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Stereochemistry of the Menthyl Grignard Reagent: Generation, Composition, Dynamics, and Reactions with Electrophiles

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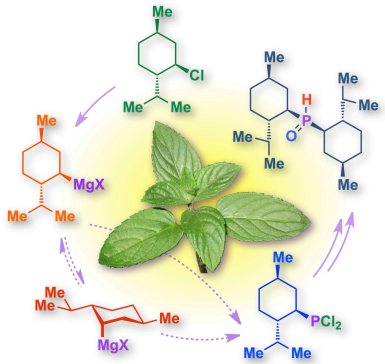


ABSTRACT

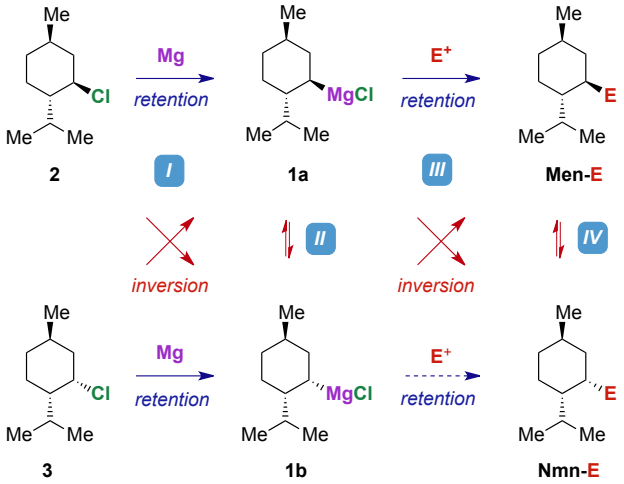
Menthyl Grignard reagent **1** from either menthyl chloride (**2**) or neomenthyl chloride (**3**) consists of menthylmagnesium chloride (**1a**), neomenthylmagnesium chloride (**1b**), *trans-p*-menthane (**4**), 2-menthene (**8**), 3-menthene (**9**) and Wurtz coupling products including symmetrical bimenthyl **13**. The diastereomeric ratio **1a**:**1b** was determined in situ by ^{13}C NMR-, or after D_2O-quenching by ^{2}H NMR analysis. Hydrolysis of the C–Mg bond proceeds with retention of configuration at C-1. The kinetic ratio **1a**:**1b** from Grignard reagent generation (dr 59:41 at 50 °C in THF) is close to the thermodynamic ratio (56:44 at 50 °C in THF). Carboxylation of **1** at –78 °C separates diastereomers **1a/b** to give the anion of menthanecarboxylic acid (**19**) from **1a**, which combines with unreactive **1b** to give neomenthylmagnesium menthanecarboxylate (**1b^{I}**). The kinetics of epimerization for the menthyl/neomenthyl-magnesium system was analyzed ($\Delta H^{‡}$ = 98.5 kJ/mol, $\Delta S^{‡}$ = –113 J/mol·K for **1b^{I}→1a^{I}**). Reactions of **1** with phosphorus electrophiles proceed stereoconvergently at C-1 of **1a/b** to give predominantly menthyl-configured substitution products: PCl_3 and two equivalents of **1** give Men_2PCl (**6**), which hydrolyzes to dimenthylphosphine *P*-oxide (**7**), whereas Ph_2PCl with a single equivalent of **1** gave *P*-menthyl-diphenylphosphine oxide (**27**), after workup in air.

INTRODUCTION

Menthyl Grignard reagent **1** is prepared in the usual way from menthyl chloride (**2**) and magnesium in etheric solution.[1,2] This chiral organometallic reagent is widely used to attach menthyl groups to electrophilic centers. Reactions have been described *e.g.* with carbon dioxide,[3,4,5,6,7,8,9] formaldehyde,[9] dichloromethane,[4] PCl_3,[1,10,11] $PhPCl_2$,[12,] Ph_2PCl,[2,13,14] $GeCl_4$,[15] $SnCl_4$ or organotin chlorides.[11a,d,16] The reagent has also been used in cross-coupling[17,18] or transmetallation reactions.[19] The products tend to retain menthyl configuration, and the sequence from **2** via **1** to various substitution products (**Men-E**)

has usually been assumed to proceed with retention of configuration in all steps (Scheme 1).[8,9,14,20,21] The occasional observation of epimeric products (**Nmn-E**) as minor components revealed that retention is not strict. It is not immediately obvious if inversion occurs at the stage of metal insertion (Scheme 1, **I**), by epimerization of menthyl- (**1a**) to neomenthylmagnesium chloride (**1b**) upon storage (**II**), during electrophilic substitution (**III**), by epimerization of the final product (Scheme 1, **IV**), or in several of those steps.[22]

Scheme 1. Stereochemical aspects of reactions via menthyl Grignard reagent to electrophilic substitution products.[a]



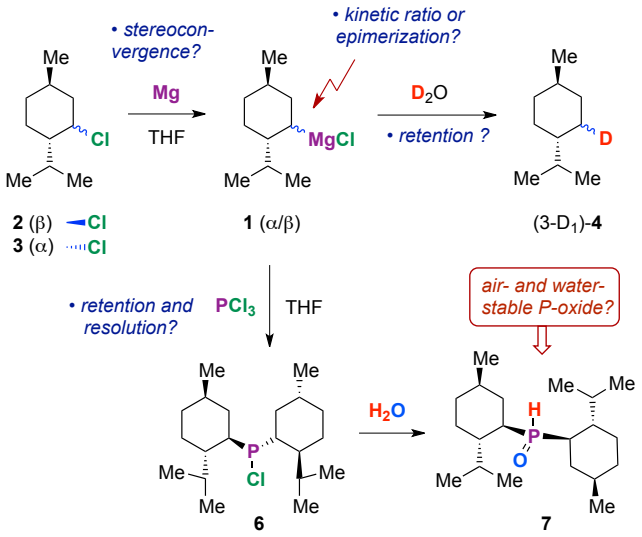
a) E^+ = electrophile. Men-E and Nmn-E represent menthyl or neomenthyl configured substitution products. Men (menthyl) is (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl, Nmn (neomenthyl) is (1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl.

Duthie *et al.* have developed a refined picture of **1** and its reactions:[2] they found equal amounts of diastereomeric (3-D_1)-*p*-menthanes ((3-D_1)-**4**) by quenching **1** with D_2O and concluded that the reagent is a

1:1 mixture of configurationally stable epimers **1a/b**, which forms *stereoconvergently* from either **2** or neomenthyl chloride (**3**).[2] They also obtained the same product spectrum in reactions of Ph_2SnCl_2 with Grignard reagents from either **2** or **3** and proposed that the higher *nucleophilicity* of **1a** over **1b** – and thus kinetic resolution – was responsible for the usual preference of menthyl-configured substitution products. Their model implies that **1b** remains unchanged in the reaction, that a maximal yield of 50 % of **Men-E** will be formed in reactions with a single equivalent of **1**, and that use of two or more equivalents of **1** might raise yields to quantitative. This analysis (convergence in **I**, resolution in **III**) assumes that **III** proceeds with retention of configuration at C-1, and that **1a/b**, as well as products **Men-E**/**Nmn-E**, are configurationally stable under reaction conditions.[22,23] Both assumptions are unproved; in terms of deuteration, Knochel and coworkers observed that menthylzinc iodide is an epimeric mixture with dr 65:35, but may react with MeOD to give (3-D_1)-**4** with dr >99:1 (Men/Nmn).[18,24,25] As for epimerization of **1a**/**b**, no experimental data is available. A complementary, direct analysis of reagent **1** and the elucidation of its equilibration kinetics are required to benchmark the validity of the D_2O-quenching method and permit secure assignments of the stereochemistry of steps **I** and **III**. Statements on the composition of **1** and the stereoselectivity of **III** that are solely based on the Men/Nmn-ratio of a substitution product are insecure. Particularly so, if the isolated product quantities are substantially lower than the molar amount of **1** applied, meaning that kinetic resolution may have occurred.

The present work emerged from an analysis of synthetic routes to *P*,*P*-dimenthylphosphane-based chiral phosphorus ligands.[26,27] We have previously reported on the nucleophilic chlorination of menthol (**5**)[28] to menthyl chloride (**2**) and accompanying rearrangements.[29] In continuation of those studies, we wished to investigate the synthesis of Men_2PCl (**6**)[1] from **1** and PCl_3, which is low-yielding (13 %,[10] 25–35 %[1]) and suffers from the difficult separation of the water- and oxygen-sensitive **6** from by-products. We anticipated that hydrolytic workup would convert **6** to dimenthylphosphine *P*-oxide (**7**),[30] whose expected stability towards water and air might facilitate its isolation (Scheme 2).

Scheme 2. In situ synthesis of *P*-chloro-dimenthylphosphane (6) and hydrolysis to dimenthylphosphine *P*-oxide (7).



If so accessible, **7** might find application as chiral secondary phosphine oxide (SPO) ligand,[31,32] or as platform chemical for chiral phosphine and phosphine oxide synthesis.[33] Objectives of the present work were thus: a) to study the synthesis and composition of Grignard reagent **1**; b) to determine the diastereomeric ratio **1a**:**1b** by NMR spectroscopy in solution, and to validate D_2O-quenching as quantitative analytical method for analyzing dr; c) to elucidate the temperature-dependent kinetics of equilibration of **1a/b**; d) to determine the stereochemistry of substitution of **1** with selected electrophiles; e) and to access and isolate Men_2PHO (**7**).

RESULTS AND DISCUSSION

Synthesis and Qualitative NMR Analysis of 1

Menthylmagnesium bromide had been prepared within a year of Grignard's discovery[34] of his magnesium organometallics.[5] The analogous chloride **1** was later obtained from **2** in Et_2O[6,7] or THF solution.[1,9,13] According to Duthie *et al.*[2] reagent **1** is composed of non-epimerizing diastereomers **1a/b** in a 1:1 ratio in THF, irrespective of its generation from **2** or **3**, which would imply kinetic control over the

diastereomeric ratio. Increasing the proportion of **1a** in the mixture would then be desirable in syntheses of menthyl configured targets, since the latter were assumed to emerge from the kinetically preferred reaction of **1a** with electrophiles.[2] NMR spectroscopy should offer direct evidence of the composition of Grignard reagent **1**, and provide structural proof of all components.

We prepared **1** from **2** (≥96 % purity)[29] and excess magnesium, activated by iodine and 1,2-dibromo-ethane, in (D_8)-THF.[35] The majority of signals in the ^{1}H NMR spectrum (Figure 1) overlap in the aliphatic region (δ_H 0.5–2.5).

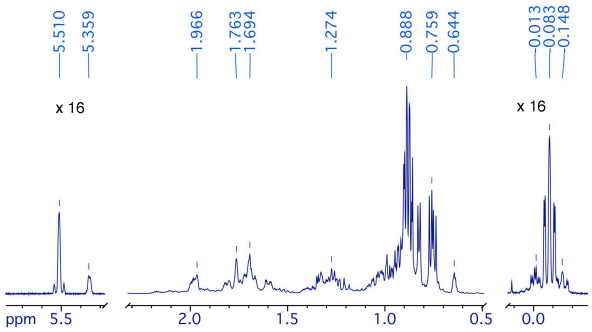


Figure 1. Excerpts from the ^{1}H NMR spectrum (500 MHz) of **1** in (D_8)-THF. The olefinic (δ 5.5) and high field (δ 0) regions are scaled by a vertical factor of 16.

Olefinic signals at lower field are due to 2-menthene (**8**; δ 5.51) and 3-menthene (**9**; δ 5.36), sometimes accompanied by ψ-menthene **10**.[36,37] A group of signals below δ_H 0, centered by a major signal (δ –0.08) with multiplicity *ddd* ($^3J_{H,H}$ = 13.3, 11.9, 2.9 Hz) show the typical shape of an axial H-1 in menthyl-derivatives and are due to menthylmagnesium species that collectively belong to **1a**. The major signal likely represents MenMgCl(THF)$_n$ (**1a'**). A slightly broadened signal of similar shape at lower frequency (δ –0.15) is ascribed to Men_2Mg as component of the Schlenk equilibrium (*vide infra*). Minor signals at higher frequency tend to be less structured (see Figure S3 for examples) and may belong to MenMgX compounds with other co-ligands or counter-ions.[38,39] Integration of the CHMg-region against internal

standard naphthalene in many experiments accounted for only 30–50 mol % of the RMgX-concentration determined by titration.[40] Therefore, ^{1}H NMR spectroscopy gives an incomplete picture of the composition of **1**. The ^{13}C NMR spectrum of **1** features a prominent signal at δ 52.8, later assigned to C-2 of **1b'**, which was set to 100 area-% as reference. Approximately 80 peaks at ≥5 area-% were detected in total, besides those of the solvent and of the internal standard naphthalene. Signal sets for 2-menthene (**8**;[37] 10 peaks, 19–24 area-%) and 3-menthene (**9**;[37] 10 peaks, 10–12 area-%) were assigned by reference data.[41] Out of 26 major peaks (40–120 area-%), 6 were assigned to *trans*-*p*-menthane (**4**),[42] and 10 each to the predominant organomagnesium species **1a'**/**b'**.[43] Connectivity and peak assignments for **1a'**/**b'** and **4** were elucidated by 2D NMR methods (HSQC, HMBC). The ^{13}C NMR signals for the major organometallic species are mapped in Figure 2.

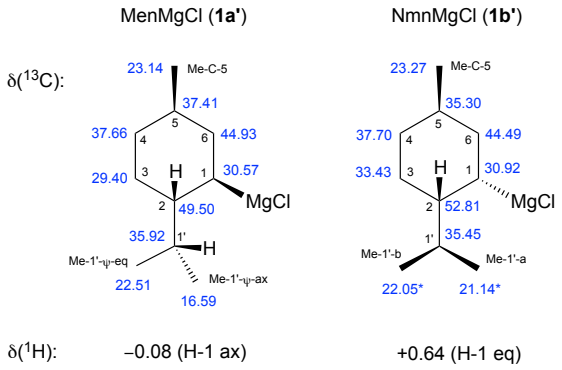


Figure 2. NMR data in (D_8)-THF for the major components in **1**, MenMgCl (**1a'**) and NmnMgCl (**1b'**). Solvent coordination or aggregation is not taken into consideration for simplicity. See the Supporting Information for complete ^{1}H NMR assignments.

