Solution-phase combinatorial synthesis using multicomponent Grignard reagents

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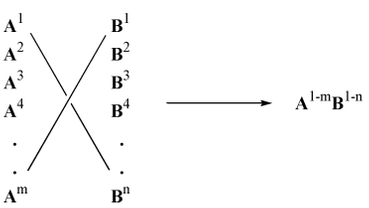
Mixtures of up to 8 different alkyl Grignard reagents were prepared from the reaction of alkyl halides with magnesium. These multicomponent Grignard reagents were reacted with aldehydes, ketones or esters to produce mixtures of alcohols. Analysis of the product mixtures showed that from the reactions of aldehydes and ketones uniform mixtures of products were formed, while from the reaction with esters uniform libraries were only obtained after slow addition of the Grignard reagent.

Introduction

Combinatorial chemistry is a range of techniques, some possibly automated, that permits the rapid synthesis of a large number of chemical compounds usually through the 'combination' of several different synthetic building blocks (Scheme 1).[1–3] Combinatorial chemistry started taking shape in the

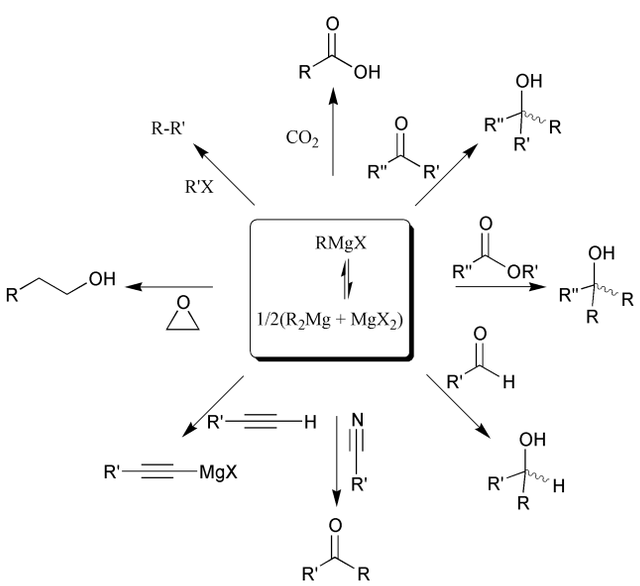


Scheme 1 Solution-phase combinatorial synthesis of a mixed library of *n* times *m* products **AB** from *n* reagents **A** and *m* reagents **B**.

mid-80's starting in peptide-chemistry.[4,5] However biologically active peptides do not normally make good drugs, as they are poorly absorbed orally or are subject to rapid metabolism and excretion, so in the early 1990's, several foresighted organic chemists began to make combinatorial libraries of small drug-like organic molecules.[6,7] Today, combinatorial chemistry has become an important tool for the discovery and optimisation processes for novel drugs, affinity ligands, new materials, and catalysts. The technology has been applied in both academic and industrial institutions to provide a number of unique approaches to satisfy the ever-growing need for new chemical entities with proven or new utility.

While combinatorial chemistry has its origin in solid-phase synthesis, combinatorial methods based on chemistry in solution is increasingly popular.[8,9] Though solution-phase combinatorial chemistry potentially offers some advantages over solid-phase combinatorial chemistry (such as a wider number of accessible reactions, easy monitoration by TLC, HPLC *etc*., less limitation on solvents and temperatures, unlimited reaction scale-up) combinatorial chemistry of mixed libraries is carried out on solid phase for good reason. The insoluble reactants ensures that forcing a reaction will produce each library member in equal amount. The lack of control of the rate of individual library reactions in solution makes it difficult to make uniform mixed libraries in solution unless the reactions employed are fast and high-yielding for each library member.

The Grignard reaction is one of the most frequently used name reaction in organic synthesis.[10] The great value of Grignard reactions to the synthetic chemist is its generality as a tool to synthesise compounds with an impressive range of structures and functional groups. Grignard reagents act as both prototypical carbon nucleophiles that can undergo addition or substitution reactions and as strong bases that can deprotonate acidic substrates, giving conjugate bases or products of elimination reactions. These reagents react with most organic functional groups containing polar multiple bonds (*e.g.*, carbonyl, nitriles, sulfones, imines), highly strained rings (*e.g.*, epoxides and some cycloalkenes), acidic hydrogens (*e.g.*, alkynes), and some highly polar single bonds (*e.g.*, carbon–halogen or metal–halogen). Some representative reactions are outlined in Scheme 2.



