer ratio results as in *Experiment 1*, the organometallic species is configurationally labile relative to the time scale defined by the rate of reaction of **1** with the electrophile. If the diastereomer ratio in *Experiment 2* approaches or is equal to 50:50, the organometallic species is configurationally stable on that time scale.

There are some further implications: The time scale relative to which configurational lability or stability is defined can be measured, i.e. by determining macroscopically the rate of reaction of **1** with the electrophile. Moreover, by using different chiral electrophiles, i.e. slower or faster reacting electrophiles, different time scales can be set. Finally, if the situation arises in which the enantiomerization of **1** and its addition to the electrophile occur at similar rates, the product *r* in *Experiment 2* should be between 50:50 and the value defined by the kinetic resolution (k_{SS}/k_{RS}).

Such a situation is found e.g. in the Kumada coupling of a racemic benzylic Grignard reagent **5** with an enantiomerically pure palladium complex **6**[15] (Scheme 6): When a deficiency of the "electrophile" was used, the enantioselectivity in the formation of the product **7** was reported to be 85% e.e. These conditions correspond to *Experiment 1*, defining the kinetic resolution to ca. 93:7. When an excess of the "electrophile" **6** was used, the enantioselectivity was only 77%. This indicates that the rate of enantiomerization of the Grignard reagent **5** is comparable to the rate of trapping by the complex **6**. In case the rate of enantiomerization of **5** would have been much faster than the rate of coupling, both experiments should have given the same e.e. values for the product **7**. In case the Grignard reagent were configurationally stable, the second experiment should have led to the product **7** with an e.e. value approaching 0%.

Scheme 6



The proposed test is simple, provided that only two diastereomeric products are formed, and not four, as in our first encounter[12] with this phenomenon. Actually, in the example shown in Scheme 3, four products might be obtained due the prochiral nature of the aldehyde group. Fortunately, with the aldehyde **2** the 1,2-asymmetric induction is so high[14] that essentially only two products **3** and **4** result. The relative configuration of the products does not have to be determined. It simply suffices to identify the products as the two diastereomers and to determine their ratio. We have since then used this test successfully to obtain information on the configurational stability of **1d**[6] and **1e**[16]. Here we would like to discuss the aspects, which limit the application of this test, and the situations, under which this test should give reliable results.

Effects of the Level of Conversion

The discussion above was based on a complete conversion of the organometallic species to the diastereomeric products **3** and **4** in *Experiment 2*, which, in the case of configurational stability of **1** should ultimately reach a diastereomer ratio of 50:50. In order to ensure complete conversion, an excess of the chiral electrophile can and should be applied. Nevertheless, the faster reacting combination will give one of the diastereomers more rapidly, whereas the slower reaction will trail behind. Therefore, compared to *Experiment 1*, longer reaction times are required to reach the same extent of conversion or completion of the reaction. The lengthening of the reaction period depends on the degree of kinetic resolution k_{SS}/k_{RS}. This term is frequently designated[17a] as the stereoselectivity factor s. The larger s, the longer is the time needed to reach a complete reaction in *Experiment 2* compared to *Experiment 1*. The "delay factor" can be estimated to be $(s + 1)/2$. From this, the advantage of having small s values of 1.5 – 3.0 is apparent, because longer reaction times in *Experiment 2* due to higher values of s may cause the starting material or the products to deteriorate, especially when sensitive organometallic reagents are involved. Such side reaction may render the results of the test questionable (see below). Moreover, the **3**/**4** product ratio in *Experiment 2* is a function of the extent of conversion. Therefore, at low ($\rightarrow 0$) conversion, the diastereomer ratio will be that defined by kinetic resolution, and even at 90 or 95% conversion the diastereomer ratio may still deviate significantly from the ultimate value of 50:50. This is illustrated in Figure 1, which holds for second-order as well as pseudo first-order reactions, as long as side reactions, be they competitive or consecutive, do not occur (see below).

Figure 1 shows that the approach of the diastereomer ratio to the ultimate 50:50 value in *Experiment 2* is similar over the last 5 – 10% of conversion for various values of s. However, since the time required to reach high conversion is a function of s (see above), it is again adviseable to study reactions in which s is small.