The CHMg-unit of **1b'** gives rise to a poorly structured multiplet at δ_H 0.64 in (D_8)-THF (cf. Figure 1). This signal was often obscured in the more commonly analyzed THF–C_6D_6 mixtures. Assignment of signal sets to structures **1a'**/**b'** relies on the characteristic shape of the H-1-signals. Furthermore, menthyl and neomenthyl fragments are discernible by ^{13}C NMR spectroscopy, where peaks for the diastereotopic

methyls of C-2-isopropyl are either clearly separated with one signal at δ ≈ 15–17, the other at δ ≈ 22–23 (in Men-Y), or both found in close vicinity at δ ≈ 21–22 (Nmn-Y).[44] These chemical shifts reflect the preferred conformation of the C-2-isopropyl group, which stands equatorial, with both methyl groups in ψ-equatorial positions relative to the cyclohexane chair in Nmn-Y derivatives (Y = variable substituent; Figure 3, b), unless Y becomes sterically very demanding (Figure 3, c). In most menthyl derivatives including **1a'**, repulsion of groups Y at C-1 and *i*Pr at C-2 causes the isopropyl group to rotate such that one methyl arranges ψ-axial and the other ψ-equatorial relative to the cyclohexane chair (Figure 3, a).[44,45]

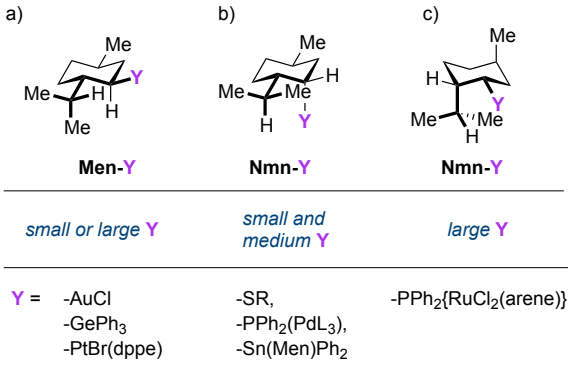


Figure 3. Preferred conformations of Men-Y and Nmn-Y derived from NMR and X-ray crystal structure data. a) Conformation of menthyl derivatives. b) Conformation of neomenthyl derivatives. c) Ring-flipped conformation in neomenthyl derivatives with large Y-groups.[45]

At this point, 34 signals in the region δ 15–48 of the ^{13}C NMR spectrum of **1** remained unassigned. GC-MS-analysis (Figures S15–S17) of a D_2O-quenched sample of **1** indicated that the signals belong to three stereoisomeric hydrocarbons (*m*/*z* 278.3), namely bimenthyl (**13**), menthyl-neomenthyl (**14**) and bineomenthyl (**15**). A batch of **1** was quenched with aqueous acid, washed with concd H_2SO_4 and vacuum distilled. The more volatile fraction consisted of **4**, with a minor amount of ψ-menthane (1-isobutyl-3-methylcyclopentane; **16**, 96:4 ratio).[46] Distillation of the residue in high vacuum gave a bimenthyl isomer fraction (**13**:**14**:**15** = 39:45:16) as colorless oil. Its ^{1}H NMR spectrum covered the narrow shift range of

δ 0.6–2.2 with signal overlap even at 950 MHz (Figure S18). Based on HMBC and HSQC and the δ_C criterion for discerning menthyl from neomenthyl fragments, all 40 carbon and 52 proton signals in **13**–**15** could be assigned (Figures 4, S19, S21, S22).

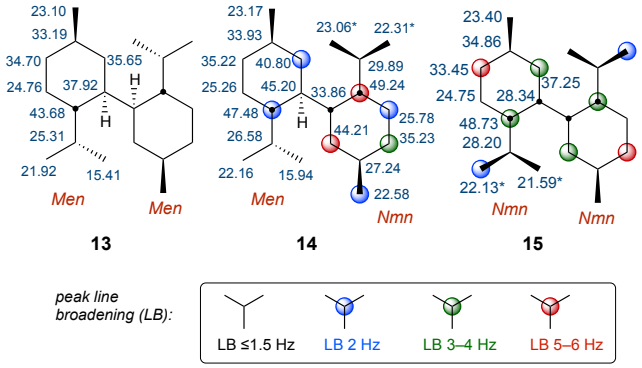


Figure 4. ^{13}C NMR assignments for the Wurtz hydrocarbon byproducts Men-Men (**13**), Men-Nmn (**14**), and Nmn-Nmn **(15**). An asteriks (*) indicates interchangeable assignments.

Unlike symmetrical bimenthyl **13**, hydrocarbons **14** and **15** show δ_C line broadening in specific positions, indicative of a dynamic chair-flip of the neomenthyl units. The oily hydrocarbon mixture separated crystals of bimenthyl (**13**) upon standing, as revealed by NMR spectroscopy and X-ray crystal structure analysis (Figure 5). Compound **13** melts at 105–106 °C, and is thus identical with a crystalline bimenthyl isomer from the Wurtz-coupling of **2** described in the older literature.[47]

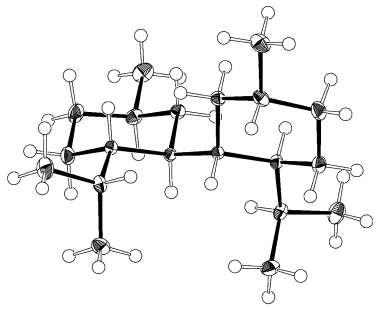


Figure 5. X-ray solid-state molecular structure of bimenthyl **13**. Ellipsoids are shown at 50 % probability.

Quantitative Analysis of Menthyl Grignard Reagent

Grignard reagent **1** was analyzed volumetrically for total alkylmagnesium,[40] and for total magnesium by EDTA-titration of acid-quenched samples.[48] Quantitative ^{1}H NMR spectroscopy (qNMR) with naphthalene as internal standard permitted quantification of menthenes **8**/**9** by integration of the well-separated olefinic signals. Since the δ 0.5–4 region did not contain well resolved signals for integration, we usually prepared **1** in non-deuterated THF and admixed C_6D_6 for locking prior to NMR analysis. As in a previous study of the composition of crude menthyl chloride,[29] the high resolution and information density of ^{13}C NMR recommended use of this technique for quantitative analysis.[49,50,51] Naphthalene (δ 128.6) served as internal standard under routine analysis conditions, and empirical correction factors for peaks of individual components, positions and carbon types (CH vs. CH_2 vs. CH_3) were applied.[52] Correction factors were derived from analysis of reference materials (**4**, **13**–**15**) against internal standard, or by referencing to quantitative ^{1}H NMR data (**8**, **9**). Since reference material is not available for **1a**/**b**, their correction factors were estimated from structurally similar model compounds.[52] Deconvolutive peak fitting was applied to reduce subjective errors and correct for peak overlap. Quantification of **1a**/**b** presented additional challenges due to the Schlenk and other ligand exchange equilibria. The population of Men-Mg and Nmn-Mg units is not correlated with the signal intensity of a single species (**1a'**/**b'**), but must be summed over various chemical forms, some of which display chemical exchange-broadened signals (Figure 6).

a) b) c)

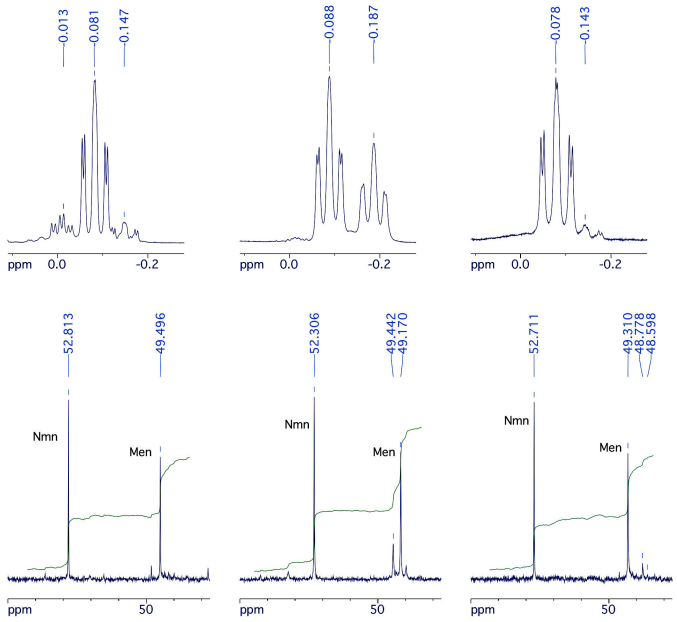
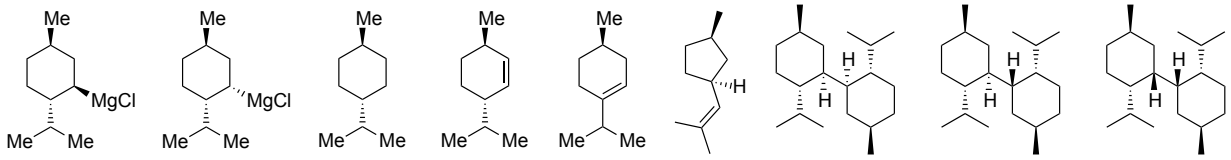


Figure 6. Excerpts from ^{1}H (top; 500 MHz) and ^{13}C NMR (bottom; 101 MHz) spectra of Grignard reagent **1**. a) Reagent prepared from **2** and Mg in (D_8)-THF (prepared at 70 °C, nominal concentration 0.9 M); [RMg]/[Mg] = 0.49. b) Higher concentrated **1** in THF (50–70 °C, 1.55 M) with C_6D_6 added for locking, displaying a high content of Men_2Mg; [RMg]/[Mg] ratio = 0.9. c) Reagent prepared from **3** and Mg in (D_8)-THF (rt, 0.9 M); [RMg]/[Mg] ratio = 0.4; ^{1}H NMR at 400 MHz.

Figure 6a shows excerpts of the ^{1}H and ^{13}C NMR spectra for **1**. The characteristic signal of **1a'** in the ^{1}H NMR spectrum (H-1, δ_H 0.08) correlates (by HMBC) with C-2 at δ_C 49.5, whereas H-1 of NmnMgCl (**1b'**; δ_H 0.64, cf. Figure 1) correlates with C-2 at δ_C 52.8. The intensity ratio of the major C-2-peaks does not reflect the ratio **1a**/**b**: the major C-2 peak for **1a'** is accompanied by broad signals, and the total integral δ_C 48–51 (**1a**-region) surpasses that of δ_C 51–54 (**1b**-region).[53] Figure 6b shows spectra of **1** at high [R-Mg]/[Mg] ratio.[54] As expected, the signal at δ_H –0.19 for Men_2Mg is more intense than for a low [RMg]/[Mg] ratio.[55] The **1a**-region contains at least three broadened signals for C-2 of **1a'**, Men_2Mg and either MenMgBr[38] or more complex species.[56] Satisfactory analytical results for the population and dr of **1** resulted from area integration of δ 51–54 (for **1b**) and δ 48–51 (for **1a**), after subtraction of overlapping

peak signals.[57] The peak area correction factor for C-2 in **1a/b** relative to internal standard signal was set to the value for menthol (**5**) as model compound. This introduces an unknown systematic error, which we estimate to be below 5–10 % of the absolute values,[58] but will be even less important for the ratio **1a**:**1b**, where such systematic errors cancel out.[50a] The data thus obtained for all key components in Grignard reagent **1** will be subject to additional systematic errors by variation of T_1 and the NOE effect with sample composition, but even if accuracy for individual component concentrations is limited, parameter variation effects on the composition of **1** can now be systematically studied.

Table 1. Analyses of menthyl Grignard reagent 1, prepared from 2 or 3 under variable reaction conditions.[a]



1a **1b** **4** **8** **9** **10** **13** (Men_2) **14** (Men-Nmn) **15** (Nmn_2)

Entry	Solvent	*t* [°C]	Conc. [M][b]	[RMg] [M][c]	[Mg] [M][d]	Yield [%][e]	**1** [%]	**1a**:**1b**	**4** [%]	**8** [%]	**9** [%]	**13**–**15** [%][f]	**13**:**14**:**15**	Recov. [%][g]
Reactions starting from menthyl chloride (**2**)														
1	THF	rt	1.8	0.97	1.59	53	54.1	55:45	12.2	5.5	2.9	25.9	36:47:17	100.5
2	THF	rt	0.9	0.64	0.90	72	74.0	62:38	9.7	3.5	1.9	20.1	32:50:18	109.4
2a							(D_2O:	62:38)						
3	THF	50	1.8	1.44	1.88	80	72.5	59:41	6.4	2.4	1.2	11.8	32:50:18	94.5[h]
4	THF	50	0.9	0.77	0.95	86	74.3	59:41	8.3	2.9	1.5	11.8	36:49:15	98.8
4a							(D_2O:	59:41)						
5	THF	50[i]	0.9	0.76	0.85	85	76.9	58:42	7.2	2.3	1.2	11.7	31:57:12	99.4
5a							(D_2O:	55:45)[j]						
6	THF	70	0.9	0.74	0.92	81	87.5	55:45	6.5	1.6	0.9	8.8	38:45:17	105.3
7	Et_2O	RT	0.9	0.65	1.18	72[k]	45.1	56:44	15.3	6.0	3.1	29.2	37:47:16	99.1
8	THF–PhMe	RT	1.1	0.72	1.04	67	68.6	53:47	10.6	4.4	2.3	20.5	36:48:16	106.6[l]
9	THF–PhMe	50	1.8	1.24	1.51	70	71.4	55:45	8.4	3.5	1.7	16.2	40:44:16	101.3

10	THF–PhMe	50	1.1	0.80	1.00	75	73.0	54:46	8.2	2.4	1.4	10.8	37:45:18	96.0[m]
11	THF–PhMe	70	1.8	1.33	1.58	75	78.4	55:45	6.7	1.6	0.9	8.5	32:54:14	96.2
11a							(D_2O:	56:44)						
12	THF–PhMe	70	1.1	0.95	1.10	85	85.3	58:42	4.9	1.1	0.6	5.3	44:47:9	97.2
Reactions starting from neomenthyl chloride (**3**)														
13	THF	rt	0.9	n.d.	n.d.	n.d.	45.7	45:55	20.5	5.5.	2.5	20.3	36:45:19	105.0[n]
14	THF	30	0.9	0.55	1.39	60	44.2	48:52	9.9	5.1	2.7	20.7	35:46:19	83.7[o]
14a							(D_2O:	42:58)[p]						
15	THF	50	0.9	0.66	1.37	73	63.6	54:46	13.6	3.0	2.0	16.6	35:48:17	100.2[q]

[a] Sample composition in mol % of initial **2** (or **3**); concentrations in M = mol/L. [b]Nominal concentration calculated from initial **2**/**3** and volumes of starting material and solvent, rounded to 0.1 M. [c]Total concentration of RMg-entities by titration.[40] [d]Total Mg^{2+}-concentration by EDTA titration. [e]Yield of **1** calculated from $[RMg]_{tot}$ and nominal concentration. [f]Value expressed in mol % of Men/Nmn groups; the true molarity of dimers is half this value. [g]Recovery is the sum of analytically detected Men and Nmn groups in mol %; deviations from 100 % are due to undetected components and systematic errors. [h]Including 0.2 mol % of **10**. [i]Reagent prepared at 50 °C over 1 h, then heated to 70 °C for 2 h. [j]D_2O-quenching result **1a**/**1b**/**16**: 43.3:35.5:3.0 mol % by ^2H NMR against C_6D_6 as internal standard. [k]Large deviation due to solvent loss and heterogeneity; NMR analysis performed after evaporation of Et_2O and redissolution in THF. [l]Including 0.2 % of **10**. [m]Including 0.3 % of **10**. [n]Including 10.4 % of **3**. [o]NMR analysis after ≥ 4 h, with 1.0 % of remaining **3**. [p]D_2O quench performed after 2 h, at 10 % of remaining **3**. [q]Including 1.4 % of **3**.

