Chiral Grignard Reagents

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New Insights into the Classic Chiral Grignard Reagent (1*R*,2*S*,5*R*)-Menthylmagnesium Chloride**

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A broad range of phosphines with chiral substituents have been used in asymmetric synthesis for many years. Some of these chiral substituents are derived from menthol, for example, the diastereomeric phosphines $MenPh_2P$ and $NeomPh_2P$ (Men = menthyl, Neom = neomenthyl).[1] Organotin hydrides that contain menthyl groups (for example, $MenPh_2SnH$ and Men_2PhSnH) are also known, and have shown promise as chirality-transfer reagents in enantioselective reductions involving free radicals.[2] The reaction of MenCl with Mg to form the menthyl Grignard reagent directly appeared to be atypical for this type of reaction, because subsequent reactions with Ph_2PCl and Me_3SnCl resulted in exclusive formation of the products $MenPh_2P$[3] and $MenMe_3Sn$,[4] respectively, with complete retention of all stereogenic centers within the menthyl substituents.[5] Although (1*R*,2*S*,5*R*)-menthylmagnesium chloride (**1**) is listed in the CAS structure database, there is no mention of (1*S*,2*S*,5*R*)-neomenthylmagnesium chloride (**2**). $NeomPh_2P$ has been synthesized, but from reaction of Ph_2PNa with MenCl.[8]

Our attempts to prepare menthyltriphenyltin, $MenPh_3Sn$, from the reaction between the menthyl Grignard reagent and Ph_3SnCl led to the formation of mixtures of $MenPh_3Sn$ and $NeomPh_3Sn$, the latter apparently resulting from epimerization at the C1 position in the original menthyl moiety.[9] At that time, we believed that the menthyl Grignard reagent was

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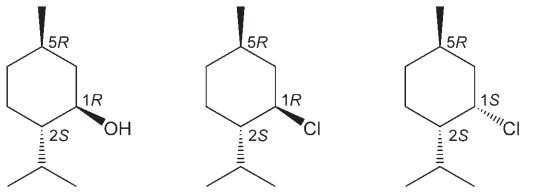
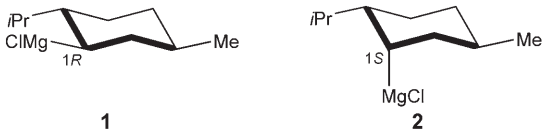


(-)-menthol (-)-menthyl chloride MenCl (+)-neomenthyl chloride NeomCl

formed with complete retention of configuration, and that epimerization occurred during subsequent reaction of the Grignard reagent with some electrophiles.[9] Recently, Hoffmann proposed a single-electron-transfer (SET) mechanism for this type of reaction, in which triphenyltin and menthyl radicals would be formed and subsequently would recombine with little or no diastereoselectivity.[7] This mechanism appeared to provide a rational explanation for our observation of the formation of both $MenPh_3Sn$ and $NeomPh_3Sn$.

However, during studies to optimize the yield of Men_2Ph_2Sn (**3**) formed from the reaction between Ph_2SnCl_2 and the Grignard reagent derived from MenCl, we observed the formation of $NeomMenPh_2Sn$ (**4**), a product in which one of the menthyl groups had undergone epimerization at the C1 carbon atom. Interestingly, the reaction between menthyl Grignard reagent and Ph_2SnCl_2 has been previously reported to yield Men_2Ph_2Sn,[10] although the physical properties reported for the product, including the optical rotation (an oil, $[\alpha]_D^{20} = -30.5°$), differ significantly from those we found for **3**. A crystal structure of **3** was obtained and has confirmed the stereogenic centers in the menthyl groups to indeed be those of Men_2Ph_2Sn.[11]

These observations provoked a more detailed investigation of the stereochemical integrity in the reactions of Grignard reagents derived from MenCl (1*R*) and its epimerization partner, NeomCl (1*S*).[12] The two major conformations[14] are shown in Scheme 1.



1 (1*R*,2*S*,5*R*)-menthyl Grignard reagent

2 (1*S*,2*S*,5*R*)-neomenthyl Grignard reagent

Scheme 1. The two major conformations of the Grignard reagent: equatorial (left) and axial (right).