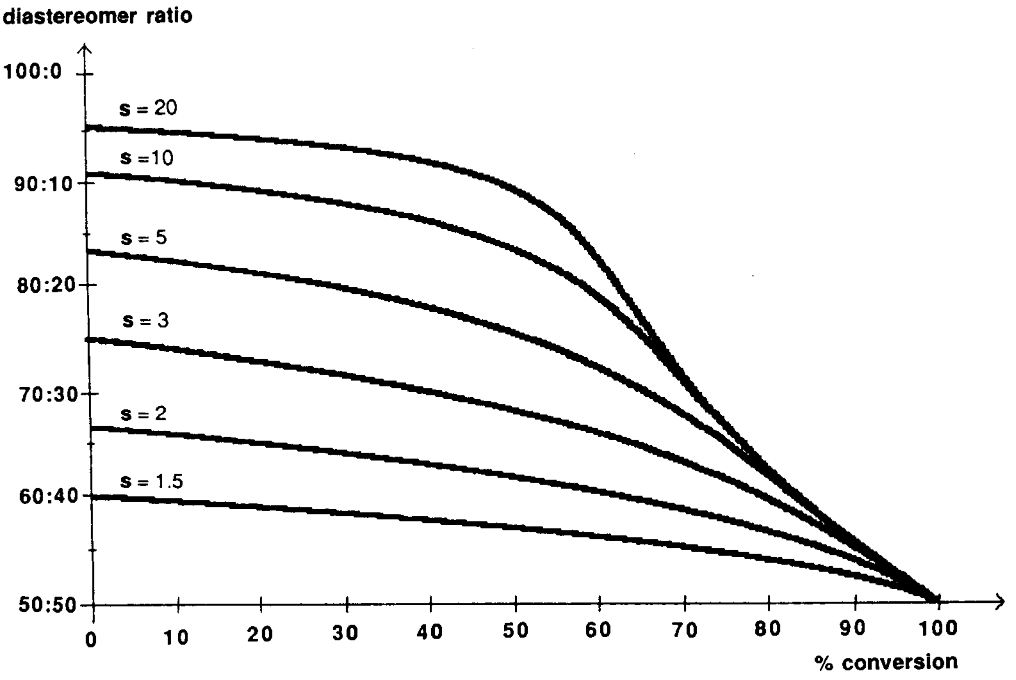


Figure 1. Evolution of the diastereomeric ratio in *Experiment 2* during the reaction; the various curves refer to different values of s

It is to be pointed out, that in *Experiment 1* – the reaction between the two racemates – conversion is not of concern. The ratio of the diastereomeric products **3** and **4** should be independent of the extent of conversion. Thus, it is possible to determine the degree of kinetic resolution at low conversions or with even a deficiency of the chiral electrophile. Nevertheless, it is practical to run *Experiment 1* with the same excess of the electrophile that is to be applied in *Experiment 2*. The time that has been found optimal to reach high conversion in *Experiment 1* can then be multiplied by the "delay factor" $(s + 1)/2$ to indicate the reaction time necessary for *Experiment 2*.

In *Experiment 1* it does not matter, whether the electrophile is added to the organometallic reagent (normal addition) or the organometallic reagent is added to the electrophile (inverse addition). However, in *Experiment 2* inverse addition is called for in all those cases, in which the rate of reaction is faster at the chosen temperature than the rate of addition of the reagent to the reaction mixture. Otherwise, on normal addition of the aldehyde **2** to the organolithium compound **1**, the enantiomerically enriched **1** remaining after reaction of the first drops of the electrophile may racemize before the next drop of electrophile is added; cf. the results in ref.[6]. Thus "normal addition" may cause the time scale of the test not to be defined by the rate of reaction between the organometallic species and the electrophile, but by the speed of addition of the electrophile to the reaction mixture!

Table 1. Diastereomer ratio r = **3**/**4** for complete consumption of configurationally stable **1** on reaction with one equivalent of an electrophile **2** of less than 100% e. e.

Initial e.e. of **2**	Selectivity factor s of the main reaction				
	2	3	5	10	15
99	50.3:49.7	50.4:49.6	50.4:49.6	50.5:49.5	50.5:49.5
97	50.8:49.2	51.1:48.9	51.2:48.8	51.4:48.6	51.4:48.6
95	51.3:48.1	51.8:48.2	52.1:47.9	52.3:47.7	52.4:47.6
90	52.7:47.3	53.5:46.5	54.1:45.9	54.6:45.4	54.7:45.3
80	55.2:44.8	56.9:43.1	58.2:41.8	59.1:40.9	59.4:40.6
70	57.5:42.5	60.1:39.9	62.1:37.9	63.6:36.4	64.1:35.9

Table 2. Diastereomer ratio r = **3**/**4** for complete consumption of configurationally stable **1** on reaction with two equivalents (top), five equivalents (middle), and a large excess of an electrophile **2** of less than 100% e. e.

