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# Exploration of the diastereoselectivity in an unusual Grignard reaction and its application towards the synthesis of styryl lactones 7-*epi*-(+)-goniodiol and 8-*epi*-(−)-goniodiol†

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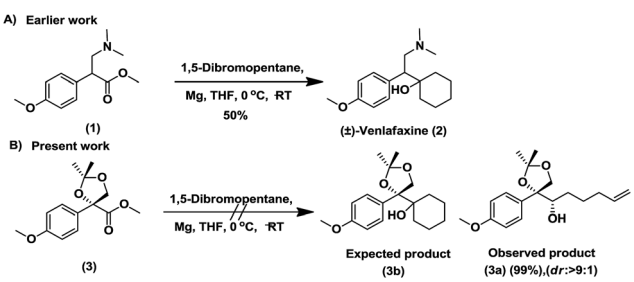
An unusual diastereoselective Grignard reaction is explored, where the Grignard reagents are derived from 1,*n*-dihaloalkanes. A steric bias due to the presence of a quaternary centre adjacent to the acetonide ester at the benzylic position is responsible for the formation of an intramolecularly reduced product in almost quantitative yield. This steric hindrance is responsible for the diastereoselectivity observed with a variety of aromatic as well as aliphatic esters. The unusual Grignard reaction furnishes long chain secondary alcohols possessing a terminal olefin, which are synthetically important intermediates. As an application of this method, the diastereoselective synthesis of styryl lactones *viz.* 7-*epi*-(+)-goniodiol (**29**) and 8-*epi*-(−)-goniodiol (**30**) has been achieved.



The Grignard reaction is one of the most fundamental and convenient tools for the formation of carbon–carbon bonds, hence it is an essential and widely performed reaction in organic synthesis. To date, Grignard reagents have been extensively utilized organometallic species in total synthesis. Since its invention, a number of different modifications of the original reaction have been reported in the literature. Kohler *et al.*[1] reported on the reducing power of Grignard reagents, which was earlier mistaken for enolization. Whitmore and co-workers[2a,b] reported an abnormal Grignard reaction that frequently depends upon the mode of addition of the reagent to the carbonyl group. Nenitzesku[3] reported that the reaction between terminal di(bromomagnesio)alkanes and esters furnished cyclic alcohols. The addition of di(halomagnesio) alkanes to various lactones as well as acid anhydrides furnished diols and spirolactones, which was observed by Canonne.[4] Ferles[5] reported the reaction of 1,4-di(bromomagnesio)butane with ethyl isonicotinate, with a very low (<10%) yield for the annelation product. Canonne *et al.*,[6] inspired by Ferles' observation, have reported on steric effects with Grignard reagents derived from alkyl halides, like for the reaction of 1,5- and 1,4-dibromobutane. When these di(bromomagnesio)alkanes were treated with different aromatic and heteroaromatic esters, this furnished a secondary alcohol, whose formation was postulated to occur by an intramolecular reduction, as the major product instead of the tertiary alcohol. There was no such report for aliphatic esters.

As a part of one of the total synthesis projects, a practical synthesis of the commercially important antidepressant drug (±)-venlafaxine **2** was reported from our laboratory.[7] Here, the aminoester **1** was treated with a Grignard reagent derived from 1,5-dibromopentane to furnish the product **2** in 50% yield (Scheme 1). In order to improve the overall yield and render the process more efficient, we planned an enantioselective approach for synthesis of the drug. In this context, the Grignard reaction was carried out on an acetonide protected ester **3**, with the hope of obtaining alcohol **3b**. Surprisingly, this did not furnish the desired addition product **3b**. After careful investigation and characterization of the product formed, it was found to contain a secondary alcohol with a terminal double bond. It is clear that instead of routine nucleophilic addition, **3** underwent a simultaneous elimination–reduction sequence of reactions (Scheme 1). Almost quantitative formation of compound




Scheme 1 Observation of an unusual Grignard reaction.