Scheme 2 Some of the many reactions that can be carried out with Grignard reagents.

It would be highly desirable if the Grignard reaction could be used in solution-phase combinatorial chemistry. By one-pot reaction between a series of Grignard reagents and an electrophile it would be possible to synthesise in a single step a mixture of analogously C-substituted compounds that could be tested for a specific application. To be useful it requires however that one can depend on each product being present in the product

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mixture, which can only be ensured if each individual Grignard reaction reacts with roughly equal rate or if each reaction can be forced to run to the same degree of completion. Based on what is known about the Grignard reaction the chances for the first event occurring seemed grim. The rate of reaction of various alkylmagnesium halides has been shown to vary widely.[11] Thus the ratio of the pseudo-first order rate constants in reaction of CH_3MgBr, C_2H_5MgBr and *n*-C_4H_9MgBr with acetone are 2 : 4 : 1. The rate of reaction of Grignard reagents with benzophenone is even more variable.

The purpose of the present work was to investigate whether uniform compound libraries could be produced through reaction of Grignard reagents with aromatic and aliphatic ketones, aldehydes or esters. Our strategy involved reaction of a substrate S with multiple Grignard reagents, R^1, R^2, $R^3 \cdots R^n$, to produce a compound library of *n* individual products SR^1, SR^2, $SR^3 \cdots SR^n$ (Scheme 3), followed by careful investigation of

$$\mathbf{S} + \mathbf{R^1, R^2, R^3 ..... R^n} \longrightarrow \mathbf{SR^1, SR^2, SR^3 ..... SR^n}$$

Scheme 3 Solution-phase combinatorial synthesis of alcohols as carried out in this work. S is the substrate (aldehyde, ketone or ester) and R a Grignard reagent.

whether or to what extent the individual library members were formed. Mixtures of Grignard reagents were synthesised in one pot from the halides and magnesium. To the best of our knowledge, no Grignard reaction has been used in compound library synthesis, though Grignard reagents have been used in solid-phase synthesis.[12]

Results and discussion

The most challenging problem in solution phase combinatorial synthesis is whether a reaction proceeds uniformly and, in other words, whether a substrate reacts equally with each of the reagents. For this purpose, a series of simple experiments were designed. Benzaldehyde (**1**) was reacted with a mixture of three different Grignard reagents (CH_3MgI, *n*-C_3H_7MgBr and *n*-$C_8H_{17}MgBr$), which were chosen as typical examples of straight chain aliphatic Grignard reagents. The mixture of Grignard reagents in diethyl ether was prepared either in one-pot or by sequentially adding each halide to excess magnesium. When using the latter procedure observation of the exothermic reaction of each halide can be used to ensure that formation of each Grignard reagent has taken place. The 1 : 1 : 1 mixture of Grignard reagents, two equivalents in total, was added quickly to a solution of benzaldehyde in diethyl ether at room temperature giving after stirring for 2–3 h and usual workup a mixture of secondary alcohols. The obtained mixture was first subjected to ^1H NMR analysis, which showed that no starting material was left and was consistent with a roughly equal mixture of the products **2**, **3** and **4**. HPLC analysis was then carried out using individually prepared pure alcohols **2**–**4** as references, which showed that the Grignard products had been formed in a ratio of 4 : 5 : 6 (Scheme 4). This showed clearly that the reactivities of the three reagents were quite similar, which was somewhat surprising given the kinetic information available about the Grignard reaction.[10,11] However the fact that only 0.67 equivalents of each Grignard reagent is present ensures a more even distribution of products that would otherwise occur.

In exactly the same manner, addition of five different Grignard reagents, CH_3MgI, C_2H_5MgBr, *n*-C_3H_7MgBr, *n*-C_4H_9-MgBr, *n*-$C_5H_{11}MgBr$, to benzaldehyde was carried out (Scheme 5). NMR and HPLC (using comparison with pure reference compounds) showed that a library of the five compounds **2**, **3**, **5**, **6** and **7** had been obtained, with the ratio between **2**, **3**, **5**, and **6** + **7** being 1 : 1 : 1 : 2. Since no baseline separation was obtained between compounds **6** and **7** the exact amount of each of these two could not be quantified (Fig. 1).