Effects of Reaction Conditions on the Composition of 1

Effects of varying the solvent, reaction temperature and total concentration in the reaction of **2** and magnesium were studied by analyzing the composition of the resulting Grignard reagent (Table 1, entries 1–12). The yield of **1** was higher at 50 or 70 °C than at ambient temperature or 30 °C, and also higher in dilute (0.9–1.1 M) over concentrated (1.8 M) solution. Synthesizing the reagent in THF–toluene at 70 °C or in THF at 50–70 °C gave similar, satisfactory results with a yield of 75–85 mol %, whereas diethyl ether (entry 7) was less satisfactory. Reagent yields in THF and Et_2O agree with earlier reported titration results.[1,6] Spectroscopic yields of **1** do not correlate exactly with [RMg] from titration, since yield calculations depend on estimated reaction volumes, which are inaccurate in small scale experiments.

In a first approximation, the diastereomeric ratio **1a**:**1b** deviates not much from an average value of 57:43, irrespective of the reaction conditions. Complementary data for dr was in some cases obtained by

quenching a sample with D_2O and analyzing the ratio of (3-D_1)-**4** stereoisomers by ^2H NMR spectroscopy (Figure 7).[2,59]

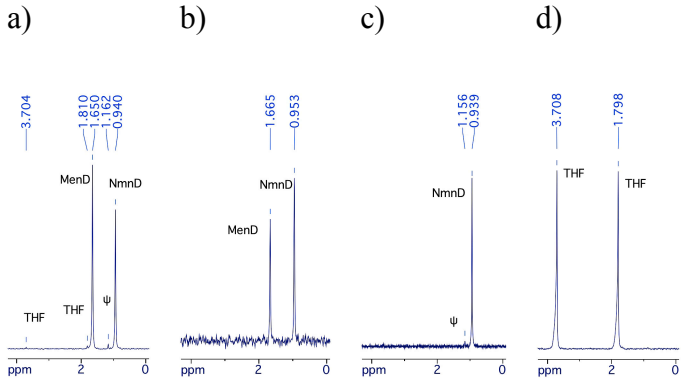


Figure 7. $^2H\{^1H\}$ NMR spectra (61 MHz) of quenched samples of **1**. a) D_2O-quenched sample of equilibrated **1**. b) D_2O-quenched sample of the reaction **3** + Mg in THF, before completion (Table 1, entry 14a). c) Carboxylated and D_2O-quenched **1** composed mainly of α-(3-D_1)-**4**. d) H_2O-quenched sample of **1** generated in (D_8)-THF. Most (D_8)-THF was removed by washing with water prior to analysis; only residual (D_8)-THF is present. "ψ" marks peaks for (D_1)-**16**.

The signals δ_D 1.65 and 0.94 correspond to the centers of multiplets in the ^1H NMR spectrum of **4** at δ_H 1.68 and 0.97 for equatorial and axial H-3, respectively. A small peak at δ_D 1.16 corresponds to D-1' of ψ-menthane (**16**; δ_H 1.18) from deuterolysis of *sec*-ψ-MenMgCl (**12**).[39] A Grignard reagent from NmnCl (**3**; Table 1, entries 13–15) was largely identical to that from **2**, as also evident from the similar NMR spectra (Figure 6, a vs. 6, c)[2,60] – at least if prepared at 50 °C (Table 1, entry 4 vs. 15). The room temperature Grignard reaction of **3** was sluggish to initiate and required several hours for reaching completion (entries 13, 14). A D_2O-quenched sample after 2 hours at 30 °C gave (3-D_1)-**4** with dr 42:58 at 90 % conversion (entry 14a; ^2H NMR in Figure 7, b), which rose to dr 48:52 after 4 h (at 99 % conversion; entry 14). Conversely, if **1** was generated from **2** at ambient temperature, a sample at 40 % conversion displayed a higher dr 62:38 (Table 1, entry 2). Thus, Grignard reagent **1** is formed with a

small degree of retention of configuration at ambient temperature, but approaches dr 56:44 if prepared at 50 or 70 °C from either **2** or **3**, which implies that the latter is an equilibrium ratio (vide infra).

The abundance of byproduct *p*-menthane (**4**) is always higher than the sum of menthenes **8** and **9**. Radical abstraction from the solvent provides no source of **4**, because when **1** was prepared in (D_8)-THF, no trace of (3-D_1)-**4** or solvent coupling-product was detected by $^2H\{^1H\}$ NMR after protic workup (Figure 7, d).[61] Byproducts **4**, **8** and **9** are most abundant at room-temperature (Table 1, entries 1, 2, 13) and decrease at higher temperature (entries, 3, 6, 12). Alkenes **8**/**9** are formed in similar amounts and isomeric ratio from both **2** and **3** (entry 15), which excludes E2-elimination (with **1** as base) as an important reaction pathway.[62] This points to a specific mechanistic route for products **4**/**8**/**9,** besides the obvious source of some **4** by reaction of **1** with adventitious water. We suggest that β-H-elimination of surface-bound ^{S}MgR (R = Men or Nmn) to surface-bound ^{S}Mg–H and alkenes **8**/**9** is followed by combination of ^{S}MgH and ^{S}MgR to give **4**. Bimenthyl isomers **13**–**15** will similarly be formed by combining two surface-bound ^{S}MgR units, which agrees with the observation that the extent of Wurtz-coupling and the generation of **4**+**8**/**9** is correlated. The observation of higher amounts of neutral byproducts (R–H, R–R) at ambient temperature, but higher selectivity for Grignard reagent **1** at elevated temperature might be a consequence of rate-limiting detachment of RMgCl from the metal surface. This process, involving major solvent reorganization, will have a higher activation barrier than the release of apolar hydrocarbons (RH, RR), which is likely limited by diffusion-controlled encounter of two surface groups. The stereoconvergence from **2** and **3** to give **1a**/**b**, the generation of bimenthyls **13**–**15** and the absence of solvent-derived-products all point to a key mechanistic role of ^{S}MgR-units, in which R inverts at experimental timescale, much slower than a free radical, but faster than the final RMgX.[63,64]

Conclusions on the Generation of 1

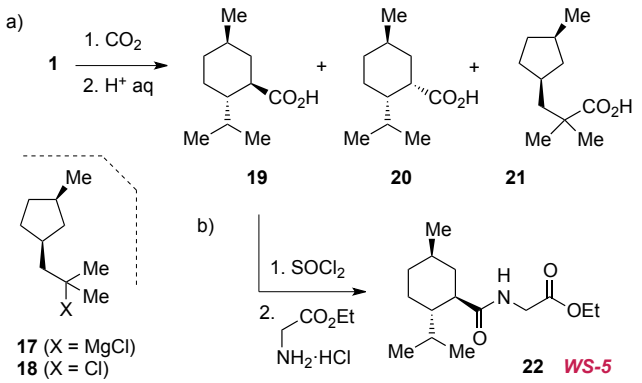
The analyses in Table 1 validate the hypothesis that menthyl Grignard reagent **1** is a diastereomeric mixture **1a**/**b**, formed in a kinetically controlled and stereoconvergent process from either **2** or **3** in similar

amounts.[2] Irrespective of reaction conditions, the ratio **1a/b** varies only little around an average dr of 57:43. Presumably, this ratio is not just kinetically controlled, but close to thermodynamic equilibrium. In spite of the valuable data obtained through ^{13}C NMR spectroscopy, the faster and more accurate option for analyzing the dr of **1a**/**b** is $^{2}H\{^{1}H\}$ NMR spectroscopy of D_2O-quenched samples. The method gives accurate results that agree with the in situ ^{13}C NMR data, but does not suffer from complications caused by species partitioning in the Schlenk equilibrium. Total [RMg] or individual R^nMgX concentrations in mixtures can be quantified using the D_2O-quenching technique, if a deuterated internal standard is added for $^{2}H\{^{1}H\}$ NMR analysis.[65] Given that the ratio **1a**:**1b** cannot be satisfactorily controlled by the reaction conditions used for generating the Grignard reagent, an understanding of the stereochemistry of the reactions of **1a/b** with electrophiles becomes even more vital.

Carboxylation of Menthyl Grignard Reagent

Carboxylation of **1** has been reported repeatedly, but with inconsistent results:[8,3,6] By pouring a THF solution of **1** over solid CO_2, Bose *et al.* obtained 76 % of acids **19**/**20** (Scheme 3) with a dr of 68:32,[3b] while Grayson *et al.* obtained pure **19** (dr >100:1) in 88 % yield.[8] By bubbling CO_2 into etheric **1**, Smith and Wright got 29 % of crystalline **19**, and distilled another 32 % of a liquid (believed to be **20**) from the mother liquors.[6,66] The same procedure provided Ueda *et al.* with 36 % of **19**/**20** in a ratio of 92.6:7.4,[20c] whereas a 1975 patent found almost pure acid **19** (dr 99:1) in 53 % yield.[67] Among the highest yielding carboxylations is a patent that finds 93 % of **19** by concurrent addition of CO_2 and **2** to magnesium in 2-MeTHF–cymene at 90 °C.[68]

Scheme 3. Carboxylation of menthyl Grignard reagent 1, and synthesis of physiological coolant compound WS-5 (22).



To understand the various results, we approached the problem with own experiments. Dry ice was added to a Grignard reagent from crude **2** that contained *tert*-ψ-MenCl (**18**) as major impurity.[29] Acid/base-extraction gave a carboxylic acid fraction with **19**, **20** and **21** in a ratio 77:19:4 (Scheme 3, a). Coupling with ethyl glycinate gave a mixture of peptide esters (ratio 78:18:4) from which the major component **22** crystallized (Scheme 3, b). Compound **22** is commercially available under the name WS-5[69] as *physiological coolant* for inducing a cooling sensation on skin.[70] The substance has so far only been described in the patent literature, thus we characterized it by 2D NMR methods in solution (Figure S26, Tables S21/22) and by X-ray crystal structure analysis in the solid state (Figure 8).

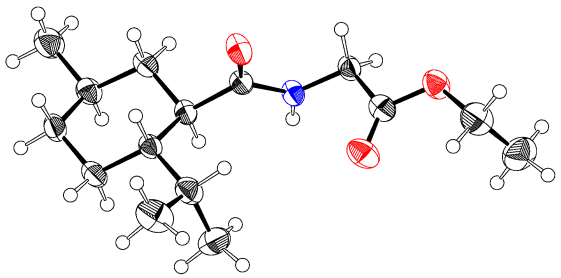
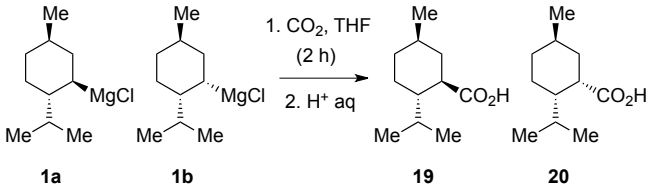


Figure 8. Solid state molecular structure of WS-5 (**22**). Ellipsoids are shown at 50 % probability. Oxygen is red, nitrogen blue. The common arrangement of the C-2 isopropyl group with ψ-axial and -equatorial methyl groups (δ_C 16.16 and 21.49) is evident. The unit cell contains six independent molecules, which differ in the conformation of the peptidic side-chain [Men-C^1(O)-NH-$C^{2'}H_2$-$C^{1'}$(O)O-

$C^{1''}H_2C^{2''}H_3$], in which the torsional angles $C^{1}(O)–N–C^{2'}–C^{1'}(O)$ and $C^{1'}(O)–O–C^{1''}–C^{2''}$ are variable. The individual conformers and their angles are: a) –75/–89; b) –87/–179; c) +91/+96; d) +86/+180; e) +60/+178; f) +58/–173. The pictured conformer is (c). See Figure S28 for depictions of all conformers.

The complexity of crude menthyl chloride had translated into regio- and stereoisomeric carboxylic acids (**19**–**21**) *via* metallation and carboxylation, but the ratio **1a**/**b** (57:43) was not retained in acids **19**/**20** (dr 80:20). In ensuing carboxylation experiments, Grignard reagent **1** from purified menthyl chloride (**2**+**3** ≥97 %) was used and the yield of **19**/**20** was determined by accurate qNMR methods. In one expriment, **1** was added dropwise to a saturated solution of CO_2 in THF at –20 °C and the reaction was quenched with water at the same temperature (Scheme 4, a).

Scheme 4. Carboxylation of Grignard reagent 1 with quantification of carboxylic acids 19/20.



1a **1b** **19** **20**

a) *Addition of **1** to CO_2 (THF) at –20 °C*

1a	**1b**		Yield	*dr*	**19**	**20**
57%	43%	⟹	58.7%	95:5	55.9%	2.8%

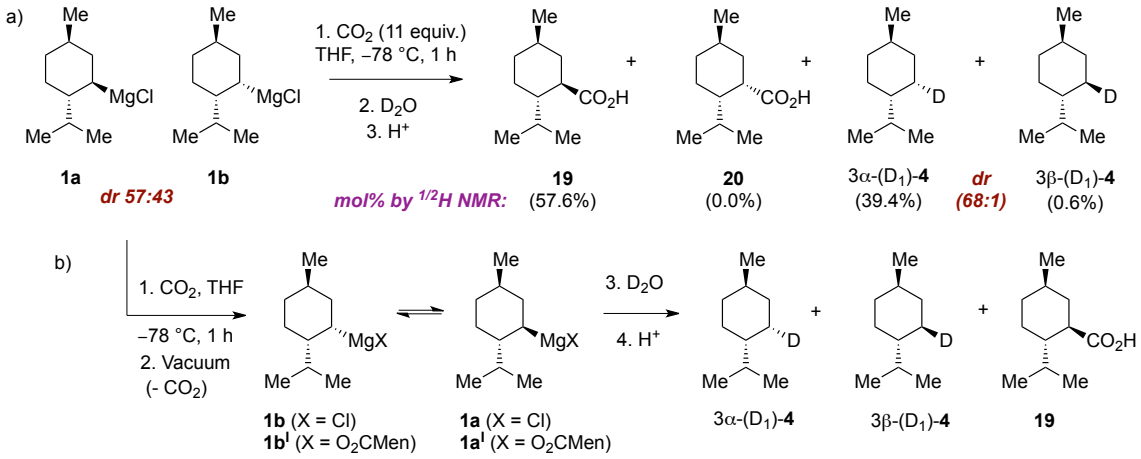
b) *Addition of CO_2 (s) to **1** at ambient temperature*

1a	**1b**		Yield	*dr*	**19**	**20**
57%	43%	⟹	67.8%	89:11	60.2%	7.6%

A second experiment involved the addition of small pieces of CO_2 (*s*) into the solution of **1** at ambient temperature, which corresponds to an inverted addition mode (Scheme 4, b). The outcome in (b) agrees with several literature reports that find **19** as major and **20** as minor component (dr ≈ 8:1; Scheme 4, b). Surprisingly, experiment (a) in which **1a/b** are continuously exposes to excess electrophile showed *higher* selectivity for **19** (dr 19:1) rather than approaching the ratio **1a**/**b** (57:43). The data in Scheme 4

suggest that dr **19**/**20** is not controlled by availability of (excess) electrophile, but by kinetic preference of **1a** over **1b** in the reaction with electrophile. The lower yield and higher dr in (a) reflect improved kinetic resolution at lower reaction temperature. To verify this assumption, not only the reaction products **19**/**20**, but also the unreacted Grignard reagents **1a/b** must be analyzed, which was achieved by D_2O-quenching in combination with use of a deuterated internal standard for $^2H\{^1H\}$ NMR.[71] Such experiments prove that the reaction of **1** with excess CO_2 at –78 °C is limited to epimer **1a** and proceeds with retention of configuration at C-1 to give **19** (Scheme 5, a). Neomenthyl epimer **1b** remains largely unreacted and gives rise to enriched 3α-(D_1)-**4** after quenching with D_2O (Scheme 5, a). In repeat experiments, the kinetic resolution was consistently high, up to the extent where no more 3β-(D_1)-**4** could be detected (≥99.5:0.5).