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**3a**, rather than the annelation product **3b**, prompted us to investigate the observed result in detail. It could be explained by considering two transition states as shown in Fig. 1. After the first nucleophilic addition of di(bromomagnesio)pentane to the carbonyl carbon of the acetonide protected ester, there are two alternative possibilities: (i) a second intramolecular nucleophilic addition reaction with the ketone, which is now comparatively more electrophilic than the starting ester, or (ii) instead of the expected addition reaction, intramolecular elimination at the terminal carbon–carbon bond, leading to hydride transfer to the carbonyl carbon of the ketone to give a straight chain secondary alcohol containing a terminal double bond as the only product and not the expected tertiary cyclohexanol. The steric hindrance of the acetonide functionality at the benzylic center positioned alpha to the ester resulted in hydride transfer preferentially from one face. This hydride shift could occur either from the alpha or beta face with respect to the orientation of the acetonide steric bulk, hence is responsible for the diastereoselectivity observed in the present reaction. We believe that this transformation proceeds through a six-membered, stable and favourable transition state (II), which thus explains the outcome of the reaction. This rigid and sterically hindered system blocks a second nucleophilic attack of the Grignard reagent on the more electrophilic intermediate ketone, as compared to hydride transfer, and so formation of the annelation product was not observed, as shown in transition state model (I). To place our hypothesis on even firmer ground, we decided to undertake DFT calculations.

DFT calculations were done at the PBE/TZVP level of theory in order to understand the mechanism as well as the formation of the addition (VIII) and unusual (VI) products of the reaction.[18] In the first step – the nucleophilic addition of the Grignard reagent[19] to the carbonyl carbon of the acetonide protected ester I – the activation energy barrier *via* transition state II was found to be 17.3 kcal mol$^{-1}$ ($\Delta G$). The second step of the reaction is much more important, because there are two possibilities – (i) another nucleophilic addition of the Grignard to the more electrophilic carbonyl carbon leading to the formation of (VIII), or (ii) the hydride transfer to the carbonyl carbon of the ketone to give the straight chain secondary alcohol containing a terminal double bond (VI). From our DFT study, two transition states, V and VII, were found corresponding to the two different pathways starting from the same reactant geometry IV (Fig. 2). In the case of the addition product (VIII), the energy barrier was found to be 16.9 kcal mol$^{-1}$, whereas for the unusual product (VI) the energy barrier was reduced by almost 15.0 kcal mol$^{-1}$. Therefore, the second pathway, where the energy barrier was found to be only 1.9 kcal mol$^{-1}$, is kinetically much more favourable and leads to the formation of an undesired straight chain secondary alcohol as the major product. This low barrier suggests that in this reaction, the eventual outcome of the reaction is governed by the kinetics of the reaction.

The reaction of *in situ* generated Grignard reagents obtained from terminal dihalogenated alkyl compounds was systematically studied for a diverse range of esters and the results obtained are depicted in Table 1. It is noteworthy that in the case of esters **4–9**, excellent yields as well as diastereoselectivities were observed not only in the case of sterically crowded aromatic esters but also in the case of aliphatic esters. When acetonide protection is placed on the secondary carbon alpha to the carboxylic carbon and not at the benzylic position for esters **10**, **11** and **12**, this resulted in a notable decrease of the yields of the respective reduced products. So, positioning the acetonide functionality on the tertiary carbon proved to be critical and essential, for high diastereoselectivity.

In addition to above results, when the methyl ester of phenyl acetic acid **13** and its *p*-methoxy derivative **14** were treated under similar conditions, alcohols **13a** and **14a** were obtained in 32% and 37% yields respectively (Table 2). It should be emphasized that the introduction of one methyl group at the benzylic position, as in ester **15**, results in significant enhancement of the yield of the reduced product (**15a**). The presence of two methyl groups at the benzylic position of starting ester **16**,

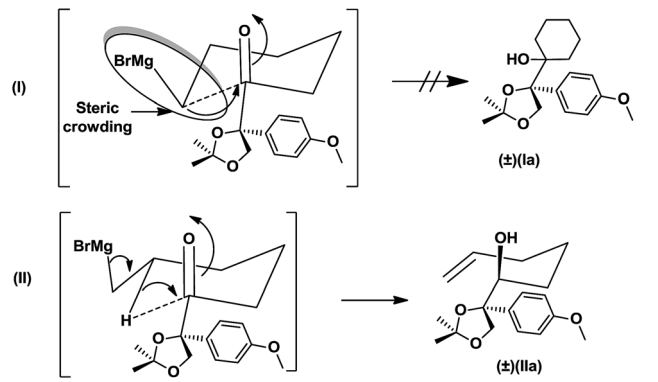



Fig. 1 Transition state model for the unusual Grignard reaction.