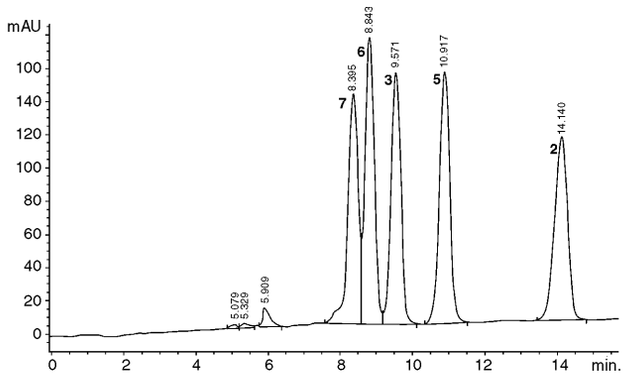
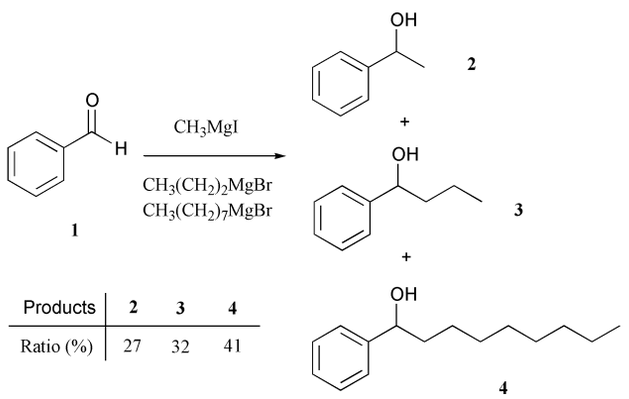
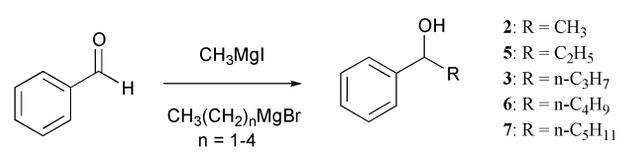


Fig. 1 HPLC chromatogram of the library obtained from the reaction of benzaldehyde (**1**) with a series of Grignard reagents (Scheme 5). The column was a silica gel column (Nucleosil) and the eluent *n*-hexane–propan-2-ol 97 : 3.



Products	2	3	4
Ratio (%)	27	32	41

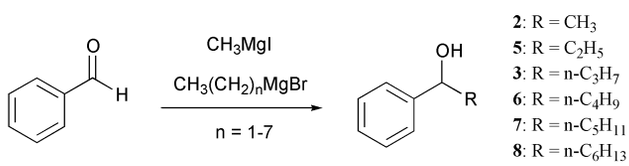
Scheme 4 Reaction of benzaldehyde (**1**) with three Grignard reagents in equimolar amounts (0.67 equiv. of each with respect to **1**).



Products	2	5	3	6+7/2
Ratio (%)	19	21	20	20

Scheme 5 Reaction of benzaldehyde (**1**) with five Grignard reagents in equimolar amounts (0.4 equiv. of each with respect to **1**).

The complexity was then enhanced to generate an 8-membered library using the exact same conditions on the reaction of **1** with the series of Grignard reagents from methyl to octylmagnesium halide (Scheme 6). While NMR analysis



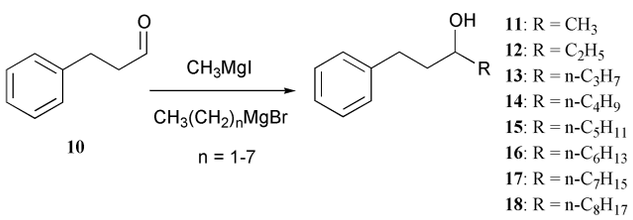
Products	2	5	3	6 + 7 + 8 + 9 + 4 / 5
Ratio (%)	14	14	12	12

Scheme 6 Reaction of benzaldehyde (**1**) with eight Grignard reagents in equimolar amounts (0.25 equiv. of each with respect to **1**).

showed total conversion and was consistent with the formation of each of the products **2**–**9**, HPLC-analysis could not separate all products in this case, and only **2**, **3** and **5** were base-line separated. However, integration of these 3 peaks, and the sum

of integration of **4**, **6**, **7**, **8** and **9** was consistent with each library contributing 12% to the product mixture, and that equal amounts of each compound had been formed. These experiments convinced us that libraries of simple linear Grignard reagents can react with aromatic aldehydes to form uniform libraries of products without the need for special tricks or precautions.