Initial e.e. of **2**	Selectivity factor s of the main reaction				
	2	3	5	10	15
99	50.3:49.7	50.5:49.5	50.8:49.2	50.9:49.1	51.0:49.0
97	51.0:49.0	51.6:48.4	52.3:47.7	52.8:47.2	52.9:47.1
95	51.7:48.3	52.7:47.3	53.8:46.2	54.6:45.4	54.8:45.2
90	53.3:46.7	55.2:44.8	57.3:42.7	59.2:40.8	59.6:40.4
80	56.2:43.8	59.6:40.4	63.6:36.4	67.7:32.3	68.9:31.1
70	58.7:41.3	63.5:36.5	68.9:31.1	74.9:25.1	77.3:22.7

Initial e.e. of **2**	Selectivity factor s of the main reaction				
	2	3	5	10	15
99	50.4:49.6	50.6:49.4	51.0:49.0	51.7:48.3	52.0:48.0
97	51.1:48.9	51.8:48.2	53.0:47.0	54.8:45.2	55.8:44.2
95	51.8:48.2	53.0:47.0	54.8:45.2	57.7:42.3	59.4:40.6
90	53.4:46.6	55.7:44.3	59.0:41.0	64.1:35.9	67.1:32.9
80	56.3:43.7	60.3:39.7	65.7:34.3	73.4:26.6	77.7:22.3
70	58.8:41.2	64.2:35.8	70.8:29.2	79.4:20.6	83.8:16.2

Initial e.e. of **2**	Selectivity factor s of the main reaction				
	2	3	5	10	15
99	50.4:49.6	50.7:49.3	51.2:48.8	52.4:47.6	53.5:46.5
97	51.1:48.9	51.9:48.1	53.4:46.6	56.5:43.5	59.2:40.8
95	51.8:48.2	53.1:46.9	55.4:44.6	60.1:39.9	63.8:36.2
90	53.5:46.5	56.0:44.0	59.9:40.1	67.0:33.0	71.9:28.1
80	56.6:43.5	60.7:39.3	66.8:33.2	75.8:24.2	80.9:19.1
70	59.0:41.0	64.5:35.5	71.7:28.3	81.0:19.0	85.7:14.3

When the conditions mentioned above are met, a product ratio of 50:50 will be approached, but not necessarily reached in *Experiment 2* in cases of configurationally stable organometallic compounds. Anyway, a significant difference in the product ratios between *Experiment 1* (defining kinetic resolution) and *Experiment 2* (approaching 50:50) is sufficient to give clear evidence for the configurational stability of the species investigated.

Effects of the Enantiomeric Purity of the Electrophile

A product ratio of 50:50 can be reached in *Experiment 2* only, if the electrophile used is enantiomerically pure. Especially with α-substituted chiral aldehydes as electrophiles, there is the possibility of racemization either prior to or during the test reaction. It therefore became of interest to evaluate the consequences of a degradation in the enantiomeric purity of the trapping agent. Numerical calculations of this effect are recorded in Table 1. They give the diastereomer ratio for complete conversion of a configurationally stable organometallic species after reaction with one equivalent of a chiral electrophile of less than 100% e.e. The e.e. value of the electrophile given in the left column of Table 1 refers to the initial e.e. value of the reagent at the beginning of the reaction. During the reaction the e.e. value of the reagent increases due to mutual kinetic resolution[17].

The product ratios that will ultimately be reached depend on the value of the selectivity factor s. It becomes clear that for small values of $s\,(\leqslant 3)$ low levels of racemization (e.g. $\leqslant 5\%$) have no significant effect; i.e. for configurationally stable organometallic reagents the diastereomer ratio should still approach $(50 \pm 2):(50 \pm 2)$. The situation becomes more serious if an excess of the chiral electrophile is used, because this offers a larger amount of the wrong enantiomer of the electrophile for reaction. This is illustrated by the calculations reproduced in Table 2, which refer to excess amounts of the chiral electrophile over the reacting organometallic species (factors 2, 5, or ∞).

