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Incremental Solvation Precedes Ion-Pair Separation in Enantiomerization of a Cyano-Stabilized Grignard Reagent

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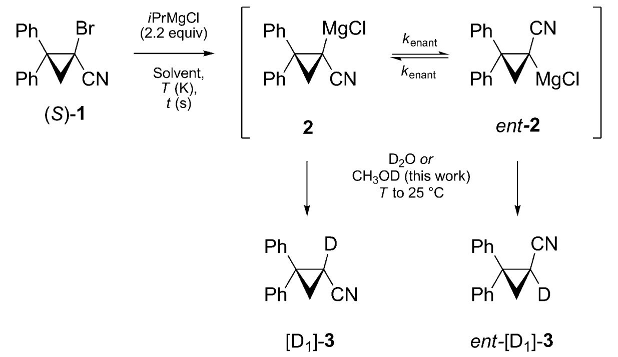
Dedicated to Professor K. Barry Sharpless on the occasion of his 70th birthday

Configurationally stable enantioenriched organolithium compounds are important in asymmetric synthesis.[1] Studies of the enantiomerization pathways of these compounds are useful for improving the stereochemical outcome of these reactions, and provide insight into the structure and dynamics of these compounds.[1a,f,2] The composition of the organic fragment,[1a,f,2a,d] the presence of additives,[2d,3] and the identity of the solvent[2d,4] are all known to affect configurational stability. In contrast, few such studies have been reported for enantioenriched organomagnesium compounds, perhaps reflecting the relative paucity of these reagents.[5] Herein we report Eyring analyses and reaction order studies of the racemization of enantioenriched Grignard reagent **2** in ethereal solvents. Enantiomerization rates increase in the order Et_2O < 2-methylTHF < THF. A highly negative activation entropy for enantiomerization ((−49 ± 4) eu) is seen under conditions where reaction is zero-order in $[Et_2O]$ and first-order in [Mg]. These results are consistent with an ion-pair separation enantiomerization mechanism wherein association of solvent precedes rupture of the Mg–C bond. To our knowledge this is the first experimental determination of the timing of incremental solvation and ion-pair separation for a Group I or II organometallic reagent.

We previously reported[5h] that enantioenriched cyano-stabilized Grignard reagent **2** could be prepared by Mg/Br exchange[6] of enantiopure α-bromonitrile (*S*)-**1** with *i*PrMgCl (Scheme 1). The overall transformation of (*S*)-**1** to $[D_1]$-**3** was shown to favor retention, and measurements of the e.r. of $[D_1]$-**3** with increasing delay time *t* demonstrated that **2** possessed a racemization half life ($t_{1/2}(rac)$) of 11.4 h in Et_2O at 173 K. The extrapolated e.r. at $t=0$ for **2** from these experiments was 91:9, suggesting that Mg/Br exchange was not perfectly retentive.

To explore the role of solvent in the enantiomerization process, we reinvestigated this reaction in Et_2O, 2-methyltetrahydrofuran (2-MeTHF), and THF, at several temperatures. A key feature of our reinvestigation was the use of a precooled CH_3OD quench in place of room-temperature D_2O.[7] Delay times *t* varied from 60 to 3600 s and >95 % recovery of $[D_1]$-**3** (>98 % deuterium incorporation) was obtained after workup even at the shortest time points (60 s) at 175 K. First-order rate constants for enantiomerization of **2** (k_{enant}) derive from slopes ($-2k_{enant}$) of the plots of ln(|$2X_R([D_1]$-**3**)-1|) versus delay time *t* (Figure 1).[8]



Scheme 1. Mg/Br exchange/deuteration reactions of (*S*)-(+)-**1**; structures of **2** are not meant to imply a particular aggregation or solvation state.