We also carried out experiments with an aliphatic aldehyde as the behavior of alkylmagnesium halides towards aliphatic and aromatic ketones can be widely different.[10,11] Therefore the 8 membered mixture of Grignard reagents used in the experiment above was also added in two fold excess (total) to phenylpropanal (**10**). Also in this experiment NMR and HPLC was consistent with total conversion of **10** into an 8-membered library of the alcohols **11**–**18** (Scheme 7). Again not all



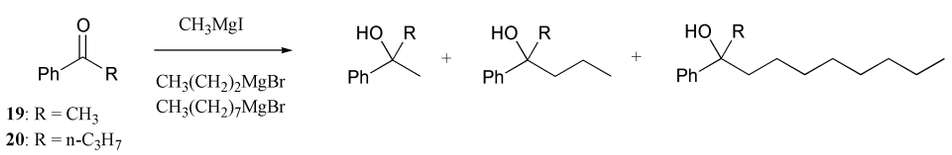
Product	11	12	13	14 + 15 + 16 + 17 + 18 / 5
Ratio (%)	14	14	12	12

Scheme 7 Reaction of **10** with eight Grignard reagents in equimolar amounts (0.25 equiv. of each with respect to **10**).

products could be separated on HPLC. The chromatogram showed seven peaks of which only three were base-line separated. However the integrals of the individual and mixed peaks were such that it was consistent with an equal amount of each product.

The reaction of ketones was now investigated. Two ketones, acetophenone (**19**) and 1-phenylbutan-1-one (**20**), were each reacted with 2 equivalents of a mixture of CH_3MgI, *n*-C_3H_7-MgBr and *n*-$C_8H_{17}MgBr$. Each reaction gave total conversion of ketone and the expected products **21**–**23** and **22**, **24**, **25**, respectively (Scheme 8). HPLC analysis showed that these tertiary alcohols were formed in 1 : 1 : 1 ratio. In these reactions significant amounts, 3% to 10%, of secondary alcohols formed from reduction of the ketones **19** and **20** were observed. Reduction of the carbonyl compound is a common byproduct in Grignard reactions especially with hindered ketones.[13]

Finally the combinatorial reaction of Grignard reagents with an ester was investigated. As each ester will react with two equivalents of Grignard reagents this is a considerably more complex situation. Firstly multiple Grignard reagents can react with the same ester creating a diversity of tertiary alcohols through 'combination'. Secondly the kinetics are complicated by both the ester and ketones acting as electrophiles in the reaction. In a preliminary experiment, the reaction conditions that had been used in the reaction of ketones and aldehydes above were used *i.e.* 4 equivalents of Grignard mixture was quickly added to the ester. Thus, a mixture of CH_3MgI and *n*-C_8H_{17}-MgBr was reacted with methyl benzoate (**26**) at room temperature giving full conversion to the three possible products **21**, **23** and **27** (Scheme 9). If the rate of reaction between the two Grignard reagents and **26** and the intermediate ketones were identical, the theoretical ratio between the products **21**, **23** and **27** would be 1 : 2 : 1 since **23** is racemic and is formed in two ways. The observed ratio of **21**– **23**–**27** was however 5 : 5 : 1, which was determined from HPLC analysis using reference compounds. This result shows that octylmagnesium bromide is much less reactive than the methylmagnesium iodide towards the ester functionality. We already know from the ketone experiments above that CH_3MgI and *n*-$C_8H_{17}MgBr$ have the same reactivity towards **19** or **20** so the excess formation in methylated products must be caused in the ester reaction. The result is consistent with an initial conversion of **26** to a 5 : 1 mixture of methyl and octylketone, which then uniformly react with the methyl and octyl Grignard reagents. The ester **26** was much less reactive than the other carbonyl compounds investigated in this work, and while most of the above mentioned reactions were practically instantaneous the reaction between **26** and *n*-$C_8H_{17}MgBr$ took more than 30 min to complete. To overcome the unequal reactivities of CH_3MgI and *n*-C_8H_{17}-MgBr towards **26**, the mixture of these two Grignard reagents was added slowly using a syringe pump to a solution of **26** over 8 h. In this way added Grignard reagents are allowed to react before more reagent is added. This afforded a ratio of the three