The data thus reveal that a moderate excess (e.g. 1–5 equivalents) of an electrophile of slightly degraded enantiomeric purity ($\geqslant 97\%$ e.e.) can be tolerated.

Effects of Side Reactions

The simple scheme considered above is based on a 100% conversion of the organolithium compound **1** into the adducts **3** and **4**, which are assumed not to be consumed by any undesired subsequent transformations. These assumptions are certainly unrealistic. It therefore is of interest to find out, to what extent the answers given by the above test remain reliable or become even questionable, if minor side or consecutive reactions occur. The most likely event on reaction of organolithium species is that they become protonated to a significant extent, be it by the solvent or by an acidic carbonyl compound applied. This way, the organolithium compound would be consumed in parallel to the desired process. The occurrence of such a parallel reaction will become apparent in a decrease of the product yield. This holds for *Experiment 1* in which these side reactions will not affect the product ratio. In *Experiment 2* such parallel side reactions will affect both the product yield (to a different degree than in *Experiment 1*) and the ultimate diastereomer ratio that can be attained.

Table 3. Maximum attainable yield of **3** and **4** (top) and diastereomer ratio $r = 3/4$ (bottom) in *Experiment 2* for complete consumption of configurationally stable **1** by a main reaction leading to **3** and **4** and a parallel side reaction with $s^* = 1$

Yield (%) in *Experiment 1*[a]	Selectivity factor *s* of the main reaction 2	3	5	10	15
99	98.9	98.7	98.2	97.1	96.0
97	96.6	96.1	94.8	91.9	89.3
95	94.4	93.5	91.7	87.4	83.8
90	89.0	87.5	84.4	78.2	73.7
80	78.5	76.2	72.0	65.0	60.8
70	68.3	65.8	61.6	55.4	52.0

Yield (%) in *Experiment 1*[a]	Selectivity factor *s* of the main reaction 2	3	5	10	15
99	50.4:49.6	50.6:49.4	51.0:49.0	51.7:48.3	52.0:48.0
97	50.6:49.4	51.0:49.0	51.8:48.2	53.5:46.5	55.1:44.9
95	50.9:49.1	51.6:48.4	52.9:47.1	55.6:44.4	58.0:42.0
90	51.9:48.1	53.2:46.8	55.6:44.4	60.3:39.7	54.1:35.9
80	53.7:46.3	56.3:43.7	60.3:39.7	67.6:32.4	72.6:27.4
70	55.4:44.6	59.1:40.9	64.5:35.5	73.1:26.9	78.3:21.7

[a] The relative rate of the main and side reaction is expressed as the yield of **3** and **4** in *Experiment 1*; in case there is no side reaction, the yield of **3** and **4** is 100%.

In the simplest case, both enantiomers of the substrate **1** are consumed by a side reaction at the same rate (i.e. the selectivity factor s^* of this process is 1). The concomitant reduction in yield in *Experiment 1* can be correlated with the maximum attainable yield in *Experiment 2* as shown in Table 3 (top). To illustrate the data: If the side reaction (protonation) occurs 1/5 as fast as the main reaction, the yield in *Experiment 1* will be reduced to 80%; i.e. the last line of Table 3 (top and middle) applies. In *Experiment 1* a larger amount of the substrate will be consumed by the side reaction due to the time delay as a function of s as discussed on p. 977. This is reflected in a further decrease in the maximum product yield attainable. Side reactions of the substrate **1** affect not only the yield but also the diastereomer ratio r in *Experiment 2*. The diastereomer ratio r (= **3**/**4**) at 100% conversion of a configurationally stable organometallic substrate **1** is given in Table 3 (bottom) as a function of the same parameters as in Table 3 (top). The deviation from the ideal value of 50:50 will not be serious, as long as the extent of the side reaction remains small (< 5%, equivalent to a yield in *Experiment 1* of > 95%), and the selectivity factor s of the main reaction remains small (< 3).

The calculations on which the data in Tables 3, 4, and 5 are based, refer to a situation in which both the main reaction and the side reaction have the same reaction order, e.g. second order.