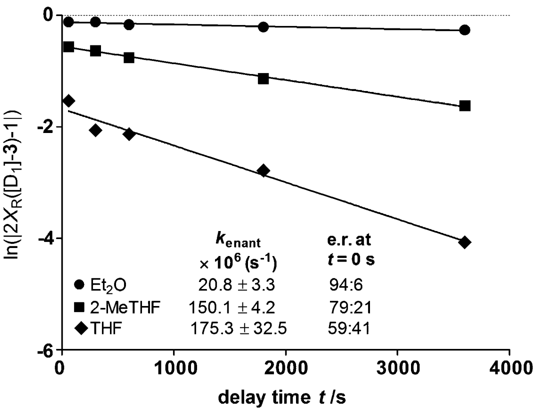


Figure 1. Determination of enantiomerization rate constants k_{enant} and extrapolated $t=0$ e.r. for **2** at 195 K and $[Mg]_{total}=0.0342$ M in Et_2O, 2-MeTHF, THF. X_R is the mole fraction of the *R* enantiomer; note that e.r. = $100*X_R$: $100*(1-X_R)$. The slope of each plot is $-2*k_{enant}$, and intercept of each plot is $\ln(2X_R(t=0)-1)$, from which the extrapolated $t=0$ e.r. can be determined.

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As can be seen, at 195 K enantiomerization in Et_2O is seven- to eightfold slower than in 2-MeTHF and THF; the same ordering is seen at the other temperatures as well. Because Mg/Br exchange is complete within 1 min even at 175 K, the *y* intercepts of these plots reflect the approximate e.r. values of **2** following Mg/Br exchange. Whereas Mg/Br exchange in Et_2O at 195 K is highly retentive (extrapolated $t=0$ e.r. is 94:6), reactions are significantly less selective in 2-MeTHF and THF (extrapolated $t=0$ er values of 79:21 and 59:41, respectively).

These divergent results suggest significant involvement of the solvent in the both the Mg/Br exchange and enantiomerization. To determine the activation parameters for enantiomerization in these solvents, Eyring[9] analyses of the enantiomerization rate constants were performed, using the linear form $\Delta G^{\ddagger}=\Delta H^{\ddagger}-T\Delta S^{\ddagger}$ (Figure 2).[10]

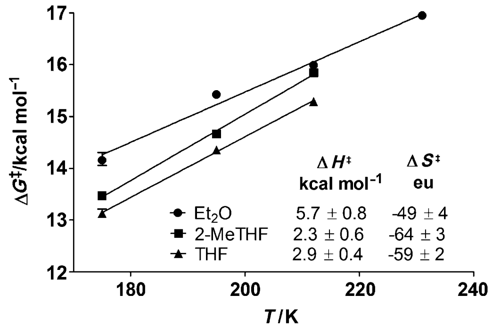


Figure 2. Plot of calculated $\Delta G^{\ddagger}$ values versus temperature T and activation parameters for the enantiomerization of **2** in Et_2O. $\Delta G^{\ddagger}$ values were calculated from k_{enant} values (175 K, 195 K, 212 K, 231 K) using the Eyring equation. In most cases the error bars are smaller than the symbol. Note that measurement of k_{enant} at 231 K was practical only in Et_2O; in 2-MeTHF and THF at this temperature, Mg/Br exchange reactions gave nearly racemic products.

In all three solvents, large negative entropies of activation $\Delta S^{\ddagger}$ were calculated (Et_2O: (-49 ± 4) eu; 2-MeTHF: (-64 ± 3) eu; THF: (-59 ± 2) eu), accompanied by relatively small enthalpies of activation $\Delta H^{\ddagger}$ (Et_2O: (5.7 ± 0.8) kcal mol^{-1}; 2-MeTHF: (2.3 ± 0.6) kcal mol^{-1}; THF: (2.9 ± 0.4) kcal mol^{-1}). Capriati et al. recently reported[1f] a similarly high negative entropy of activation ((-44 ± 1) eu) for the enantiomerization of 1-lithio-1-(3-trifluoromethylphenyl)oxirane. A highly negative entropy of activation (-33 eu) for enantiomerization was also reported for the related structure 1-lithio-1-arylcyclopropane,[11] and smaller negative values have been noted by other workers for enantiomerization of other organolithium compounds.[2a,12] Such results are generally interpreted as evidence for enantiomerization by an ion-pair separation mechanism, rather than by a "conducted tour" mechanism.[2a] Two distinct phenomenon have been proposed as the origin of the negative entropy of activation: either an increase in solvation number concerted with ion pair separation (solvent capture), or rearrangement of the secondary solvent shell during Li–C cleavage of a fully solvated contact ion pair, to stabilize developing charge separation (solvent electrostriction).[12] These hypotheses, though appealing, merit additional scrutiny. One approach that could discriminate between them, and eliminate other possibilities, would be to measure reaction orders.[13]