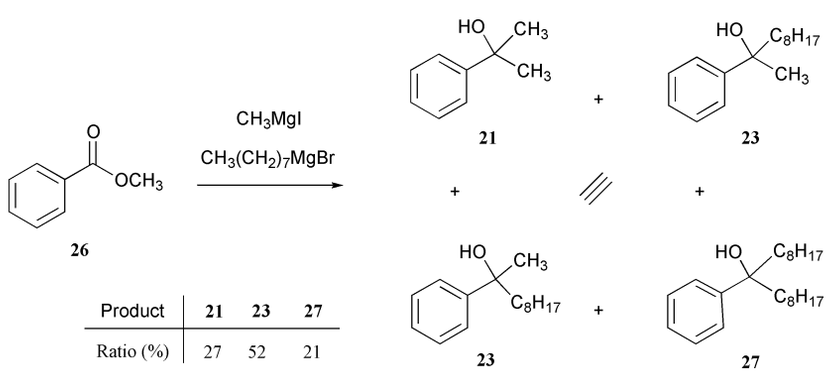
R = CH_3

Product	21	22	23
Ratio (%)	34	32	34

R = n-C_3H_7

Product	22	24	25
Ratio (%)	35	29	36

Scheme 8 Reaction of ketones **19** and **20**, respectively, with three Grignard reagents in equimolar amounts (0.67 equiv. of each with respect to ketone).



Product	21	23	27
Ratio (%)	27	52	21

Scheme 9 Reaction of methyl benzoate (**26**) with two Grignard reagents in equimolar amounts (2 equiv. of each with respect to **26**).