Scheme 5. Kinetic resolution of menthyl Grignard reagent 1 by low-temperature carboxylation, and epimerization studies.



a) D_2O-quenching for analysis of unreacted Grignard reagent. b) Experimental course for studying the epimerization of resolved neomenthylmagnesium menthanecarboxylate **1b**$^{\mathbf{I}}$.

Kinetics and Equilibrium in the Epimerization of 1

The kinetic resolution of **1** with CO_2 gives access to highly enriched solutions of neomenthyl-configured Grignard reagent **1b^{I}**, from which excess electrophile can be completely removed in vacuum. The kinetics of epimerization[72] of chiral Grignard reagent **1b^{I}** could now be studied by warming to a target temperature and taking samples for D_2O-quenching (Scheme 5, b). Analysis of the dr of 3-(D_1)-**4** by $^{2}H\{^{1}H\}$ NMR provided consistent results as shown in Figure 9. The Nmn-Grignard reagent is configurationally rather stable at 0 °C, but epimerizes notably upon warming to 30 °C ($t_{1/2}$ = 14 h).[73]

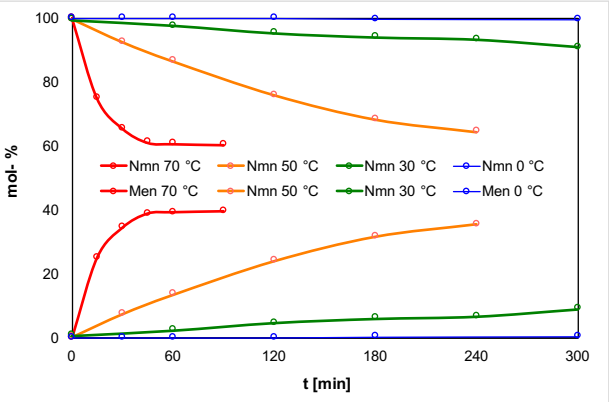
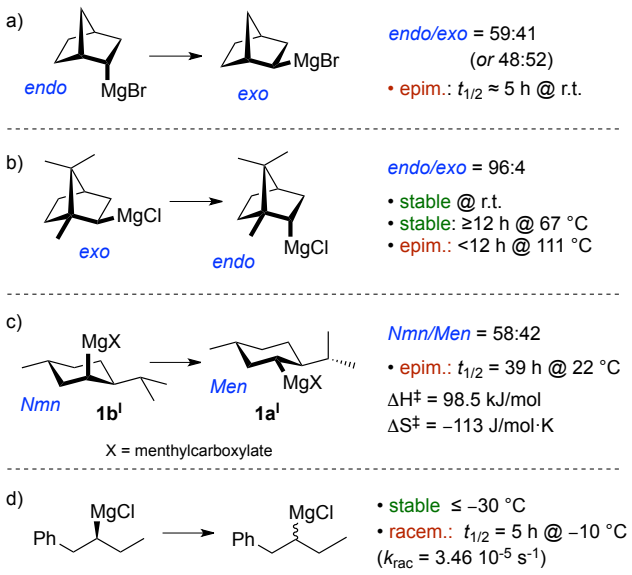


Figure 9. Temperature-dependent epimerization of NmnMg(O_2CMen) (**1b^{I}**) in THF solution. The 300 min data-point at 0 °C was extrapolated for graphical reasons. Curves are interpolated and serve as guidelines only.

Clean first-order kinetics with $t_{1/2}$ of 62 min (50 °C) and 8 min (70 °C) operate at higher temperature. The activation energy is ≈ 100 kJ/mol. The rate **1b^{I}**→**1a^{I}** is characterized by $\Delta H^{‡}$ = 98.5 kJ/mol and $\Delta S^{‡}$ = –113 J/mol·K by Eyring analysis ($\Delta H^{‡}$ = 96.1 kJ/mol and $\Delta S^{‡}$ = –110 J/mol·K for **1a^{I}**→**1b^{I}**), with calculated epimerization half-lives of 39 h at 22 °C, or 65 days at 0 °C.[73]

Scheme 6. Configurational stability of secondary alkyl-Grignard reagents.



a) Norbornylmagnesium halides are known to slowly epimerize at rt. Reported data are faintly conflicting.[74] b) Bornylmagnesiumchloride forms as kinetic *endo*/*exo* 67:33 mixture, but changes to 96:4 upon heating.[75,76] c) Menthylmagnesium compounds slowly epimerize at rt (*this work*). d) Hoffmann's open-chain chiral Grignard reagent racemizes quickly at rt.[79]

Primary alkyl-Grignard reagents invert fast already below room temperature.[77] Properties of secondary alkyl-magnesium species are collected in Scheme 6. Norbornylmagnesium bromide equilibrates over a day at room temperature (Scheme 6, a)[74,78] whereas bornylmagnesium chloride is stable under the reflux-conditions of its synthesis, but epimerizes if refluxed in the higher-boiling solvent toluene (Scheme 6, b). Both the solvent and counter-ion differ between systems, making it difficult to assess the importance of additional methyls on configurational stability. In any case, cyclic **1b^{I}** (Scheme 6, c) is more inert than Hoffmann's open-chain secondary alkyl Grignard reagent, which racemizes below 0 °C (Scheme 6, d).[79] The **1a^{I}**/**b^{I}** equilibrium ratios dr 38.3:61.7 (50 °C; after 144 h) and 39.5:60.5 (70 °C, after 1.5 h) deviate markedly from those seen in the thermal equilibration of **1a**/**b** (22 °C; dr 57.3:42.7 after 1 d, increased to 58.2:41.8 after 3 months; 50 °C, dr 55.6:44.4; 70 °C, dr 54.8:45.2). This is not contradictory, because the major chemical species in **1** differ from those in carboxylated reagent **1a^{I}**/**b^{I}** by the presence of chloride

vs. menthyl carboxylate as counter-ion (Scheme 5, b). Yet, the carboxylated reagent shows a surprising prevalence of the axially substituted Nmn-diastereomer **1b^{I}**, which may be a consequence of secondary dimerization and solvation equilibria,[80] because MgX usually favors the equatorial position in cyclohexanes.[81,82] Independent confirmation that the change of conformational preference is caused by the carboxylate counter-ion was obtained by combining **1** with lithium salts of hindered carboxylic acids and determining the composition of the *in situ* generated (Men/Nmn)Mg(O_2CR) species after thermal equilibration. With 2,4,6-trimethylbenzoate (mesitoate), the shift was from dr 57:43 (**1a**/**b**, rt) to 47:53 (**1a^{II}**/**1b^{II}**, 60 °C; after 24 h). The recovery of RMgX (by quantitative ^{2}H NMR[71]) was 98 %, which proves that the change of composition is caused by isomerization and not kinetic ablation (*e.g.*, by hydride elimination) of one isomer.[71] In another experiment with lithium pivalate, the resulting **1a^{III}**/**1b^{III}** was allowed to equilibrate at 70 °C and the reaction progress was followed by sampling and D_2O-quenching (Figure 10).

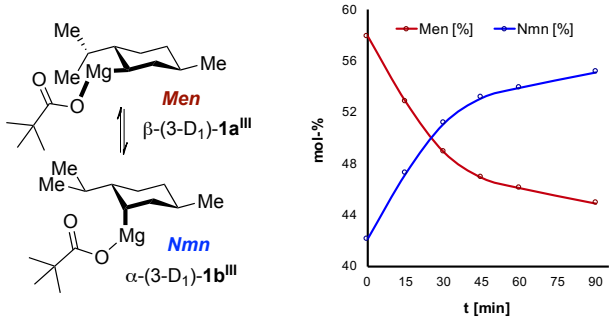


Figure 10. Equilibration of in situ prepared MenMg(OPiv)/NmnMg(OPiv) (**1a^{III}**/**b^{III}**) in THF solution at 70 °C. A solution of **1** was mixed with LiOPiv and heated to 70 °C. Equilibrium ratio **1a^{III}**/**1b^{III}** = 42.9:57.1 (after 69 h).

The initial excess of menthyl diastereomer **1a^{III}** epimerizes with a half-life of 26 min (*cf.* 8 minutes for **1a^{I}**/**1b^{I}**) to a new equilibrium at 42.9 % **1a^{III}**, which is less than in case of mesitoate (46.8 % **1a^{II}**), but

higher than for menthanecarboxylate (39.5 % of **1a**$^{\mathbf{I}}$) as counter-ions. The influence of counter-ion X in MenMgX on Men/Nmn-equilibrium composition and epimerization kinetics is substantial and contributes to the complexity of reaction systems involving reagent **1** with other ionic components.

Stereochemistry and Relative Kinetics of Electrophilic Substitution at C-1 of Menthyl Grignard Reagent

The result of the low-temperature carboxylation of **1** (Scheme 5, a) is expressed in tabular form in Table 2, entry 1. Based on the known initial amount of **1a** and **1b**, analysis of remaining **MenD** (β-(3-D_1)-**4**) and **NmnD** (α-(3-D_1)-**4**)) in the product mixture reveals how much of each diastereomer was converted in a reaction. This quantity is expressed as **Δ1a**/Δ**1b** in mol % (–56/–3 mol %) and compared to the quantity of epimeric substitution products formed (+58/+0 mol %; Table 2, last column). Since the numbers are close, the conclusion can be reached that CO_2 reacts with **1** by a retentive mechanism. This agrees with the observation of retention of configuration at the stereogenic carbon in the carboxylation of Hoffmann's chiral Grignard reagent (cf. Scheme 6).[79a] Reactions of other *H*- and *P*-centered electrophiles with Grignard reagent **1** were similarly investigated, and the results are collected in Table 2.

Table 2. Quantitative investigation of the reactions of Grignard reagent 1 with various electrophiles.[a,b]

Entry	RMgX (**1a**, **1b**)[b,c] [mol %]	T[d] [°C]	**E**$^{+}$[e] [mol %]	**Men-D** (Δ**1a**)[f] [mol %]	**Nmn-D** (Δ**1b**)[f] [mol %]	dr (D$_1$)-**4**	**R-E**[g] (mol %)
1	100 (57, 42)	–78	CO_2 (xs)	1 (-56)	39 (-3)	1:99	MenCO$_2$H (**19**; 58 %); NmnCO$_2$H (**20**; 0 %)
2	100 (57, 42)	–78 → rt	H_2O (25)	36 (-21)	41 (-1)	47:53	–
3	100 (57, 42)	–78 → rt	H_2O (50)	5 (-51)	28 (-13)	16:84	–
4	100 (57, 42)	–78 → rt	MeOH (50)	33 (-23)	32 (-9)	51:49	–
5	100 (57, 42)	–78 → rt	MenOH (50)	32 (-25)	30 (-11)	52:48	–
6	100 (57, 42)	–78 → rt[h]	PCl_3 (200)	n.d.	n.d.	n.d.	MenPO$_2$H$_2$ (**25a**; 92 %); NmnPO$_2$H$_2$ (**25b**; 6 %)
7	300 (170, 127)	0 → 50	PCl_3 (100)	25 (-145)	34 (-93)	43:57	Men$_2$POH (**7**; 61 %)
8a[i]	300 (170, 127)	0	PCl_3 (100)	41 (-129)	49 (-78)	45:55	Men$_2$POH (**7**; 75 %)
8b[i]	300 (170, 127)	0	PCl_3 (100)	44 (-126)	48 (-79)	48:52	Men$_2$POH (**7**; 73 %)
9	100 (57, 42)	0 → rt	Ph_2PCl (100)	8 (-49)	21 (-21)	28:72	MenPOPh$_2$ (**27**; 72 %)

[a]General conditions: **1** was added to electrophile E^{+} in THF at –78 or 0 °C. After stirring for 1–3 h, reactions were quenched with D_2O and warmed to rt. [b]Reactant quantities and analytical compositions are given in mol %, rounded to the next nearest integer number. See the supporting information for more precise values expressed in μmol. [c]The composition of **1** varies from **1a**/**b** = 57:43 to 58:42, with *ca.* 1 mol % of ψ-MenMgCl (**12**) present; the composition of starting **1** (57:42:1 mol %) represents an average value. [d]Room temperature (rt) is *ca.* 22 °C. [e]**E**$^{+}$ = electrophile, quantity in mol % relative to **1** in brackets. [f]Remaining quantity of **1a**/**b** upon conclusion of the reaction, as determined by D_2O-quenching and $^2H\{^1H\}$ NMR quantification of (D$_1$)-**4**. The number in brackets indicates change (loss) of organometallic reagent over the course of the reaction. [g]**R-E** = electrophilic substitution product. [h]Reaction duration 3 h at –78 °C, followed by warming to rt with stirring overnight. [i]8b is a repetition experiment of 8a.