In an attempt to obtain $Neom_2Ph_2Sn$, we reacted the Grignard reagent prepared from NeomCl with Ph_2SnCl_2. Surprisingly, this reaction gave products **3** and **4** in similar yields to those obtained from reaction of the Grignard reagent prepared from MenCl. We found no evidence for the formation of the anticipated product, $Neom_2Ph_2Sn$. These observations suggest that magnesium reacts with either MenCl or NeomCl to give an identical mixture of Grignard reagents. The results of quenching the reactions with D_2O were particularly informative. Quenching each of the Grignard reagents formed from MenCl and NeomCl with D_2O gave identical results, in each case a 1:1 ratio of [D]menthane and [D]neomenthane.

On reexamination of the reaction between the Grignard reagent mixture and Ph_2PCl, we gained additional information. The reaction between an approximately equimolar ratio of the Grignard reagent and Ph_2PCl had been reported to give $MenPh_2P$ in 51% yield.[3] We repeated this reaction and after quenching with D_2O, investigated the product array by NMR spectroscopy. We found that half of the Grignard reagent was consumed to form $MenPh_2P$ and the remaining half reacted with D_2O to form NeomD. Apparently only MenMgCl (**1**) is a sufficiently strong Lewis acid to lower the relatively high-energy LUMO of Ph_2PCl, which is attacked along the axial plane (opposite chloride) by the strongly nucleophilic menthyl group. NeomMgCl (**2**) appears to be more involved in the Schlenk equilibrium because of its axial magnesium chloride group, with a concomitant decrease in its Lewis acidity and shielding of its carbocation. Hence, in addition reactions, MenMgCl (**1**) acts simultaneously as a strong Lewis catalyst and as a strong nucleophile towards substrates.[15] As a result, we found no evidence for $NeomPh_2P$, which is consistent with **2** being much less nucleophilic than **1**.

Closer inspection of experimental details in the original report for the synthesis of $MenMe_3Sn$[4] revealed that reaction between the Grignard reagent and Me_3SnCl in a 2:1 stoichiometric ratio produced $MenMe_3Sn$ in 94% yield (based on Me_3SnCl). This observation is consistent with preferential reaction of the menthyl component **1** of the Grignard reagent (that is, half of the total Grignard reagent originally formed). The fate or nature of the unreacted Grignard reagent, presumably the neomenthyl component **2**, remained unaccounted for, and **2** was most likely hydrolyzed during the workup. Additional experiments involving the reaction of Me_3SnCl with a limited amount of Grignard reagent revealed that $NeomMe_3Sn$ was not formed at all, an observation similar to those made from the reaction of the Grignard reagent with Ph_2PCl.

The strong Lewis acidity of Ph_2SnCl_2, combined with the preferential attack by the more reactive MenMgCl, means that it is not possible to selectively form $NeomPh_2SnCl$ from a Grignard reaction. However, the weaker acidity of the triorganotin species results in lower rate discrimination between the menthyl and neomenthyl components of the Grignard reagent. Consequently, increasing the ratio of the Grignard reagent to Ph_3SnCl from 1:1 to 4:1 resulted in an increase in the product ratio of $MenPh_3Sn$ to $NeomPh_3Sn$ from 65:35 to 99:1.

When the Grignard reagent and Ph_2SnCl_2 are reacted together, depending on the reaction conditions, two different products can be obtained, namely Men_2Ph_2Sn (**3**) and $NeomMenPh_2Sn$ (**4**); these products were crystallized and isolated in yields of 32% (m.p. 75–76 °C, $[\alpha]_D^{25} = -50.2°$) and 21% (m.p. 58–59 °C, $[\alpha]_D^{25} = -13.9°$), respectively from separate reactions.[16] The identity of the novel compound $NeomMenPh_2Sn$ (**4**) was unambiguously confirmed by ^1H and ^{13}C NMR spectroscopy as well as by X-ray crystallography. The molecular structure of one of the two crystallographically independent conformers of **4** is shown in Figure 1.

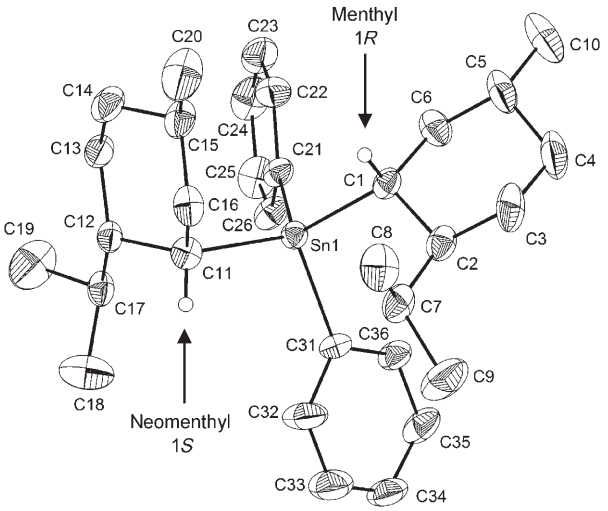
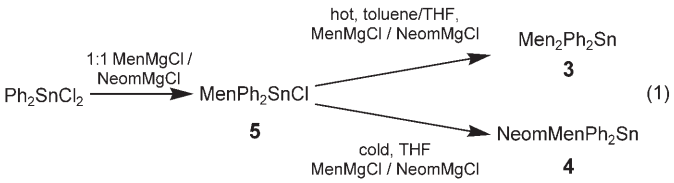