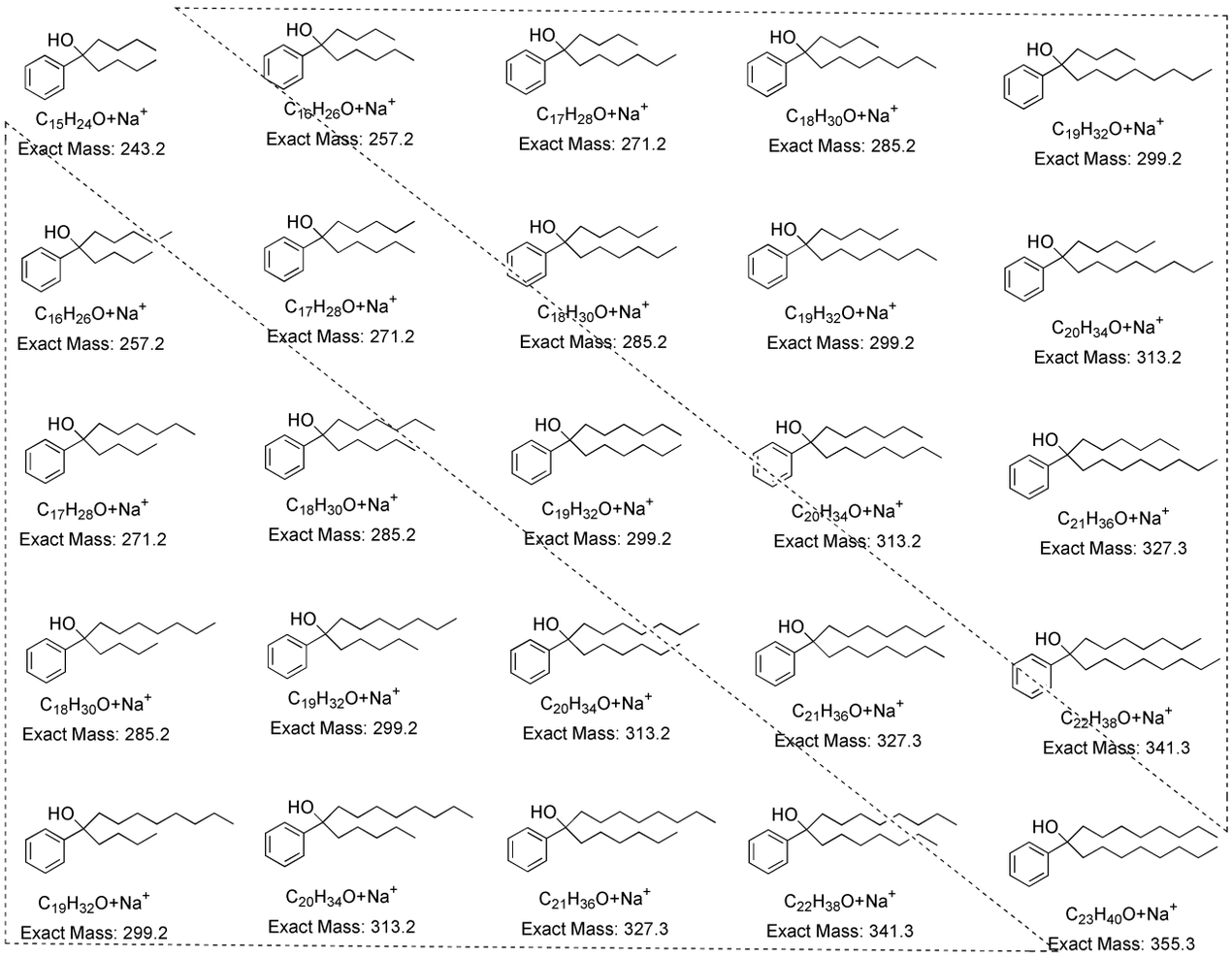


Fig. 2 Products from the reaction of methyl benzoate (**26**) with *n*-C_4H_9MgBr, *n*-$C_5H_{11}MgBr$, *n*-$C_6H_{13}MgBr$, *n*-$C_7H_{15}MgBr$ and *n*-$C_8H_{17}MgBr$ in equimolar amounts (0.8 equiv. of each with respect to **26**). The compounds have been organised so that compounds on South-west/North-east diagonals have identical molecular weights.

products **21**, **23** and **27** of 3 : 10 : 4 and thus relatively close to the statistical value of 1 : 2 : 1.

Now the experiment was carried out with five Grignard reagents. *n*-C_4H_9MgBr, *n*-$C_5H_{11}MgBr$, *n*-$C_6H_{13}MgBr$, *n*-$C_7H_{15}MgBr$ and *n*-$C_8H_{17}MgBr$ were reacted with **26** using the slow addition procedure giving potentially 25 different products if counting stereoisomers or 15 different products if not discriminating between enantiomers. These products are listed in Fig. 2 together with their molecular weights. While the complete conversion of the ester could be ensured by NMR it was impossible to determine the presence of individual library members with NMR or HPLC analysis due to the complexity of the library, but the mixture could be analysed by electrospray mass spectroscopy. As can be seen from Fig. 2 a considerable number of compounds have identical molecular weights. In fact between the 25 compounds only 9 different molecular weights exist. As can be seen from Fig. 2 the number of compounds with each molecular weight is distributed in the ratio 1 : 2 : 3 : 4 : 5 : 4 : 3 : 2 : 1 from smallest to largest value (Fig. 3). While the MS spectrum does show the 9 individual peaks, and even though the intensity of the 9 peaks was quite close to the statistical value, the peak intensities cannot be relied on to reflect the concentration of each compound. Therefore the individual concentration of each substance may be different.

An aliphatic acid ester, methyl 3-phenylpropanoate was also reacted with the five Grignard reagents using the same procedure giving a similar result (Fig. 4). Again all nine peaks could be observed from the MS spectrum.

In summary, we have shown that uniform mixed libraries of secondary and tertiary alcohols can be made by solution-phase combinatorial synthesis using multicomponent Grignard reagents. This methodology is easy to use. Depending on the carbonyl compound some adaptation may be needed, but with slow addition of the Grignard reagent mixture uniform libraries must be expected. Further investigations will focus on using this methodology in the search for useful compounds.

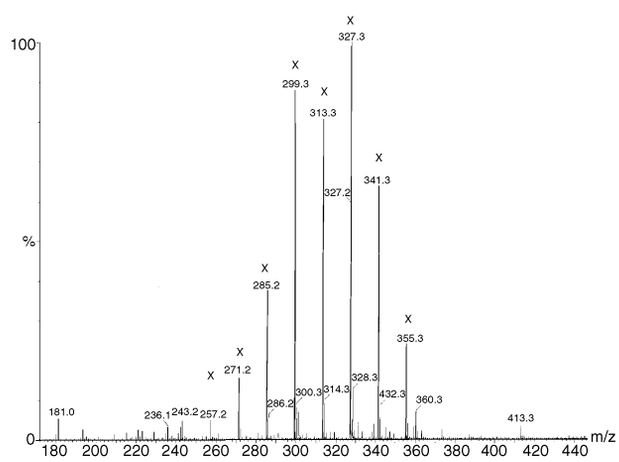


Fig. 3 Electrospray mass spectrum of the product mixture obtained from reaction of **26** with five Grignard reagents (Fig. 2). The **X** marked peaks correspond to expected compounds in the product mixture.