For these studies we restricted ourselves to the use of Et_2O as solvent. In addition to providing the most retentive Mg/Br exchange and smallest enantiomerization rate constants, the structure of the Grignard reagent in solution is considerably simpler in Et_2O than in THF. Unlike the wide array of structures proposed in THF,[14] in Et_2O, alkyl magnesium chlorides are known by ebullioscopy to be dimeric.[14b,15] X-ray crystallography of Et_2O solvates of RMgCl show a preference for bis(μ_2-Cl) dimers,[16] suggesting this structural motif in solution. Furthermore, our studies of the stoichiometry of Mg/Br exchange of **1** with *i*PrMgCl in Et_2O are consistent with the formation of a mixed aggregate of **2** and *i*PrMgCl. Reaction of **1** with 1.1 equiv *i*PrMgCl in Et_2O (titrated, 10 min, 212 K, CH_3OD quench), gave only (59 ± 5) % conversion of **1** (^1H NMR), and (65 ± 4) % of the expected amount of *i*PrBr (GC/MS, internal standard). Increasing the amount of *i*PrMgCl to 2.2 equiv gave >98 % conversion of **1**, and (92 ± 4) % of the expected amount of *i*PrBr. We account for these observations by proposing that *i*PrMgCl, which is known to be a dimer in Et_2O,[15b] reacts quickly with one equivalent of **1**, to form a **2**·*i*PrMgCl heterodimer and *i*PrBr. Apparently reaction of the heterodimer with another equivalent of **1** is slow under these conditions, as is disproportionation of the mixed dimer to regenerate the reactive *i*PrMgCl homodimer. In contrast, otherwise identical studies in THF demonstrate that 1.1 equiv of *i*PrMgCl (titrated) provides >95 % consumption of **1**, and generation of (90 ± 4) % of the expected amount of *i*PrBr, consistent with the expected monomeric state of *i*PrMgCl in THF.[15b]

To address the possibility that the large negative $\Delta S^{\ddagger}$ observed in Et_2O was due to aggregation of **2**·*i*PrMgCl on the enantiomerization path,[17] k_{enant} was measured at 195 K over a 25-fold range in $[Mg]_{\mathrm{total}}$, from 0.063 to 0.0025 M (see the Supporting Information). If Grignard reagent aggregation necessarily precedes enantiomerization, the measured first-order rate constants k_{enant} would increase with increasing $[Mg]_{\mathrm{total}}$.[18] Yet, within experimental error, no change in k_{enant} was seen over this range, thus firmly establishing first-order kinetics,[19] and ruling out required aggregation (or deaggregation) at this temperature on the enantiomerization path.

To directly test the hypothesis that the solvation number of **2** increases in the rate-determining transition state, the reaction order in $[Et_2O]$ was studied by performing the Mg/Br exchange in Et_2O/toluene mixtures at a fixed Grignard concentration of 0.00625 M. The concentration of Et_2O was varied over a 158-fold range, from 0.056 M (9 equiv Et_2O) to 9.5 M (neat Et_2O, 1520 equiv) at two temperatures (212 K and 195 K, Table 1).