Figure 1. Molecular structures of one of the two crystallographically independent conformers of **4**, showing 30% probability displacement ellipsoids and the crystallographic numbering scheme. For clarity, only the hydrogen atoms connected to the C1 and C11 atoms are shown.

The ratio of products **3** and **4** could be significantly altered by changing the temperature, solvent, and the amount of Grignard reagent. Hence, when a hot solution of Ph_2SnCl_2 in toluene was added to a hot THF solution of Grignard reagent prepared from five equivalents of MenCl, and the reaction was stirred at reflux for two hours, Men_2Ph_2Sn (**3**) formed as the major product;[17] ^{119}Sn NMR spectroscopy showed the ratio of **3** and **4** to be 93:7 [Eq. (1)]. When a cold solution



(1)

(0 °C) of Ph_2SnCl_2 in THF was added to a cold THF solution (0 °C) of Grignard reagent prepared from 2.5 equivalents of MenCl, and the reaction mixture was stirred for two days at room temperature, $NeomMenPh_2Sn$ (**4**) formed predominately [Eq. (1)]; ^{119}Sn NMR spectroscopy showed the ratio of **3** and **4** to be 28:72.[18] Significantly, there was no evidence for formation of either $Neom_2Ph_2Sn$ or $(NeomPh_2Sn)_2$, which suggests that under both hot and cold reaction conditions, the first substitution reaction affords exclusively the intermediate $MenPh_2SnCl$ (**5**).[19] These observations are consistent with a mechanism in which the first step is nucleophilic attack by the more reactive menthyl component of the Grignard reagent on the Lewis acidic tin species to give **5**. The second substitution is slower because of the decreased Lewis acidity and increased steric bulk of **5**, and thus, depending on the reaction conditions, either **3** or **4** is obtained. It may therefore be possible to prepare $Neom_2Ph_2Sn$ by first removing the more reactive MenMgCl (**1**) by reaction with Ph_2PCl.

In conclusion, direct synthesis of Grignard reagents from enantiomerically pure alkyl halides will always result in a 1:1 ratio of the two possible epimers. Once formed, the two components of the reagent are configurationally stable—there is no equilibrium between them. If the reactivity of the two epimers differs significantly, as in the case of MenMgCl (**1**) and NeomMgCl (**2**), it is possible to selectively use each component in reactions with electrophiles. This can be achieved by using thermodynamic/kinetic control of the reaction, altering temperature, solvent polarity, and stoichiometry. These findings reveal possible uses of Grignard reagents in asymmetric synthesis. Full consumption of the more reactive epimer (for example, **1**) by reaction with an appropriate electrophile (for example, Ph_2PCl) results in a reaction mixture that contains a pure chiral Grignard reagent (for example, **2**). Subsequent reaction with carbonyl groups opens the pathway to chiral alcohols. Fine-tuning of the reaction conditions will no doubt permit the application of pairs of Grignard epimers in which the difference in the reactivity is not as pronounced as in the case of **1** and **2**.

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[1] The substituent names menthyl (Men) and neomenthyl (Neom) stand for the (1*R*,2*S*,5*R*)- and the (1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl group, respectively.
[2] "Asymmetric Free-Radical Reductions Mediated by Chiral Stannanes, Germanes and Silanes": J. Beckmann, D. Dakternieks, C. H. Schiesser in *Handbook of Chiral Chemicals* (Ed.: D. Ager), Marcel Dekker, New York, **2005**, chap. 27, pp. 531–538.
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[5] The formation of Grignard reagents by direct synthesis at a magnesium surface proceeds via alkyl radicals and furnishes racemic Grignard reagents, even when the precursor (in this case MenCl) is enantiomerically pure.[6] The preparation of true chiral Grignard reagents would require a route that avoids any intermediates radicals.[7]
[6] H. M. Walborsky, A. E. Young, *J. Am. Chem. Soc.* **1964**, *86*, 3288.
[7] R. W. Hoffmann, *Chem. Soc. Rev.* **2003**, *32*, 225, and references therein.
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[11] D. Dakternieks, K. Dunn, B. R. Vincent, E. R. T. Tiekink, *Main Group Met. Chem.* **2000**, *23*, 329.
[12] The Grignard reagent was freshly prepared from the reaction of enantiomerically pure MenCl or NeomCl with Mg in THF; the reaction temperature was allowed to rise to the boiling point of THF and then kept there for 2 h. The Grignard reagent was typically found by titration to be formed in greater than 85% yield.[13]