Since the compounds **1** to be investigated are chiral, enantiomer discrimination may occur in the side reaction if it involves the chiral electrophile **2**, e.g. enolization of a chiral aldehyde or ketone. To get an idea, how much this could affect the diastereomer ratio of the products **3** and **4** in *Experiment 2*, calculations similar to those in Table 3 were performed, this time with the selectivity ratio of the side reaction s^* being set in one case to 5, and in another case to 0.2. A value of $s^* > 1$ signals that the particular enantiomer of **1** which reacts faster in the main reaction is also consumed faster in the side reaction. For $s^* < 1$ the opposite applies. The results are compiled in Tables 4 and 5.

It was to be anticipated that if both the selectivity factor s of the main reaction and s^* of the side reaction are the same, all that is changed compared to the ideal situation is the yield of the products **3** and **4**. It is decreased to the same extent in *Experiment 1* and *Experiment 2*. Otherwise the data of *Experiment 1* and *Experiment 2* should correspond to the ideal situation. One notes that inverted diastereomer ratios may result in *Experiment 2* if s^* is larger than s. If the electrophile **2** is not used in large excess, the main reaction will be second order, whereas side reactions of **1** involving the solvent or its thermal decomposition may be of first order. In such a situation both the yields in *Experiment 1* and *Experiment 2*, as well as the attainable diastereomer ratio in *Experiment 2* may deviate for a configurationally stable substrate **1** more from the ideal values than given in Tables 3, 4, and 5.

These calculations thus indicate that parallel side reactions which occur to the extent of less than 10% will not jeopardize the test. The product ratios found in *Experiment 1* will be fully valid. In cases were the side reaction consumes less than 5% of **1**, the product ratios of *Experiment 2* will approach or exceed, but not necessarily reach the ideal value of 50:50 when dealing with a configurationally stable organometallic species. In particular, these deviations will not

Table 4. Maximum attainable yield of **3** and **4** (top) and diastereomer ratio r = **3**/**4** (bottom) in *Experiment 2* for complete consumption of configurationally stable **1** by a main reaction leading to **3** and **4** and a parallel side reaction with s^* = 5

Yield (%) in *Experiment 1*[a]	Selectivity factor *s* of the main reaction				
	2	3	5	10	15
99	99.1	99.1	99.0	98.6	98.2
97	97.4	97.3	97.0	95.9	94.9
95	95.6	95.5	95.0	93.3	91.6
90	91.3	91.1	90.0	86.9	84.1
80	82.5	82.0	80.0	75.0	70.9
70	73.7	72.8	70.0	63.9	59.5

Yield (%) in *Experiment 1* [a]	Selectivity factor *s* of the main reaction				
	2	3	5	10	15
99	49.8:50.2	49.9:50.1	50.0:50.0	50.2:49.8	50.4:49.6
97	49.4:50.6	49.7:50.3	50.0:50.0	50.7:49.3	51.3:48.7
95	49.1:50.9	49.4:50.6	50.0:50.0	51.1:48.9	52.1:47.9
90	48.1:51.9	48.9:51.1	50.0:50.0	52.2:47.8	54.1:45.9
80	46.2:53.8	47.7:52.3	50.0:50.0	54.3:45.7	57.7:42.3
70	44.2:55.8	46.6:53.4	50.0:50.0	56.2:43.8	60.8:39.2

[a] The relative rate of the main and side reaction is expressed as the yield of **3** and **4** in *Experiment 1*; in case there is no side reaction, the yield of **3** and **4** is 100%.

Table 5. Maximum attainable yield of **3** and **4** (top) and diastereomer ratio r = **3**/**4** (bottom) in *Experiment 2* for complete consumption of configurationally stable **1** by a main reaction leading to **3** and **4** and a parallel side reaction with $s^* = 0.2$

Yield (%) in *Experiment* *1*[a]	Selectivity factor *s* of the main reaction				
	2	3	5	10	15
99	98.6	98.3	97.5	95.7	94.0
97	96.0	95.0	93.0	88.7	85.1
95	93.5	92.0	89.1	83.2	78.9
90	87.8	85.3	81.1	73.8	69.2
80	77.8	74.6	69.8	63.0	59.4
70	69.3	66.2	62.0	56.5	53.9

Yield (%) in *Experiment* *1* [a]	Selectivity factor *s* of the main reaction				
	2	3	5	10	15
99	50.6:49.4	50.8:49.2	51.2:48.8	52.2:47.8	53.1:46.9
97	51.7:48.3	52.3:47.7	53.4:46.6	56.1:43.9	58.4:41.6
95	52.8:47.2	53.7:46.3	55.6:44.4	59.5:40.5	62.8:37.2
90	55.4:44.6	57.2:42.8	60.3:39.7	66.4:33.6	70.9:29.1
80	60.5:39.5	63.5:36.5	68.2:31.8	75.9:24.1	80.6:19.4
70	65.2:34.8	68.9:31.1	74.3:25.7	82.0:18.0	86.2:13.8

[a] The relative rate of the main and side reaction is expressed as the yield of **3** and **4** in *Experiment 1*; in case there is no side reaction, the yield of **3** and **4** is 100%.

be serious if the kinetic resolution factor s is small, a situation which is anyhow preferred for the reasons outlined before.