At 195 K, k_{enant} remained unchanged until $[Et_2O]$ fell to 0.06 M; note that a small but steady increase in $t=0$ e.r. to 98:2 is also seen as $[Et_2O]$ decreases.[20] However, at 212 K, from the lowest Et_2O concentration (0.06 M) to pure Et_2O

Table 1. Dependence of k_{enant} and extrapolated $t=0$ e.r. of **2** on [Et_2O].[a]

Entry	Temp [K]	[Et_2O] [M][b]	$k_{\mathrm{enant}} \times 10^6$ [s^{-1}]	e.r. ($t=0$)[c]
1	195	9.5	25.2 ± 5.4	94:6
2	195	0.95	24.4 ± 5.5	97:3
3	195	0.23	22.6 ± 5.8	97:3
4	195	0.15	21.6 ± 2.5	98:2
5	195	0.056	12.9 ± 3.1	98:2
6	212	9.5	179.4 ± 14.7	91:9
7	212	0.95	145.3 ± 37.9	95:5
8	212	0.23	114.5 ± 31.8	95:5
9	212	0.15	70.8 ± 17.8	96:4
10	212	0.056	12.4 ± 1.6	96:4

[a] Reactions performed at $[\mathrm{Mg}]_{\mathrm{total}} = 0.00625$ M. [b] Concentration of Et_2O in toluene, assuming neat Et_2O is 9.5 M at both 195 and 212 K. [c] Extrapolated.

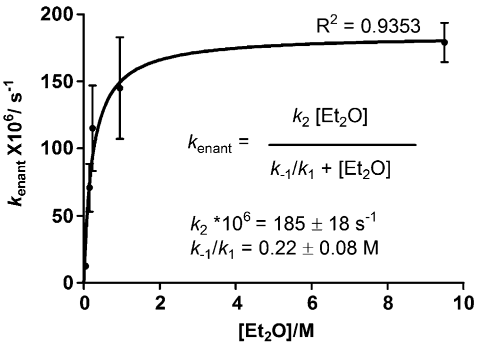
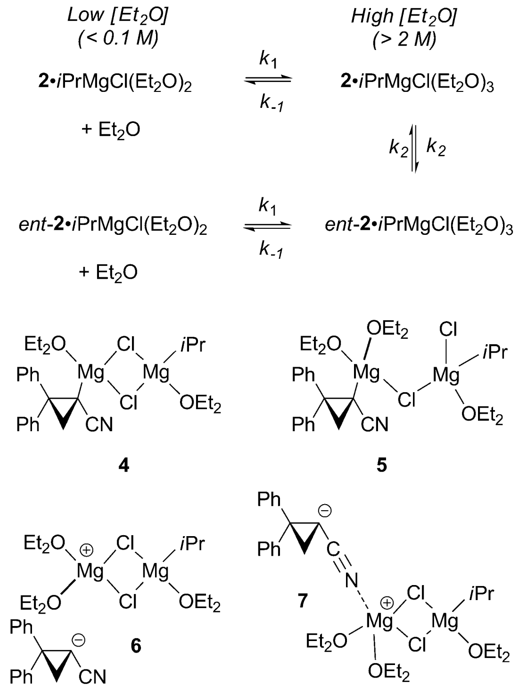


Figure 3. Plot of k_{enant} versus [Et_2O] in toluene co-solvent at 212 K at $[\mathrm{Mg}]_{\mathrm{total}} = 0.006$ M. See Scheme 2 for the definition of k_2, k_{-1}, and k_1, and the Supporting Information for derivation of the equation relating them and [Et_2O] to k_{enant}.

(9.5 M), k_{enant} increases 14.5-fold. As Figure 3 illustrates, *saturating*, not simple first-order dependence of k_{enant} on [Et_2O] is seen.

Saturation behavior in [donor solvent] has been reported for the deprotonation of hydrazones by LDA in TMEDA/hexanes,[21] and deprotonation of ketones by LiHMDS in R_3N/toluene.[22] The rate constant data in Table 1 and the saturation behavior depicted in Figure 2 are consistent with a increase in the resting solvation number of **2**·*i*PrMgCl from [Et_2O] = 0.06 M (9 equiv Et_2O) to neat Et_2O (9.5 M, 1520 equiv) (Scheme 2).