[13] "Wet Analysis of Grignard Reagents": G. S. Silverman in *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**, chap. 6, 89 – 92.
[14] D. H. R. Barton, *Experientia* **1950**, *6*, 316.
[15] P. Sykes, *A Guidebook to Mechanism in Organic Chemistry*, 6th ed., Longman Scientific & Technical, **1986**, chap. 8, pp. 221 – 223. The reaction involves a concerted polar mechanism via a six-membered cyclic transition state in which two molecules of RMgX are implicated. The second molecule of RMgX acts as a Lewis catalyst.
[16] The optical rotations of isolated **1** and **2** suggest that the material described in Ref. [6] was actually a mixture of **1** and **2**, with a ratio of approximately 54:46.
[17] There is an additional minor signal in the ^{119}Sn NMR spectrum (ca. 18%), which is attributed to the ditin species $MenPh_2SnSnPh_2Men$. This species was formed from an alternative six-membered transition state containing two molecules of $MenPh_2SnCl$ and one molecule of RMgCl.[15] RMgCl acts as a simultaneous acidic catalyst towards one moiety of $MenPh_2SnCl$ (**5**) (ClRMg→Cl-Sn) and as a basic catalyst towards the other moiety of **5** (RMgCl→Sn). The resulting stannyl anion carried out a nucleophilic attack at the axial site of the activated **5** (formally reductive elimination). This competitive reaction was favored by the reduced polarity of the solvent, which had been chosen to slow down the attack of the unwanted Neom carbanion.
[18] Under both hot and cold reactions conditions, a few additional minor ^{119}Sn NMR signals (total integral value of approximately 6%) were observed and remain unassigned.
[19] To support this theory, two equivalents of the Grignard reagent prepared from MenCl were added to a cold solution of Ph_2SnCl_2 in THF, and the mixture was immediately quenched with water. After workup, the ^{119}Sn NMR spectrum of the crude reaction mixture showed four signals at $\delta = -0.5$ (integral 27%), −54.6 (integral 62%), −89.3 (integral 4%), and −50.8 (integral 7%), corresponding to $MenPh_2SnCl$ (**5**), $(MenPh_2Sn)_2O$ (**6**), Men_2Ph_2Sn (**3**), and an unidentified component, respectively (Figure 2). Clearly most of **5** had been converted into **6** on

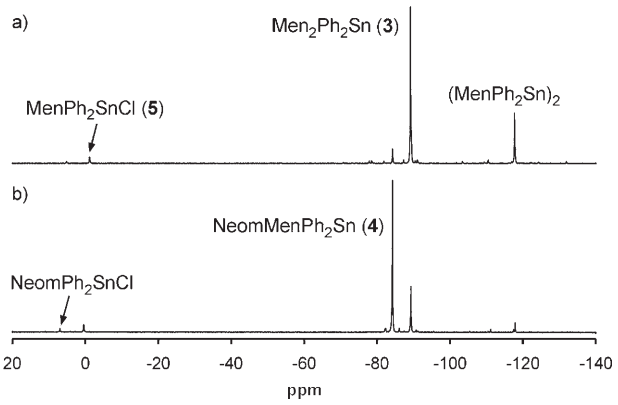

Figure 2. ^{119}Sn NMR spectrum of the crude reaction mixture prepared from the reaction of Grignard reagent with Ph_2SnCl_2 under a) hot (reflux) and b) cold (ice bath) conditions.

workup. We converted (−)-$MenPh_2SnI$[9] into **5** by halogen exchange[20] and then into **6** by base hydrolysis to confirm the assignment of these signals from the NMR spectrum.
[20] B. Zobel, A. E. K. Lim, K. Dunn, D. Dakternieks, *Organometallics* **1999**, *18*, 4889.