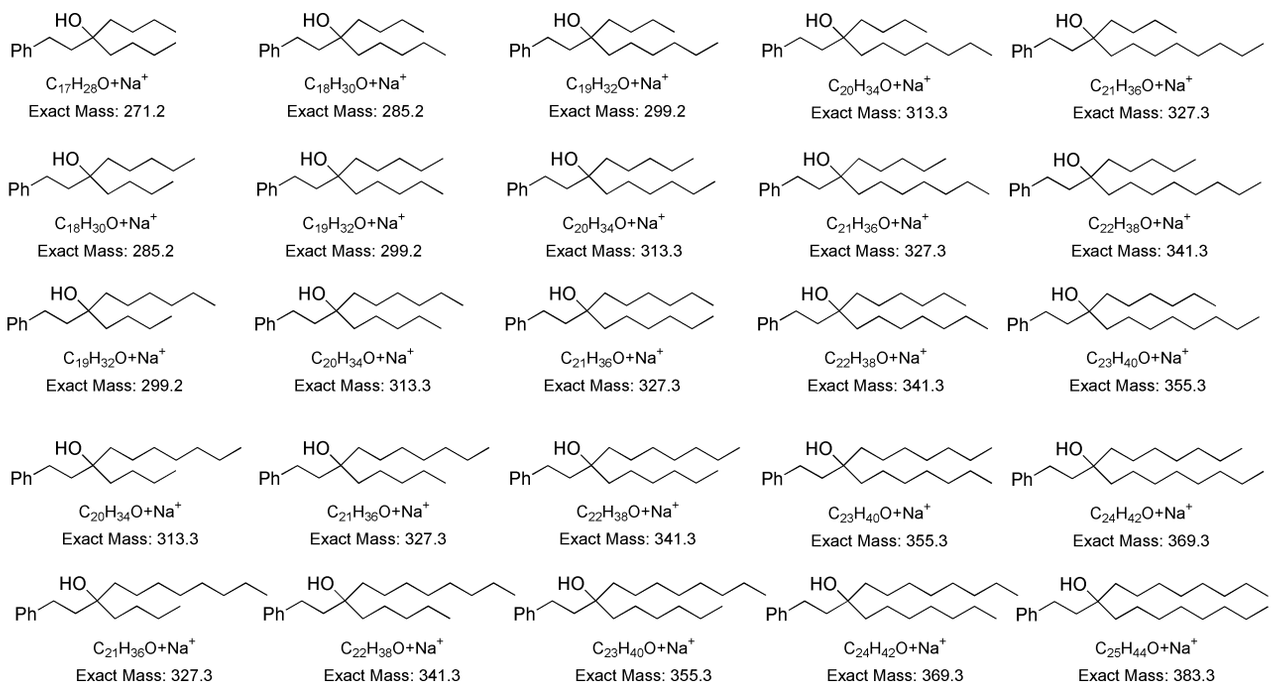


Fig. 4 Products from the reaction of methyl 3-phenylpropanoate with *n*-C_4H_9MgBr, *n*-$C_5H_{11}MgBr$, *n*-$C_6H_{13}MgBr$, *n*-$C_7H_{15}MgBr$ and *n*-$C_8H_{17}MgBr$ in equimolar amounts (0.8 equiv. of each with respect to 3-phenylpropanoate). The compounds have been organised so that compounds on South-west/North-east diagonals have identical molecular weights.

Experimental

All reagents and chemicals were commercially available. Mass spectra were carried out on a Micromass LC-TOF instrument. ^{1}H-NMR spectra were obtained on a Varian Gemini 200 instrument.

General procedures for the Grignard reactions

HPLC analysis of the compound libraries: The composition of a library was determined on a HP Instrument using a Nucleosil column. (eluent: *n*-hexane–propan-2-ol 97 : 3; flow rate: 0.5 ml min^{-1}, UV: 210 nm). Within the compound series studied molecules with a higher molecular weight had shorter retention times than those with lower molecular weight.