Coinciding analytical results for the dr of Grignard reagent **1** from ^{13}C NMR and ^2H NMR analysis (after D_2O-quenching) prove that hydro-de-metalation of **1a/b** proceeds with retention of configuration at C-1. This is also demonstrated in the quenching of **1b** with D_2O to give essentially pure α-(3-D$_1$)-**4** (Figure 9), which implies stereospecifity. Yet, protonation of **1a** and **1b** could still proceed at different rates. Reaction of **1** with a limited amount of protons, followed by quenching with excess D_2O reveals the

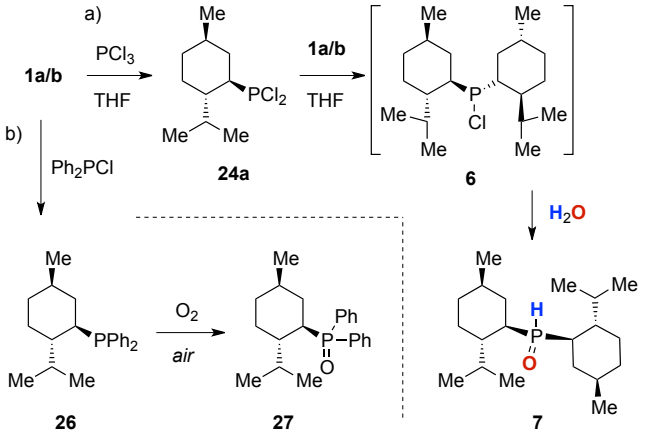
unreacted amount and dr of **1a/b** by ^{2}H NMR.[71] In the reaction of **1** with 0.25 equiv of water, **1a** is selectively attacked while **1b** initially remains (Table 2, entry 2). With twice the amount of water (0.5 equiv), **1b** is also partially protonated, but at a lower rate than **1a**, such that the remaining **1** is depleted in the latter (Table 2, entry 3). Water is a more stereoselective acid in this reaction than alcohols are (entries 4, 5). Kinetic resolution by protonation (*or*: hydronation) is only relevant if the hydron source is limiting, but will not play a role if excess D_2O is used to quench **1**. Neither is a dynamic kinetic resolution expected in view of the slow epimerization of **1a/b** under quenching conditions (at rt or below).

Turning to phosphorus electrophiles, reagent **1** was allowed to react with excess PCl_3 in the cold and the resulting, sensitive menthyl dichlorophosphane (**24**) converted to phosphinic acid RPH(=O)(OH) (**25**) by quenching with water (Table 2, entry 6). The high yield and diastereoselectivity (dr 15:1[83]) prove that the reaction proceeds with a high degree of stereoconvergence from both **1a** and **1b** to **24a**. Thus, the reported high yield of 90 % of **24a** from **1**,[11a] exceeding by far the amount of available epimer **1a** in **1** is confirmed by our experiment.

Combination of **1** with PCl_3 in a 2:1 ratio, followed by heating to reflux is the standard procedure to prepare Men_2PCl (**6**).[1] The reported yield is low at 13 %[10] or 25–35 %[1]. Analysis of the reaction mixture is considerably simplified by quenching with D_2O (**1**→[3-D_1]-**4**) and hydrolysis of **6** to phosphine oxide **7** (Scheme 7). The usual procedure (mixing at 0 °C, then heating) followed by protic, aqueous workup gave a fair spectral yield of **7** (Table 2, entry 7). The remaining **1** (dr 43:57; analyzed as (3-D_1)-**4**) displayed less enrichment than expected for a kinetic resolution, although this ratio might have been affected by epimerization of **1a**/**b** upon heating. Performing the reaction at 0 °C throughout further increased the yield of **7**, without affecting the dr of unreacted Grignard reagent (Table 2, entries 8a/b). The results show that both substitution events with nucleophile **1** along PCl_3 → $MenPCl_2$ (**24**) → Men_2PCl (**6**) proceed stereoconvergently with respect to C-1 of **1**, with both diastereomers **1a** and **1b** contributing substantially to produce **6**, with a slight kinetic preference for **1a** in reactions with P–Cl

electrophiles. Even though the generation of **7** was limited to 75 mol-%, and unreacted **1** was still present, no major organophosphorus species was detected in the organic phase. Failure to detect hydrolysis product **25** ($MenPO_2H_2$) means that both **24** (and thus also the more reactive PCl_3) must have been spent at the conclusion of the reaction. The unaccounted loss of phosphorus in entries 7–9 is approximately half the molar quantity of unaccounted loss of RMgX, which suggests that redox processes accompanying the main reaction lead to reduced, water-soluble phosphorus species and neutral hydrocarbons as side-products.

Scheme 7. Reaction of 1 with phosphorus electrophiles.



The reaction of **1** with Ph_2PCl[2,13,14] was also analyzed (Table 2, entry 9). A previous, qualitative report stated that quenching the reaction of equimolar **1** and Ph_2PCl with D_2O gave a mixture with half the original **1** (i.e., **1a**) converted to $MenPPh_2$, the other half (i.e., **1b**) returning NmnD (α-[3-D_1]-**4**). In our hands, the analytical yield of oxide **27**, which emerged from phosphane **26** during workup in air, exceeds the initially present quantity of **1a** (Table 2, entry 9; Scheme 7). Even though the kinetic preference for **1a** is marked, roughly half of epimer **1b** must have reacted with inversion of configuration at C-1 to account for the observed yield (cf. Δ**1a/b** in Table 2, entry 9), which fits the pattern observed with PCl_3 (→**24**), and which agrees with the stereoconvergent reactions of bornyl- and fenchylmagnesium reagents

with P-Cl electrophiles.[75a] Phosphine oxide **27** was isolated and structurally characterized by X-ray crystallography (Figure 11). The conformation of the menthyl group is consistent with earlier observations (Figure 3).

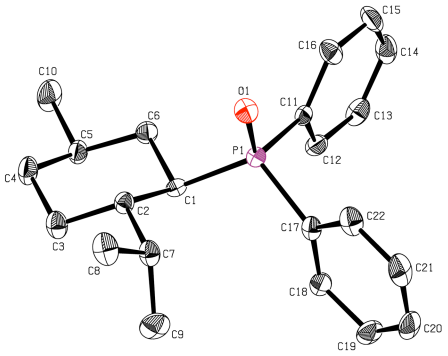


Figure 11. Solid-state X-ray molecular structure of dimenthylphenylphosphine *P*-oxide (**27**). Ellipsoids are shown at 50 % probability. Hydrogens are omitted for clarity. Oxygen is red, phosphorus purple.

Synthesis and Properties of Dimenthylphosphine Oxide

In the preparative study of the reaction of PCl_3 with of **1** to give Men_2PCl (**6**), we were initially guided by the hypothesis that 4 equivalents of **1**, corresponding to approximately two equivalents of **1a**, might provide a higher yield, if **1a** is the exclusive nucleophile.[2,75b] Yet, variation of the ratio PCl_3/**1** over 1:1, 1:3, 1:4 and 1:6 indicated that already 1:3 was optimal, and use of additional Grignard reagent had a counter-productive effect. Hydrolysis of the 1:3 reaction mixture (containing **6**) gave the expected, previously unknown dimenthylphosphine *P*-oxide (**7**; Table 2, entries 7, 8, and Scheme 7)[30] that was readily quantified by ^{1}H NMR in crude reaction mixtures. Chromatography required acetic acid as additive, with which **7** forms a hydrogen-bonded complex that must be split with base prior to solvent evaporation. The product was obtained as slowly crystallizing oil in 50% yield. Spectral properties agree with a C_1-symmetric structure, with two signal sets for diastereotopic menthyl groups (^{1}H, ^{13}C NMR), a single ^{31}P{^{1}H} NMR resonance (δ_P 41.8), and a characteristic doublet of doublets at δ_H 6.77 with the large

$^{1}J(^{31}P,^{1}H)$ of 435.5 Hz for the central P(O)H-unit. The identity of this material as **7** was further secured by single crystal X-ray crystallographic analysis (Figure 12).

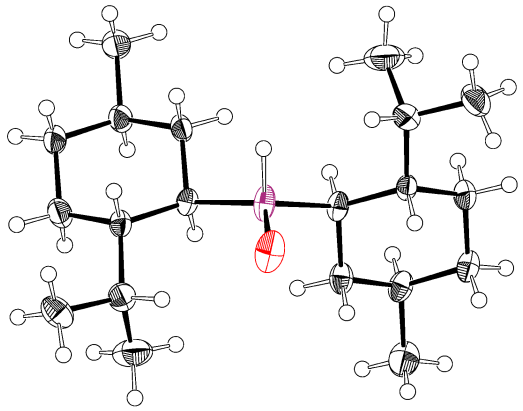


Figure 12. Solid state molecular structure of dimenthylphosphine *P*-oxide (**7**). Oxygen is colored red, phosphorus purple. Ellipsoids are shown at 50 % probability. The unit cell contains three independent molecules of very similar geometry, of which one is displayed.

Based on the 2D NMR analysis (Figure S29, Table S25), the diastereotopic menthyl groups (Men^{Re}, Men^{Si}) differ by a $^{3}J_{P,H}$ coupling (5.6 Hz) from H-P to H-1 in Men^{Re}, which is absent ($^{3}J_{P,H} \approx 0$ Hz) for H-1 in Men^{Si}. This observation is consistent with the solid-state conformation in the X-ray structure having torsional angles of –169° (to H-1 in Men^{Re}) or –50° (to H-1 in Men^{Si}). The P=O oxygen is involved in short intramolecular contacts with H-1' of the isopropyl group in Men^{Re} (237 pm), and H-2 of Men^{Si} (283 pm), and those interactions are reflected by higher frequency δ_H signals for the respective nuclei, compared to their diastereotopic counterparts. The usual conformation of C-2-isopropyl in menthyl derivatives is observed (Figure 3, a).

CONCLUSIONS

Menthyl Grignard reagent (**1**) has been known and used in asymmetric synthesis for many years. Yet, its exact chemical composition and reaction stereochemistry have remained insecure in the absence of direct analytical studies. In the reaction sequence starting from **2** via **1** and leading to various substitution products (Scheme 1), the stereochemistry of the first and second steps were not known with certainty, and neither was the configurative stability of **1a/b** established. Methods to analyze the composition **1a/b** had relied on reactions with electrophiles (CO_2, D_2O), the results of which could have been affected by kinetic resolution effects. Even for D_2O-quenching, the assumption that the dr of (3-D_1)-**4** reflects the dr of **1a/b** (i.e., retention of configuration in proto-de-metalation) was unproved.

In the present study we have for the first time analyzed menthyl Grignard reagent *in situ* by combining ^1H and ^{13}C NMR methods. MenMgX (**1a'**) and NmnMgX (**1b'**) were confirmed as major organometallic components of the reagent, besides hydrocarbons *trans-p*-menthane (**4**), 2-menthene (**8**), 3-menthene (**9**) and three diastereomeric Wurz products **13**–**15**. The Schlenk equilibrium is operative and produces considerable amounts of Men_2Mg from **1a** at low halide concentration, whereas **1b** is less notably involved in equilibria. The Schlenk equilibrium complicates quantitative NMR analysis, since minor and dynamic species display exchange-broadened signals. The intensity of the characteristic ^{13}C NMR signals δ_C 49.5 and 52.8 for the major components **1a'** and **1b'** do not reflect the dr **1a**:**1b**. Use of dibromoethane or other halogenated reagents for initiating the Grignard reaction has the beneficial effect of shifting the Schlenk equilibrium towards **1a'/b'** and giving easier to analyze NMR spectra. However, integration of defined ranges of the ^{13}C NMR spectrum (δ 48–51 for C-2 of **1a**, δ 51–54 for C-2 of **1b**) led to consistent results for the **1a/b**-dr that agreed with the D_2O quenching results and confirm retention of configuration in deuterolysis of the C–Mg bond. Based on this benchmarking experiment, the technically simple and fast $^2H\{^1H\}$ NMR analysis of **1a/b** after D_2O-quenching can be carried out with confidence. Besides analyzing the peak area ratio of the α/β-(3-D_1)-**4** signals (δ_D 0.94 and 1.65), analysis in presence of a

deuterated internal standard (*e.g.* C_6D_6 for simplicity, or preferably less volatile, solid derivatives for weighing out[71]) allows the accurate quantification of **1a**/**b**.

NMR methods were used to investigate the effect of reaction conditions in the magnesium insertion of **2** or **3** on the composition of the resulting Grignard reagent **1**. The observed abundance of saturated and unsaturated hydrocarbon byproducts agrees with their generation by a Kharasch-Reinmuth-Walborsky surface radical mechanism.[63] A surprising aspect is that the abundance of byproducts is inversely proportional to the reaction temperature, with reactions at 50–70 °C giving highest yields of **1** and lowest levels of byproducts. This finding opposes a comment of Kharasch and Reinmuth: "*In general these [competing] reactions require (or at least are favored by) higher temperatures than the Grignard reagent formation reaction, and, in general, they are favored by relatively high halide (RX) concentrations*",[84] but agrees with observations made during the preparation of *t*-BuMgCl in ether.[85]

Epimerization in the course of Grignard reagent formation (Scheme 1, **I**) is extensive at any given reaction temperature, and both **2** and **3** give rise to comparable amounts of **1a/b** by kinetic stereoconvergence. In that aspect, the earlier findings[2] were confirmed. However, upon closer inspection, the dr **1a/b** shows an influence of the configuration of starting materials **2**/**3**, if the Grignard is prepared at, or close to, ambient temperature. Walborsky has previously observed partial retention of configuration in Grignard reactions and ascribed it to a concerted oxidative addition mechanism that runs parallel to the surface-group mechanism.[63,86]

The configurative stability of **1a**/**b** was formerly uncertain, or had been assumed to be high at ambient temperature.[2] It is now clear that epimerization is fast at 50–70 °C and contributes to the generation of **1a**/**b** in fractions near their thermodynamic ratio (55:45 at 70 °C), although kinetic control yields similar ratios. Upon storage of reagent **1** under ambient conditions, the dr slightly rises over several days or weeks to a room temperature equilibrium value of 58:42. The closeness of kinetic and thermodynamic selectivity renders the investigation of equilibration kinetics difficult, yet such experiments have become possible through the carboxylation of **1** at low temperature, which induces a clean kinetic separation of

1b from **1a**. Temperature-dependent kinetic equilibration studies starting with diastereomerically pure Grignard reagent **1b**$^{\mathbf{I}}$ give excellent results (Figure 9) and prove that Men/Nmn-MgX are equilibrating species. The process is slow at ambient temperature, but can be accelerated by heating to 70 °C, without loss of reagent due to decomposition. The equilibration measurements revealed a counter-ion effect on the configurational equilibrium Men/NmnMgX (X = counter-ion) that runs against the established preference in substituted cyclohexanes of preferentially accommodating large substituents in equatorial positions. Surprisingly, we find that sterically large carboxylates X prefer NmnMgX over MenMgX. Additional sterical hindrance caused by $RMgX(S)_n$-dimerization or ligand-exchange equilibria might be responsible for this deviation from the usual steric interpretation of A-values.[81]

Based on the newly established composition and diastereomerization kinetics of **1**, the stereochemistry of reactions with electrophiles was investigated. Determining the dr and yield of substitution product is not sufficient in such studies, since the interference of kinetic resolution effects is only recognized if absolute amounts of substitution products and unreacted **1a/b** are accurately known. This is evident from the reinvestigation of the carboxylation of **1a/b**, which had previously been reported with inconsistent results. We find that a sharp kinetic resolution of **1a/b** by reaction with CO_2 in the cold gives $MenCO_2H$ (**19**) in a quantity that is limited by the amount of initially present **1a**, while **1b** remains unreacted. Extended reaction time or higher temperature generate variable amounts of $NmnCO_2H$ (**20**) by slow carboxylation of **1b**. At sufficiently high temperature, dynamic kinetic asymmetric transformation of **1a/b** becomes possible, which explains the success of a patent procedure that finds a high yield of **19** by concomitant exposure of CO_2 and **2** to magnesium at 90 °C in 2-MeTHF–cymene.[68]

Rather different results were obtained in reactions of **1** with phosphorus electrophiles, where all cases investigated displayed stereoconvergence, with both **1a** and **1b** contributing to the generation of menthyl configured substitution products, even if preferential consumption of **1a** over **1b** distinguishes the former as the better nucleophile. Kinetic product control is consistent with a common intermediate and supports the SET-mechanism[20] known to be operative for a range of *C*-electrophiles, and also established in

reactions of the bornyl and fenchyl Grignard reagents with PCl_3 and other phosphorus electrophiles.[75] A consequence of the stereoconvergent SET-mechanism is the high yield of $MenPCl_2$ (**24**), which can be achieved in reactions of **1** with excess PCl_3 at low temperature, under conditions where the interconversion of **1a**/**b** is frozen. Attempts to maximize the yield of Men_2PCl (**6**) from PCl_3 by using 4 or 6 equivalents of **1** were counter-productive, since the spectral yields of hydrolysis product dimenthylphosphine *P*-oxide (**7**) did not surpass that obtained in the reaction with 3 equivalents of **1** (73–75%, Table 2). The missing 25 mol % of phosphorus in those reactions are apparently lost to redox side-reactions leading to inorganic phosphorus species. Phosphine oxide **7** is an interesting platform chemical for chiral phosphane synthesis, or may itself serve as chiral SPO (secondary phosphine oxide) ligand. Work towards both applications is currently ongoing in our laboratories.