Conclusions

In the above-mentioned test a configurational labile (organometallic) species will give identical product ratios in both *Experiment 1* (defining the level of the kinetic resolution) and *Experiment 2*. A configurationally stable (organometallic) species will give in *Experiment 2* a different product ratio as in *Experiment 1*. The product ratio in *Experiment 2* should in this case ideally approach 50:50. However, due to incomplete conversion (especially if $s > 2$), insufficient enantiomeric purity of the electrophile (<97%), or slow consumption of the starting organometallic species by side reactions, the product ratio may not actually reach 50:50. An analytically significant difference in the product ratios of *Experiment 1* and *Experiment 2* nevertheless suffices to demonstrate, that the species investigated is not racemizing more rapidly than it is trapped by the electrophile.

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Appendix

Methods Employed for Computation of Tables 1–5 and Figure 1

Calculation of the Data in Figure 1: For reactions with at least one equivalent of enantiomerically pure electrophile **2**, the conversion c_S of (*S*)-**1** and the conversion c_R of (*R*)-**1** are related by the equation

$$c_R = 1 - (1 - c_S)^s$$

while the total conversion of the nucleophile c_N is set to

$$c_N = 0.5\,(c_R + c_S).$$

The diastereomeric excess of the major over the minor product is calculated to be

$$de = 100\%\,[1 - c_S - (1 - c_S)^s]/[1 + c_S - (1 - c_S)^s].$$

A related problem was treated by Sih et al. in the context of enzymatic hydrolysis of racemic esters[18].

Calculation of the Data in Tables 1 and 2: Kinetic resolution of a racemic compound by an enantiomerically enriched compound is represented by a set of four second-order parallel reactions. Numerical integration methods[19] were applied. For a large excess of enantiomerically enriched electrophile and complete consumption of the racemic nucleophile, normalized product yields (%) are given by the following equations.

Major enantiomer of major product diastereomer:

$$y_{SS} = 0.5\,s\,(100\% + \text{e.e.})/[s\,(100\% + \text{e.e.}) + (100\% - \text{e.e.})]$$

Minor enantiomer of major product diastereomer:

$$y_{RR} = 0.5\,s\,(100\% - \text{e.e.})/[s\,(100\% - \text{e.e.}) + (100\% + \text{e.e.})]$$

Major enantiomer of minor product diastereomer:

$$y_{RS} = 0.5\,(100\% + \text{e.e.})/[s\,(100\% - \text{e.e.}) + (100\% + \text{e.e.})]$$

Minor enantiomer of minor product diastereomer:

$$y_{SR} = 0.5\,(100\% - \text{e.e.})/[s\,(100\% + \text{e.e.}) + (100\% - \text{e.e.})]$$

Calculation of the Data in Tables 3, 4, and 5: The rate constants for the consumption of (*S*)-**1** and (*R*)-**1** to give the products **3** and **4** are defined as k_{SS} and k_{RS}. The corresponding rate constants to give the side products are defined as k_{SC} and k_{RC}; hence

$$s = k_{SS}/k_{RS}$$

$$s^* = k_{SC}/k_{RC}.$$

Maximum yield y (%) and diastereomer ratio r of **3** and **4** are as follows.

Experiment 1:

$$y = 100\,(k_{SS} + k_{RS})/(k_{SS} + k_{RS} + k_{RC} + k_{SC})$$

$$r = k_{SS}/k_{RS}$$

Experiment 2:

$$y = 50\,[k_{SS}/(k_{SS} + k_{SC}) + k_{RS}/(k_{RS} + k_{RC})]$$

$$r = [k_{SS}\,(k_{RS} + k_{RC})]/[k_{RS}\,(k_{SS} + k_{SC})]$$

CAS Registry Number

2: 111060-64-1

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