Preparation of single component Grignard reagents

Alkyl halide (10 mmol) was added so slowly to a mixture of Mg (20 mmol) in diethyl ether (20 ml) that the mixture was kept refluxing. After addition, the mixture was stirred for 2 h. The solution of Grignard reagent was taken out using a syringe and employed.

Preparation of multicomponent Grignard reagents

Several different alkyl halides were mole-equivalently mixed together to give a liquid mixture (30 mmol). The solution was added so slowly to a mixture of Mg (60 mmol) in diethyl ether (20 ml) that the mixture was kept refluxing. After addition, the mixture was stirred for 2 h. The solution of Grignard reagents was taken out using syringe and employed. Alternatively each alkyl halide was added dropwise one by one in mole-equivalent amounts (30 mmol total) to the Mg (60 mmol) in diethyl ether (20 ml) at such a rate that the solution was kept refluxing. This ensures that the failure of an alkyl halide to react is detected.

Reaction of a ketone or an aldehyde with a single component Grignard reagent

To a solution of a ketone or aldehyde (5 mmol) in diethyl ether (20 ml) was added a solution of Grignard reagent (10 mmol) at 0 °C. The reaction solution was stirred for 2–3 h at room temperature. After reaction, the solution was cooled to 0 °C. To the solution was first added an aqueous saturated solution of NH_4Cl (20 ml) dropwise and then H_2O (20 ml). After stirring for 10 min, the two phases were separated. The aqueous phase was extracted with diethyl ether (20 ml × 2). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give an alcohol. Products **2**, **3**, **5**, **6**, **11**, **21** and **22** were commercially available, while products **7**,[14] **8**,[14] **9**,[15] **4**,[16] **12**,[17] **13**,[18] **14**,[19] **15**,[20] **16**,[21] **18**,[22] **23**,[23] **24**[24] and **27**[25] were otherwise known. The identity of these substances was confirmed by comparison with literature or spectral libraries. Compounds**17** and **25** were previously unknown, and their data are thus given here.

1-Phenyldecan-3-ol (17). ^{1}H-NMR ($CDCl_3$): δ 7.2 (m, 5H, Ph), 3.8 (m, 1H, H3), 2.7 (m, 2H, H1's), 1.8 (m, 2H, H2's), 1.3 (m, 12H, H4–H10's), 0.9 (m, 3H, Me). MS(ES): (obtained on acetate ester) *m*/*z* 299.1982, Calc for $C_{18}H_{28}O_2$ + Na: 299.1987.

4-Phenyldodecan-4-ol (25). Bp: 198 °C, ^{1}H-NMR ($CDCl_3$): δ 7.3 (m, 5H, Ph), 1.8 (m, 4H, H3's, H5's), 1.3 (m, 14H, H2's, H6–H11's), 0.8 (m, 6H, Me's). IR: 3390 (st, OH), 2926, 2854 (st, CH), 1466 (m, CH_2, CH_3). MS(ES): *m*/*z* 285.2196, Calc. for $C_{18}H_{30}O$ + Na: 285.2194.

Reaction of a ketone or an aldehyde with multicomponent Grignard reagent

To a solution of a ketone or an aldehyde (10 mmol) in diethyl ether (20 ml) was added a solution of multicomponent Grignard reagent (30 mmol) at 0 °C. The reaction solution was stirred at room temperature for 2–3 h. After reaction, the solution was cooled to 0 °C. To the solution was first added an aqueous saturated solution of NH_4Cl (20 ml) dropwise and then H_2O (20 ml). After stirring for 10 min, the two phases were separated. The aqueous phase was extracted with diethyl ether (20 ml × 2). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a library of alcohols.

Reaction of an ester with multicomponents Grignard reagents

To a solution of an ester (5 mmol) in ether (10 ml) was added a solution of a multicomponent Grignard reagent (20 mmol,

40 ml) slowly (8 h) at room temperature. After stirring for 8 h at the same temperature, the reaction mixture was cooled down to 0 °C. To the mixture was first added an aqueous saturated solution of NH_4Cl (20 ml) dropwise and then H_2O (20 ml). After stirring for 10 min, the two phases were separated. The aqueous phase was extracted with diethyl ether (20 ml × 2). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a library of tertiary alcohols.

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