EXPERIMENTAL SECTION

General Methods

Chemicals and solvents were obtained commercially and used without purification unless mentioned. Solvents for Grignard reactions were filtered over activated Al_2O_3 and stored under Argon over molecular sieves (3 Å). The materials used in the study were all derived from menthol (**5**) of natural (1*R*)-configuration ((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanol). Menthyl chloride (**2**) and neomenthyl chloride (**3**) were obtained as previously described.[29] Grignard solutions were titrated against salicylaldehyde phenylhydrazone.[40] ^{1}H NMR measurements for quantitative analyses were performed using a relaxation recovery delay (d1) of 20 s. ESI-high-resolution mass spectra were measured using FT-ICR detection. CCDC 1499983 (**22**), 1499984 (**7**), 1519897 (**13**) and 1567948 (**27**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Samples and Referencing. Regular NMR samples in $CDCl_3$ were referenced to TMS (δ_C and δ_H 0 ppm). Samples of Grignard reagent were measured in solvent mixtures of non-deuterated solvents (THF, Et_2O, toluene) with C_6D_6 added for locking, or in selected cases prepared and measured in fully deuterated solvent ((D_8)-THF). Naphthalene was usually added as internal standard. In view of the special media containing dissolved magnesium salts and organometallic species at high concentration, the usual practice of referencing to residual solvent signal is not advisable, since the solvent chemical shift is affected by the dissolved salts. In the majority of cases, external (machine) referencing was kept. For the key analytical samples, the chemical shift of typical components (naphthalene) and solvents is indicated to allow for comparability.

NMR data tables (supporting information) and CH–index. The substance NMR data tables list ^{13}C NMR peak chemical shifts together with peak area integration data (arbitrary units). The values were obtained by deconvolutive peak fitting. Peak area is also provided as "CH-index" value, i.e., as a dimensionless number relative to the average peak area of all CH-signals (set to 1.000). The index numbers are close to 1 for CH, CH_2 and CH_3 peaks, but <1 for quaternary carbons. The CH-index data is useful for assigning individual signals to peak sets of specific components (at variable abundance) in complex mixtures such as Grignard reagent **1**.

Abbreviations. APT = attached proton test (^{13}C NMR); *t*-BuOMe = *tert*-butyl methylether; DMF = *N*,*N*-dimethylformamide; EtOAc = ethyl acetate; THF = tetrahydrofuran; TCE = 1,1,2,2-tetrachloroethane; TLC = thin-layer chromatography.

1-Methoxy-4-(D_3-methoxy)-benzene. This deuterated compound was used as internal standard for ^2H NMR spectroscopy. Due to its volatility, applications are restricted to conditions that do not involve solvent evaporation or prolonged heating. ***Synthesis***: To a solution of 4-methoxyphenol (3.29 g, 26.5 mmol, 1.00 equiv) in DMF (20 mL) was added powdered K_2CO_3 (6.23 g, 45.1 mmol, 1.70 equiv) and

CD_3I (5.00 g, 34.5 mmol, 1.30 equiv). The suspension was stirred at room temperature for 26 h. The reaction was quenched by addition of a water/brine mixture (1:1, 30 mL). After extraction with ethyl acetate (3 × 20 mL), the combined organic phases were washed with water–brine (1:1, 4 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by rotary evaporation and the crude product was purified by column chromatography (hexanes–EtOAc 20:1) to give 3.20 g (86%) colorless crystalline solid. Spectral data (^1H, $^2H\{^1H\}$ and ^{13}C NMR) conformed with literature values.[87] ^1H NMR (400 MHz, $CDCl_3$): δ 3.76 (s, 3H), 6.83 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.0 (sept, $J_{C\text{-}D}$ = 22 Hz; CD_3), 55.9 (CH_3), 114.8 (CH), 114.8 (CH), 153.9 (2 C). $^2H\{^1H\}$ NMR (61 MHz, CH_2Cl_2; δ{$CHDCl_2$} = 5.32): δ 3.72 (s, 3 D).

Synthesis of menthyl Grignard reagent in THF (1 M); General Procedure 1 (GP1). In a 250 mL Schlenk vessel, magnesium turnings (4.99 g, 205.5 mmol, 1.37 equiv) were covered with dry THF (35 mL) and heated to 50 °C in an oil bath. A solution of menthyl chloride (98% **2**+**3**; 26.74 g, 150.0 mmol, 1 equiv) in THF (65 mL) was placed into a dropping funnel and mounted on the reaction vessel. Two crystals of iodine and 1/10 of the volume of the menthyl chloride solution were added to the magnesium. After the reaction had initiated, the oil bath heating was shut off. The remaining solution of **2** was added to the stirred Mg suspension over 45 min, such that the oil bath temperature did not exceed 60 °C. After completion of the addition, the reaction mixture was stirred for 2 h at 70 °C, then cooled to room temperature. Content of active RMgX: 1.02 M by titration.

Synthesis of menthyl Grignard reagent (1) from menthyl chloride in THF–toluene at 70 °C. In a Schlenk vessel under argon, magnesium turnings (12.5 g, 514 mmol) were covered with THF (25 mL) and toluene (50 mL). A little iodine was added and the mixture heated with stirring to 70 °C in an oil-bath. A solution of menthyl chloride (**2**; 97% isomeric purity; 49.5 g, 283 mmol) in THF (25 mL) was

added dropwise over 1 h with control of the external oil-bath reaction temperature. After completion of the addition the mixture was stirred for 2 h at 70 °C, cooled to rt and stirred overnight. Titration indicated a concentration of active [RMgX] of 1.43±0.1 mol/L.

Analytical scale synthesis of menthyl Grignard reagent; General Procedure 2 (GP2). Menthyl chloride (**1**; 0.92–0.96 g, 5.3–5.5 mmol, 1.0 equiv) was dissolved in the solvent (1.0 mL for high concentration conditions, 2.0 mL for low concentration). Magnesium turnings (0.25 g, 1.9 equiv) and a grain of iodine were stirred in the given solvent (1.0 mL for high concentration conditions, 3.0 mL for low concentration) and heated to the required temperature. For experiments in THF–toluene, **1** was dissolved in THF (1 mL), and the reaction vessel was filled with THF (1.0 mL) and toluene (2.0 mL). An aliquot of the solution of **1** was added to initiate the reaction. After the reaction had started, the solution of **1** was added over 10 minutes. Reactions at room temperature were stirred overnight unless otherwise mentioned, reactions at 50 °C for 2 h, and reactions at 70 °C for 1 h. After cooling of the Grignard reagent to rt, a weighed amount of naphthalene was added as internal standard and samples for analysis were removed.

NMR analysis of analytical scale menthyl Grignard samples: For recording ^{1}H- and ^{13}C-NMR spectra, a sample (*ca.* 0.5 mL) of the Grignard solution was filled into a septum-capped NMR-tube under argon and dry C_6D_6 (*ca.* 0.2 mL) was added for locking.

*^{2}H NMR analysis of the **1a**/**b** ratio (simplified procedure, Table 1):* For recording a ^{2}H NMR spectrum, a sample of the Grignard solution was quenched by addition of degassed D_2O. The water phase was acidified with HCl aq and extracted with $CHCl_3$. The organic layer was washed with H_2O and brine and dried over $MgSO_4$.

Specific menthyl Grignard samples for NMR analysis

Menthyl Grignard reagent in THF for NMR analysis with C_6D_6 addition (sample A). The sample was prepared as usual from menthyl chloride (5.72 mmol, 97% purity) and Mg (6.71 mmol) in THF (2.5 mL) at rt with initial addition of iodine and ethylene bromide for activation. Naphthalene (110.1 mg, internal standard) was dissolved in the reagent. A sample of reagent (0.30 mL) and C_6D_6 (0.30 mL) were combined in an NMR tube. External referencing placed the signals for THF at δ_C 25.300, 68.305; for C_6D_6 at δ_C 127.660; and for naphthalene at δ_C 125.699, 127.798, 133.633; the values are indicated with higher precision since they serve referencing purposes.

Menthyl Grignard reagent in (D_8)-THF (sample B). The sample was prepared following GP2, starting from menthyl chloride (5.45 mmol, 93.7% MenCl, 2.5% NmnCl), Mg (10.3 mmol) and 1,2-dibromoethane (ca. 50 μL) in (D_8)-THF (5.0 mL) at 70 °C. Naphthalene (105.8 mg, internal standard) was dissolved in the final reagent. A sample of 0.50 mL was combined with 0.10 mL of C_6D_6 in an NMR tube. See Figure 1 for the ^{1}H NMR spectrum. External referencing placed the residual signals of (D_7)-THF at δ_H 1.764, 3.682; silicon grease at δ_H 0.11; solvent (D_8)-THF at δ_C 24.509, 67.135, and naphthalene at δ_C 125.788, 127.847, 133.803.

Synthesis of Grignard reagent from neomenthyl chloride in (D_8)-THF (sample C). A Grignard reagent was prepared from neomenthyl chloride (5.44 mmol, 97% purity), Mg (10.3 mmol), ethylene bromide (ca. 50 μL) and ethyl bromide (ca. 50 μL) in (D_8)-THF (5.0 mL) at rt with overnight stirring for conclusion of the reaction. A sample of reagent (0.60 mL) was combined with naphthalene (34.5 mg, internal standard) in an NMR tube. External referencing placed the solvent signal of (D_8)-THF at δ_C 24.299, 67.178 and naphthalene at δ_C 125.627, 127.679, 133.585.

Synthesis of menthyl Grignard reagent in ethyl ether (sample D). The Grignard reagent was prepared from menthyl chloride (5.34 mmol, 93.7% MenCl, 2.5% NmnCl) and Mg (10.4 mmol) in Et_2O (5.0 mL) at 40 °C. After dissolution of naphthalene (107.2 mg, internal standard), a sample (0.50 mL) was

combined with C_6D_6 (0.10 mL) in an NMR tube. External referencing placed the solvent signals of Et_2O at δ_C 14.709, 65.371; of C_6D_6 at δ_C 127.518; and of napthalene at δ_C 125.521, 127.682, 133.586.

Analysis of RMgX content of menthyl Grignard reagent

By titration against salicylaldehyde phenylhydrazone.[40] In a 10 mL Schlenk tube, salicylaldehyde phenylhydrazone (100 mg, 471 μmol) was dissolved in THF (3.0 mL). Grignard solution was added dropwise from a filled syringe (1 mL, 0.01 mL graded) until the solution changed its color from yellow to orange. The titration was repeated at least once.

By quantitative $^2H\{^1H\}$ NMR spectroscopy. Grignard solution (0.50 mL) was added with efficient magnetic stirring to a 10 mL Schlenk tube containing D_2O (1 mL). After 15 min, aq HCl (2 M, 10 mL) was added. The mixture was extracted with $CHCl_3$ (2 × 15 mL). The combined organic phase was washed with water (3 × 10 mL) and sat aq NaCl (15 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated (40 °C, 450 mbar) until few mL remained, C_6D_6 (10.0 μL) or a weighed quantity of *p*-$(CD_3O)C_6H_4OCH_3$ was added and a sample removed for $^2H\{^1H\}$ NMR analysis.

Analysis of the Mg-content of menthyl Grignard reagent. Total magnesium was determined by adding a known volume of the Grignard solution (0.5–1 mL) to 1 M aq HCl (ca. 5 mL) with stirring until solids were fully dissolved. After dilution to 20.00 mL, aliquots of 5.00 mL were removed for titration. Each sample was basified with 3–4 mL of pH 10 buffer (ca. 6 M, NH_3–NH_4Cl). A few mg of eriochrome black T (ground to a powder with solid NaCl in a 1:100 ratio) was added and the solution was titrated against Na_2EDTA (0.1 M, 5 mL micro-burette).[48]

Isolation of *trans-p*-menthane (4) and bimenthyl isomer mixture (13/14/15) from menthyl Grignard reagent (1). A menthyl Grignard reagent (*ca.* 60 mL, 1 M) prepared from crude **2** (80 % purity) was quenched with sat aq NH_4Cl (50 mL) and 1 M HCl aq (50 mL). After addition of Et_2O (50 mL) and transfer into a funnel, the phases were separated and the organic phase washed with 1 M HCl aq (2 x)

and water (2 x). The organic phase was evaporated and the residual oil distilled in vacuum (bath 60–70 °C, vapor 38–45 °C, vacuum 8 mbar) to remove the menthane/menthene fraction (see below for further processing). The residual yellowish oil was transferred into a separatory funnel with hexanes (40 mL) and the solution washed with concd H_2SO_4 (4 x 10 mL); the first washing was accompanied by warming and was completed within 20 seconds, immediately removing the lower acidic layer. Finally, the organic layer was washed with 10 % aq NH_3 (*CAUTION*: exothermic reaction with H_2SO_4-residues in the funnel) and filtered over a bead of $MgSO_4$. After evaporation, a few mL of a colorless liquid remained, which was distilled in a Kugelrohr oven (170 °C, *ca.* 0.1 mbar) to give colorless oil (*ca.* 2.0 g), consisting of **13**:**14**:**15** in a ratio of 38.6:45.1:16.3. See the supporting information for a complete ^{1}H and ^{13}C NMR analysis and assignment. The menthane/menthene fraction was similarly diluted with hexanes, washed with concd H_2SO_4 and distilled (59–60 °C, 24.3 mbar) to give a mixture of *trans-p*-menthane (**4**) and ψ-menthane (**16**) in a ratio of 96:4, see the Supporting Information for spectral analyses.