Based on the available X-ray crystal structures of Et_2O–solvates of RMgCl[16] and other bis(μ_2-X) dimers,[23] at low [Et_2O], **2**·*i*PrMgCl likely exists as a disolvate (e.g. **4**). Although fits of k_{enant} to [Et_2O] (see the Supporting Information) do not allow us to discriminate between addition of one or two solvent molecules, for simplicity we assume formation of a trisolvate in pure Et_2O. One possible structure for the trisolvate would be the open dimer **5**; such a structure has been located computationally for the Et_2O trisolvate of the MeMgCl dimer.[24] However the zero-order dependence of k_{enant} on [Et_2O] at high [Et_2O] *does* allow us to rule out an increased solvation number in the rate-determining transition structure for enantiomerization, relative to the solvation number at the resting state in pure Et_2O. Therefore the large negative entropy of activation for enantiomerization ((−49 ± 4) eu) measured in pure Et_2O cannot be attributed to solvent capture in the transition structure, and must be due to solvent electrostriction. Reordering of the secondary solvent shell to stabilize the increasing dipole moment during formation of a separated ion-pair such as **6** should carry a significant entropic cost. Note that the depicted pyramidalization of the cyclopropyl anion in **6** is supported by calculations of the free anion;[25] reduced angle strain is no doubt responsible for this preference.[26] In addition we would like to point out that a "conducted tour" pathway[25] to directly generate an ion-pair like **7** would also be consistent with observed $\Delta S^{\neq}$ value and cannot be ruled out. Carbanion inversion of **7** and N → C migration would ultimately lead to enantiomerization of **2**. Such an "ionogenic conducted tour" is thus a possible alternative to direct formation of **6** by a traditional ion-pair separation mechanism.



Scheme 2. Proposed mechanism for the enantiomerization of the **2**·*i*PrMgCl heterodimer in Et_2O, and possible intermediates **4**–**7**.

In closing, we note that highly negative entropies of activation have been seen in several cases for dissociative reactions involving carbocationic intermediates.[27] In these examples, rate-limiting coordination of solvent is not likely, and solvent electrostriction provides a reasonable explanation for the observed large negative $\Delta S^{\neq}$ values (up to (−33 ± 2) eu[27a]). It thus seems likely that solvent electrostriction plays a significant role in the kinetics and thermodynamics of many ionogenic reactions, including the enantiomerization of stabilized organolithium compounds in ethereal solvents.[1f,11,28]

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Keywords: electrostriction · enantiomerization · Grignard reagents · ion-pair separation · reaction mechanisms · solvents

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[18] As we show in the Supporting Information, the term $2X_R$-1 is equivalent to $\{[(R)\text{-}\mathbf{2}] - [(R)\text{-}\mathbf{2}]^e\}/\{[(R)\text{-}\mathbf{2}]^0 - [(R)\text{-}\mathbf{2}]^e\}$, where $[(R)\text{-}\mathbf{2}]$, $[(R)\text{-}\mathbf{2}]^e$, and $[(R)\text{-}\mathbf{2}]^0$ are the time-dependent, equilibrium, and initial concentrations of (R)-**2**. For our studies on the dependence of k_{enant} on Grignard concentration, we chose the easily measurable quantity $[\text{Mg}]_{\text{total}}$: Note that $[(R)\text{-}\mathbf{2}]^e$ and $[(R)\text{-}\mathbf{2}]^0$ are both proportional to $[\text{Mg}]_{\text{total}}$, and $[(R)\text{-}\mathbf{2}]$ is related to $[\text{Mg}]_{\text{total}}$ by exponential decay from $[(R)\text{-}\mathbf{2}]^0$. Although this first-order rate constant k_{enant} does not measure the decay of [Mg], it measures the rate of decay of the excess concentration of (R)-**2** over its equilibrium value, which is related to $[\text{Mg}]_{\text{total}}$. It is therefore appropriate to study the effect of varying $[\text{Mg}]_{\text{total}}$ on k_{enant}.

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