Symmetrical bimenthyl or (1*R*,1'*R*,2*S*,2'*S*,5*R*,5'*R*)-2,2'-diisopropyl-5,5'-dimethyl-1,1'-bi(cyclohexane) (13). Upon standing of the above bimenthyl diastereomer mixture, the symmetric bimenthyl (**13**) crystallized over several days (Figure S20); one crystal was used for the X-ray crystal structure analysis. The liquid fraction was removed with a pipette (1.60 g; **13**:**14**:**15** = 23.5:56.1:20.4) and the solid was pressed between tissue paper to remove liquid. Recrystallization from hot EtOH with addition of toluene for solubilization, followed by standing at rt gave colorless crystals (240 mg). Mp. 105.6–106.2 °C; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 21.9, 23.1, 24.8, 25.3, 33.2, 34.7, 35.6, 37.9, 43.7; see the Supporting Information for comprehensive ^{1}H and ^{13}C NMR data and assignments; HR-EI-MS calcd for $C_{20}H_{38}^+$ ($[M]^+$) 278.2968, found 278.2972.

Carboxylation of 1 under different addition modes (Scheme 4)

Addition of solid CO_2 to Grignard solution at ambient temperature. Preparation of the Grignard reagent: Menthyl chloride (3.68 g, 21.1 mmol) in THF (4 mL) was added dropwise over 10 min to iodine-activated magnesium turnings (1.05 g, 43.2 mmol) in THF (4 mL) at 50 °C. After stirring for 2 h at 50 °C, the reaction mixture was stirred overnight at ambient temperature. Titration against salicylaldehyde phenylhydrazone indicated a concentration of active reagent of 1.36 mol/L. A Schlenk vessel was charged with Grignard reagent (4 mL, 5.44 mmol) under argon and placed in a room-temperature water-bath. Pieces of dry ice (CO_2 (*s*)) were added consecutively to the stirred solution such that a constant CO_2-evolution was notable (silicon oil bubbler). The reaction mixture became viscous over time. After 2 h, the reaction was quenched by addition of aq 1 M HCl (10 mL). The organic phase was collected and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phase was extracted thrice with aq 2 M NaOH (3 × 30 mL). The aqueous extract was acidified with aq 6 M HCl to pH 2 and the mixture extracted thrice with Et_2O (3 × 30 mL). The combined organic extracts were washed with sat. NaCl aq (40 mL) and dried over $MgSO_4$. Filtration and evaporation in vacuum gave colorless oil (724 mg, 72.4% crude yield). The composition was determined by adding 1,1,2,2-tetrachloroethane (317 mg, 1.89 mmol) and $CDCl_3$ (1.4 mL) to the mixture, followed by recording of a quantitative ^1H NMR (d1 = 20 sec). Analysis: 60.24 mol-% of **19**, 7.57 mol-% of **20**, combined = 67.8% (Figure S23 for spectrum).

Addition of Grignard solution to excess CO_2 in THF solution at low temperature. In a Schlenk vessel under argon, THF (6 mL) was cooled to –72 °C in an EtOH–CO_2 (s) bath. Pieces of dry ice (CO_2 (*s*); ca. 4 g) were added to the THF and the bath temperature was increased to –20 °C. Menthyl Grignard reagent (as above; 5 mL, 6.80 mmol) was added dropwise to the CO_2-solution over 20 min. The reaction was stirred for 2 h at –20 °C, with some more additions of CO_2 (*s*) to ascertain a constant gas evolution through the silicon oil bubbler vent. The reaction was then quenched at –20 °C by addition of aq 1 M HCl (15 mL). Workup as above gave a colorless oil (783 mg, 62.6% crude yield), which was

analyzed by ^{1}H NMR after addition of 1,1,2,2-tetrachloroethane (300 mg, 1.79 mmol) and $CDCl_3$ (1.4 mL). Analysis: 55.9 mol% of **19**, 2.8 mol% of **20**, combined: 58.7% (see Figure S24 for spectrum).

Selected analytical ^{13}C NMR data for carboxylic acids. Complete NMR data assignments for menthyl- and neomenthyl¬carbo¬xy¬lic acids **19**/**20** have been published.[88] The ^{13}C NMR chemical shifts for stereo- and regioisomeric carboxylic acids from the current work are listed below. The data sets have been extracted from carboxylation mixtures, and acids **21** and **23** were only detected as minor components.

*Menthylcarboxylic acid (**19**)*: ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 21.3, 22.3, 23.8, 29.3, 32.0, 34.5, 38.8, 44.2, 47.7, 183.3.

*Neomenthylcarboxylic acid (**20**)*: ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3 (overl.), 21.5, 22.4, 25.5, 27.5, 30.3, 35.3, 38.0, 42.0, 46.4, 182.2. The following acids have been detected as minor components in the carboxylation products of Grignard reagents from crude menthyl chloride isomer mixtures: *tert-ψ-Menthanecarboxylic acid (**21**)*: ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.0, 25.7* (or 2 × CH_3?), (29.1*?), 33.0, 33.5, 34.2, 37.5, 42.3, 43.8, 47.3, 184.7. *) Due to signal overlap, it is not clear if δ 25.7 corresponds to 2 × CH_3, and δ 29.1 might be an artifact. *sec-ψ-Menthanecarboxylic acid (**23**)*: ^{13}C NMR (100 MHz, $CDCl_3$), 2 diastereomers: δ 18.3/18.1, 20.84/20.78, 21.51 (overl.)/21.47, 29.1/29.0, 29.62/29.60, 33.3/33.2, 34.3/34.0, 40.1/39.9, 40.5/40.3, 57.54/57.49, 181.8/181.7.

Ethyl 2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanecarbox-amido)acetate (22).

a) *Carboxylation of Grignard reagent **1***: A *ca.* 1 M Grignard reagent **1** derived from 75 % pure menthyl chloride isomer mixture (containing regioisomeric chloromenthanes, see reference 29) and magnesium in THF (70 mL, ≥70 mmol) was combined with a piece of dry CO_2 (*s*) (*ca.* 4 g) with stirring. The mixture first warmed, then cooled. After the CO_2 (*g*) evolution had ceased, the mixture was carefully quenched with 2 M HCl aq (100 mL) in small portions and Et_2O (200 mL). The organic phase was washed with 2

M HCl aq (50 mL) and water (3 x 50 mL). The organic phase was extracted with 1 M Na_2CO_3 aq (100 mL + 2 x 50 mL). The combined basic aqueous phase was extracted with Et_2O (2 x 50 mL) and acidified with concd HCl aq (25 mL; CO_2 evolution). Extraction with Et_2O (3 x 50 mL), drying of the organic extract (Na_2SO_4), filtration and evaporation gave 8.34 g of crude viscous oil, which was used in the next step. According to ^{1}H NMR analysis, the crude product contained the carboxylic acids **19**/**20**/**21** in a molar ratio of 100:5.2:24.2.

b) *Coupling with ethyl glycinate (adapted from reference 69b)*: The crude carboxylic acid mixture (8.34 g, *ca.* 45 mmol) in CH_2Cl_2 (25 mL) was combined with $SOCl_2$ (5.0 mL, 69 mmol) and DMF (5 drops) and stirred for 2 h at 50 °C, while developing acidic exhaust gasses were absorbed into water. Volatiles were then removed at 50 °C into a cooling trap using water aspiration vacuum (12 mbar). The residue was taken up in toluene (5 mL), and volatiles were again evaporated at 75 °C in vacuum (12 mbar). The residual crude acid chloride was taken up in Et_2O (80 mL) and this solution was added to a solution of ethyl glycinate hydrochloride (10.0 g, 71.6 mmol) in water (100 mL). Solid $NaHCO_3$ (16.0 g, 190 mmol) was added in portions (CO_2 evolution) to the two-phase mixture, which was further stirred overnight (15 h) at rt. The aqueous phase was deployed and the organic phase washed with sat. aq $NaHCO_3$ and sat. aq NaCl. After drying (Na_2SO_4), filtration and evaporation, the oily residue, which had an amine smell, was taken up in EtOAc and washed with 2 M HCl aq (2 x) and water (2 x). After evaporation to dryness, viscous oil was obtained, which crystallized over the course of 2 days and consisted of a mixture of product together with the neomenthyl and *tert*-ψ-menthyl isomers (78.3:3.9:17.8, by ^{1}H NMR). The material was dissolved in hot hexanes (50 mL) and stored at –20 °C to produce colorless crystals of pure material (3.0 g, 25 %) also suitable for X-ray crystal structure analysis. Mp. 80.5–81.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, ^3J(H,H) = 6.9 Hz, 3 H; Me of 2'-*i*Pr), 0.89 (d, ^3J(H,H) = 6.5 Hz, 3 H; Me-C5'), 0.90 (d, ^3J(H,H) = 6.9 Hz, 3 H; Me' of 2'-*i*Pr), 0.96 (m, 1 H; H-4'), 1.02 (m, 1 H; H-3'), 1.23 (q, $^{2/3}J$(H,H) ≈ 12.4 Hz, 1 H; H-6' ax), 1.29 (t, ^3J(H,H) = 7.2 Hz, 3 H; Me of OEt), 1.31–1.42 (m, H-5'), 1.54 (tt,

^3J(H,H) = 11.5, 2.9 Hz, H-2') 1.65–1.77 (m, 3 H; H-3' at δ 1.68, H-4' at δ 1.73, CH of 2-*i*Pr at δ 1.74), 1.81 (dq, ^2J(H,H) = 12.7, ^3J(H,H) = 2.3 Hz, 1H; H-6' eq), 2.10 (td, ^3J(H,H) = 11.6, 3.4 Hz, 1 H; H-1'), 4.04 (ψ-d, ^2J(H,H) = 5.2 Hz, 2 H; H-2 of Gly), 4.22 (q, ^2J(H,H) = 7.2 Hz, 2 H; CH_2 of OEt), 5.97 (br. t, ^3J(H,H) = 5.2 Hz, 1 NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 16.2, 21.5, 22.4, 23.9, 28.7, 32.4, 34.7, 39.5, 41.3, 44.4, 49.6, 61.5, 170.3, 176.1; see the supporting information for comprehensive assignments; HR-ESI-MS calcd for $C_{15}H_{28}NO_3^+$ ($[M+H]^+$) 270.2064, found 270.2063.

Equilibration studies with menthyl Grignard reagent

Equilibrium composition of menthyl Grignard reagent at various temperatures: A 10 mL Schlenk tube was charged with Grignard reagent (2.94 mL, 1.02 M in THF, 3.00 mmol). The solution was stirred for 3 h at 50 °C and another 3 h at 70 °C. Samples (*ca.* 0.5 mL) were taken at the outset, after 3 h at 50 °C, and after 3 h at 70 °C. The D_2O quenching analysis was performed according to GP 4 (see below). A room-temperature sample was measured after storing reagent **1** for several weeks at ambient temperature. Recovery may be measured by adding *p*-$C_6H_4(OMe)(OCD_3)$ to the thermally equilibrated Grignard solution prior to quenching. Erratic results (overly high recovery) were obtained if the internal standard was added to hot Grignard solutions for kinetic measurements. Thus, the latter had to rely on the ratio **1a**/**1b** (i.e., $[D_1]$-**4a**/**4b**).

Kinetic resolution of 1a/b with carbon dioxide; General Procedure 3 (GP3). A 20 mL Schlenk tube was charged with THF (2 mL) and cooled to –78 °C. CO_2 (*ca.* 2.0 g) was added and the tube was closed with a septum and balloon. Then Grignard solution (5.88 mL, 1.02 M in THF, 6.00 mmol) was added dropwise over 10 min and the resulting mixture was stirred for 1 h at –78 °C. Unreacted CO_2 was removed by applying a high-vacuum (15 min at –78 °C) to give a solution of neomenthylmagnesium carboxylate **1b^I** (>99:1 neomenthyl/menthyl-Mg) as indicated by ^{2}H NMR after D_2O quench (GP4).

D_2O-quenching of Grignard carboxylate solutions; General Procedure 4 (GP4): A sample (~ 0.5 mL) of the Grignard solution (GP3) was mixed with D_2O (1 mL) and stirred vigorously for 15 min at room temperature under argon. Then 2 M HCl (10 mL) was added followed by extraction with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with sat. Na_2CO_3 (3 × 15 mL) and brine (10 mL) and dried over $MgSO_4$. After filtration the solvent was evaporated until few mL remained (750 mbar, 40 °C) which were analyzed by $^2H\{^1H\}$ NMR analysis.

Kinetic equilibration studies of neomenthylmagnesium menthylcarboxylate: Solutions of neomenthyl-magnesium menthylcarboxylate (**1b^I**) were prepared by the GP3 as described above. The reaction vessel was placed into an oil-bath at the desired temperature. In regular intervals, samples (~ 0.5 mL) were removed and quenched according to the GP4 to determine the diastereomeric ratio. For data-points and plots, see Tables S18, S19 and Figure S25.

Menthyl/neomenthyl epimerization of 1 after addition of lithium carboxylates:

a) Equilibrium epimer distribution in the presence of carboxylates: The procedure is exemplified with mesitoic acid (2,4,6-trimethylbenzoic acid): lithium mesitoate was generated from mesitoic acid (82.1 mg, 0.50 mmol; 1 equiv) in the presence of a trace of phenanthroline (basicity indicator) in THF (3 mL) by titration with *n*-BuLi in hexanes (1.6 M; ca. 0.33 mL required). Grignard solution **1** (0.49 mL; 1.02 M in THF, 0.50 mmol, 1 equiv) was added at rt. The mixture was heated to 60 °C and stirred for 24 h. Internal standard (*p*$MeOC_6H_4OCD_3$: 35.3 mg) was added and the mixture quenched with D_2O (5 mL) and stirred for 15 min under argon. The mixture was acidified with 2 M HCl aq (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phase was washed with water (15 mL) and brine (15

mL) and dried over $MgSO_4$. After filtration, the solvent was carefully concentrated in vacuum (750 mbar, 40 °C) to a few mL, which were used for $^2H\{^1H\}$ NMR analysis. The ratio Men/Nmn was 46.8/53.2, and the recovery of [RMg] (as sum of (D_1)-**4** and (D_1)-**16**): 489 µmol (= 98%).

b) Kinetic experiment with lithium pivalate: Pivalic acid (112.3 mg, 1.10 mmol) and a few crystals of phenanthroline (basicity indicator) in dry THF (3.0 mL) were titrated with *n*-BuLi solution (1.6 M in hexane; *ca.* 0.74 mL) until the color turned from yellow to brownish. Additional THF (2.0 mL) and a solution of menthyl Grignard reagent **1** (0.98 mL, 1 mmol; equilibrated at rt) were added at rt. The vessel was placed into an oil-bath at 70 °C and samples were removed after the indicated time for quenching with D_2O (GP4). See Figure S25 and Tables S19/20 for the kinetic data and analysis.

Analytical studies of reactions of 1 with electrophiles (Table 2).

Reaction of 1 with CO_2 (Table 2, entry 1): A 20 mL Schlenk tube was charged with THF (1 mL) and cooled to –78 °C. CO_2 (*ca.* 1.5 g) was added and the tube was closed with a septum and balloon. Then Grignard solution (2.94 mL, 1.02 M in THF, 3.00 mmol) was added dropwise over 7 min and the resulting mixture was stirred for 1 h at –78 °C. The cooling bath was removed and D_2O (4 mL) was added carefully in portions. After stirring for 15 min at room temperature 2 M HCl (10 mL) was added followed by extraction with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with sat. $NaHCO_3$ (3 × 15 mL, removal of carboxylic acids) and brine (10 mL) and dried over $MgSO_4$. After filtration the solvent was evaporated until few mL remained, C_6D_6 (20.0 µL) was added and a sample was taken for the ^2H NMR (no NMR solvent). The combined $NaHCO_3$-phases were acidified with 2 M HCl and extracted with ethyl acetate (4 × 20 mL). After drying over $NaSO_4$ and filtration, the solvent was evaporated to give a colorless oil. It was dissolved in $CHCl_3$ (1.5 mL) and 1,1,2,2-tetrachloroethane was added as internal standard for ^1H qNMR.

Reactions of 1 with protic acids H_2O or ROH (Table 2, entries 2–5): A 10 mL Schlenk tube was charged with Grignard solution (**1**; 0.98 mL, 1.02 M in THF, 1.00 mmol) and cooled to –78 °C (if the mixture gets too viscous, dilution with a little THF is recommended). In reactions with water, H_2O was added as stem solution in THF (250/500 μM); in reactions with alcohols, a solution of the alcohol (500 μmol) in THF (0.5 mL) was added. The mixture was stirred for 1 h at –78 °C, the cooling bath was removed and the reaction stirred for 30 min at room temperature. The mixture was placed in an ice-bath, quenched by addition of D_2O (2 mL) and stirred vigorously for 15 min at room temperature. A weighed amount of internal standard 1-methoxy-4-(D_3-methoxy)-benzene and aq. HCl (2 M, 10 mL) was added. After extraction with CH_2Cl_2 (2 × 15 mL), the combined organic phases were washed with water (15 mL) and aq. NaCl sat. (15 mL) and dried over $MgSO_4$. The solvent was evaporated (40 °C, 750 mbar) until few mL remained and a sample was removed for $^2H\{^1H\}$ NMR analysis.

Reaction of 1 with phosphorus electrophiles (Table 2, entries 6–9): A solution of the corresponding phosphorus electrophile in THF was cooled (0 or –78 °C) and the Grignard solution (1.02 M) added dropwise over 10 min. The resulting suspension was stirred for the specified time at the indicated temperature followed by appropriate work-up.

*a) Reaction of **1** with Ph_2PCl, and isolation of $MenPOPh_2$ (**27**):* The mixture was placed in an ice-bath, quenched by addition of D_2O (2 mL) and stirred vigorously for 15 min at room temperature. After addition of aq. HCl (2 M, 10 mL) and extraction with CH_2Cl_2 (2 × 15 mL), the combined organic phases were washed with water (15 mL) and aq. NaCl sat. (15 mL) and dried over $NaSO_4$. The solvent was evaporated (40 °C, 750 mbar) until few mL remained, a weighed amount of internal standard 1-methoxy-4-(D_3-methoxy)-benzene was added and a sample was removed for $^2H\{^1H\}$ NMR and ^1H qNMR analysis, which revealed the presence of 72% of $MenP(O)Ph_2$ (**27**). Isolation of the main product was performed by column chromatography (CH_2Cl_2–MeOH 50:1) and subsequent recrystallization of the

combined product fractions from hexanes–EtOAc (5:1) to give colorless solid (121 mg, 36%; not optimized).

*Data for P-menthyl-diphenylphosphine-P-oxide (**27**)*. Crystals suitable for X-ray crystal structure analysis were grown by slow evaporation (open flask) of solvent from the mother liquor. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.48 (d, J = 6.7 Hz, 3 H), 0.77 (d, J = 6.4 Hz, 3 H), 0.78 (d, J = 6.8, 3 H), 0.84–0.96 (m, 1 H), 1.04–1.16 (m, 2 H), 1.26–1.39 (m, 1 H), 1.48–1.55 (m, 1 H), 1.66–1.82 (m, 3 H), 1.99 (sept, $J \approx$ 6.1 Hz, 1 H), 2.31–2.40 (m, 1 H), 7.41–7.50 (m, 6 H), 7.74–7.89 (m, 4 H). ^{13}C NMR (101 MHz, C_6D_6): δ 16.0 (CH_3), 21.9 (CH_3), 22.7 (CH_3), 25.2 (d, J(P,C) = 12.0 Hz), 28.5 (d, J(P,C) = 3.4 Hz), 33.7 (d, J(P,C) = 13.5 Hz), 34.7 (d, J(P,C) = 1.5 Hz), 36.6 (d, J(P,C) = 2.0 Hz), 39.6 (d, J(P,C) = 70.6 Hz), 43.8 (d, J(P,C) = 3.1 Hz), 128.5 (d, J(P,C) = 0.5 Hz), 128.6 (d, J(P,C) = 0.5 Hz), 130.7 (d, J(P,C) = 8.5 Hz), 130.81 (d, J(P,C) = 2.7 Hz), 130.82 (d, J(P,C) = 2.7 Hz), 131.4 (d, J(P,C) = 8.1 Hz), 135.3 (d, J(P,C) = 92.4 Hz), 137.3 (d, J(P,C) = 90.0 Hz). ^{31}P NMR (126 MHz, $CDCl_3$): δ 33.7.

*b) Reaction of **1** with excess PCl_3:* The reaction was quenched by addition of 1 M HCl (5 mL) at 0 °C (ice-bath), followed by vigorous stirring for 30 min at 0 °C. The mixture was extracted with EtOAc (2 × 15 mL), the organic phase washed with brine (2 × 5 mL) and evaporated. The residue was dissolved in $CDCl_3$; 1,1,2,2-tetrachloroethane was added as internal standard for ^{1}H qNMR.

*Data for menthylphosphinic acid (**25**)*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78–1.11 (m, 3 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.7 Hz, 3 H), 0.95 (d, J = 7.1 Hz, 3 H), 1.28–1.41 (m, 1 H), 1.53–1.64 (m, 1 H), 1.67–1.80 (m, 3 H), 1.92–2.01 (m, 1 H), 2.21 (sept × d, J = 6.8, 2.8 Hz, 1 H), 7.12 (d, ^{1}J(P,H) = 536.7 Hz, 1 H), 11.51 (br. s, 1 H, OH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.5, 21.5, 22.5, 24.3 (d, J(P,C) = 14.2 Hz), 28.2 (br), 32.0, 32.7 (d, J(P,C) = 15.4 Hz), 34.4, 39.5 (d, J(P,C) = 95.5 Hz), 42.3. ^{31}P NMR (162 MHz, $CDCl_3$): δ 41.0 ($MenPO_2H_2$), 36.5 ($NmnPO_2H_2$).

c) Reaction with limiting PCl_3: The mixture was quenched by addition of D_2O (4 mL) at rt, followed by vigorous stirring for 15 min. Then 2 M HCl (3 mL, degassed by bubbling with argon for 1 min) was

added. After stirring for 3 h at room temperature, the mixture was extracted with diethyl ether (2 × 15 mL), the organic phase washed with 1 M HCl (3 × 10 mL) and brine (15 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated (40 °C, 500 mbar) and the residue dissolved in a little CH_2Cl_2 (*ca.* 3 mL). After addition of naphthalene and C_6D_6 as internal standards, a sample for ^2H NMR was removed; from the remainder, CH_2Cl_2 was carefully removed (40 °C, 500 mbar) and a ^1H qNMR spectrum was measured in $CDCl_3$.

Dimenthylphosphine oxide or bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)phosphine oxide (7).

Synthesis from purified 97 % menthyl chloride: All steps prior to hydrolytic workup were performed under argon. A Grignard reagent was prepared from menthyl chloride (**2**; 97 % isomeric purity; 49.5 g, 283 mmol) in THF (25 mL) by dropwise addition at 70 °C over 1 h to iodine activated magnesium turnings (12.5 g, 514 mmol) in THF (25 mL) and toluene (50 mL). The mixture was stirred for another 2 h at 70 °C, cooled to rt and stirred overnight. Titration indicated a concentration of active RMgX of 1.43±0.1 mol/L. The Grignard solution was transferred through PTFE tubing and dropped into a stirred solution of PCl_3 (8.12 mL, 93.1 mmol) in THF (40 mL) cooled to 0–10 °C (ice-water bath) in a 500 mL round bottom Schlenk-flask. The rate of addition was regulated to prevent overheating and intense stirring was applied to keep the developing slurry homogeneous and in a state of constant movement. A brownish crystalline residue of the Grignard solution was dissolved in THF (10 mL) and also added to the PCl_3 suspension. After completion of the additions (1.5 h) the reaction mixture was allowed to warm to 20–30 °C (0.5 h), and further heated to 60 °C (3 h) with intense stirring. The fine, thick gray-greenish slurry was allowed to cool to rt. After placing into an ice-bath, the mixture was quenched by addition of Et_2O (100 mL) and 1 M HCl aq (200 mL) in portions. After stirring overnight, two homogeneous phases had formed. The mixture was transferred (in air) into a separatory funnel. The aqueous phase was

extracted with Et_2O (1 x). The combined, slightly yellow organic phase was washed with 1 M HCl aq (2 x) and sat NaCl aq (1x). The organic phase was evaporated (10 mbar, 50 °C) to leave viscous oil, which was absorbed on 30 g of silica. The crude product was purified by dry column chromatography[89] in two batches, using 100 mL solvent fractions of *t*-BuOMe–hexane (1:5) with increasing percentage of HOAc from 0–3 vol-% for elution (Table S23). Product fractions of differing purity were collected separately, washed with 2 M NaOH aq (3 x 30–100 mL) and washed with brine (1 x). The organic phase was evaporated to give the product as a colorless solid (15.2 g, 50 %) in five fractions of 90–97 % purity (Table S24). A sample for analysis was recrystallized by dissolving in a small volume of hexane and cooling to –70 °C. Mp. 90.2–90.5 °C. IR (film): 1158, 1167 (P=O), 1454 (CH_2 bend), 2304 (br, P–H), 2868, 2923, 2952 (C–H st). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.81 (d, ^3J(H,H) = 6.9 Hz, 3 H), 0.85 (d, ^3J(H,H) = 6.8 Hz, 3 H), 0.93 (d, ^3J(H,H) = 6.6 Hz, 3 H), 0.94 (d, ^3J(H,H) = 7.0 Hz, 3 H), 0.95 (d, ^3J(H,H) = 6.1 Hz, 3 H), 0.97 (d, ^3J(H,H) = 6.8 Hz, 3 H), 0.8–1.2 (m, 5 H), 1.33–1.46 (m, 3 H), 1.53 (m, 1 H), 1.61–1.82 (m, 8 H), 1.96 (m, 1 H), 2.22 (sept x d, ^3J(H,H) = 6.9, 2.5 Hz, 1 H), 2.64 (sept x d, ^3J(H,H) = 6.9, 2.8 Hz, 1 H), 6.77 (dd, ^1J(P,H) = 435.5 Hz, ^3J(H,H) = 5.6 Hz, 1 H, P–H) . ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 15.5, 15.7, 21.5, 21.6, 22.6, 22.7, 24.2 (d, J(P,C) = 11.1 Hz), 24.7 (d, J(P,C) = 12.6 Hz), 27.4 (d, J(P,C) = 5.1 Hz), 28.3 (d, J(P,C) = 2.4 Hz), 32.3 (d, J(P,C) = 3.8 Hz), 32.7 (d, J(P,C) = 14.4 Hz), 32.7 (d, J(P,C) = 12.5 Hz), 34.33 (d, J(P,C) = 1.7 Hz), 34.34, 34.4 (d, J(P,C) = 1.2 Hz), 36.5 (d, J(P,C) = 62.0 Hz), 37.0 (d, J(P,C) = 64.6 Hz), 41.4 (d, J(P,C) = 3.5 Hz), 44.6 (d, J(P,C) = 3.0 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz): δ 41.8. HR-ESI-MS calcd for $C_{20}H_{40}OP^+$: 327.2811 ($[M+H]^+$), found 327.2811.

ASSOCIATED CONTENT

Supporting Information.

More detailed NMR spectral illustration, data and assignments, copies of NMR spectra of isolated compounds, kinetic datapoints and details of the data-analysis, photographs of crystals, additional ORTEP and ball and stick illustrations, general crystallographic information and CIF-files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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36 Traces of ψ-menthene **10** (1-methyl-3-(2-methylprop-1-en-1-yl)cyclopentane; δ 5.05) result from a small amount of *sec*-ψ-menthyl chloride (**11**; 1-(1-chloro-2-methylpropyl)-3-methylcyclopentane) which was present as impurity (*ca.* 2 mol %) in **2**.

37 See Table 1 or the Supporting Information for structure formulas of all components.

38 Bromide is present due to activation of Mg with ethylene bromide.

39 The impurity *sec*-ψ-menthyl chloride (**11**) in **2** produced signals for *sec*-ψ-MenMgCl (**12**). Two CHMg-signals (δ_C 45.38, 45.63) were detected by HSQC correlation to signals at δ_H –0.02 (dd, J = 7.7, 4.2 Hz) and 0.00 (dd, J = 8.2, 4.0 Hz). **12** is thus present in diastereomeric forms (1:1) at C-1'. See the Supporting Information.

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substituents at phosphorus show a ring-flip with equatorial P and axial *i*Pr. In the latter cases, the ^{13}C NMR-prediction of Men- vs. Nmn-configuration may fail.

46 The ψ-menthane component **16** results from protonation of *sec*-ψ-MenMgCl (**12**) and *tert*-ψ-MenMgCl (**17**), both of which emerge from regioisomeric impurities in crude menthyl chloride (**2**), *cf.* reference 29. Thus **16** is an artifact from impure **2**. See Figure S1 for formulas.

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