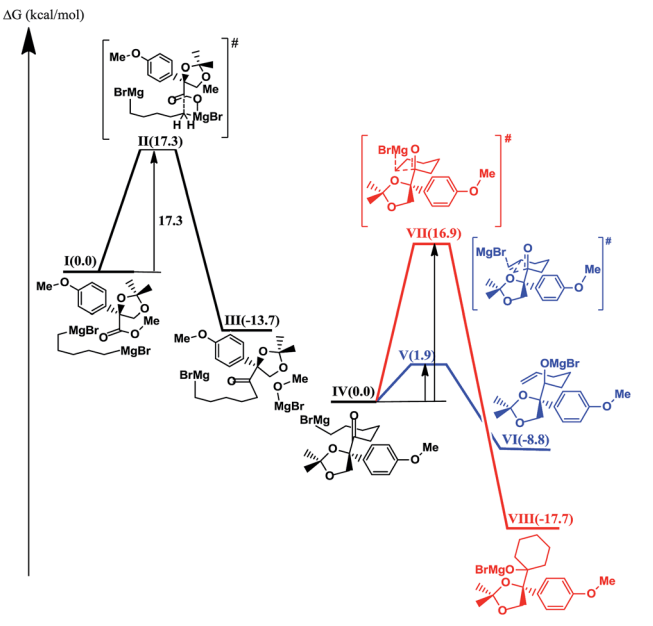
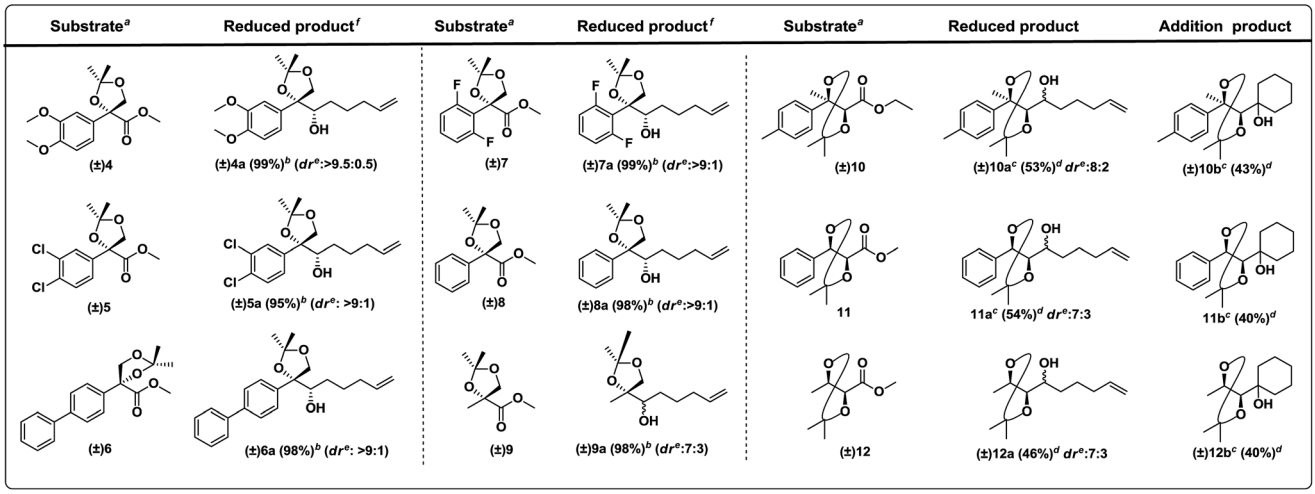



Fig. 2 DFT calculations comparing the free energy profiles *via* two different transition states.

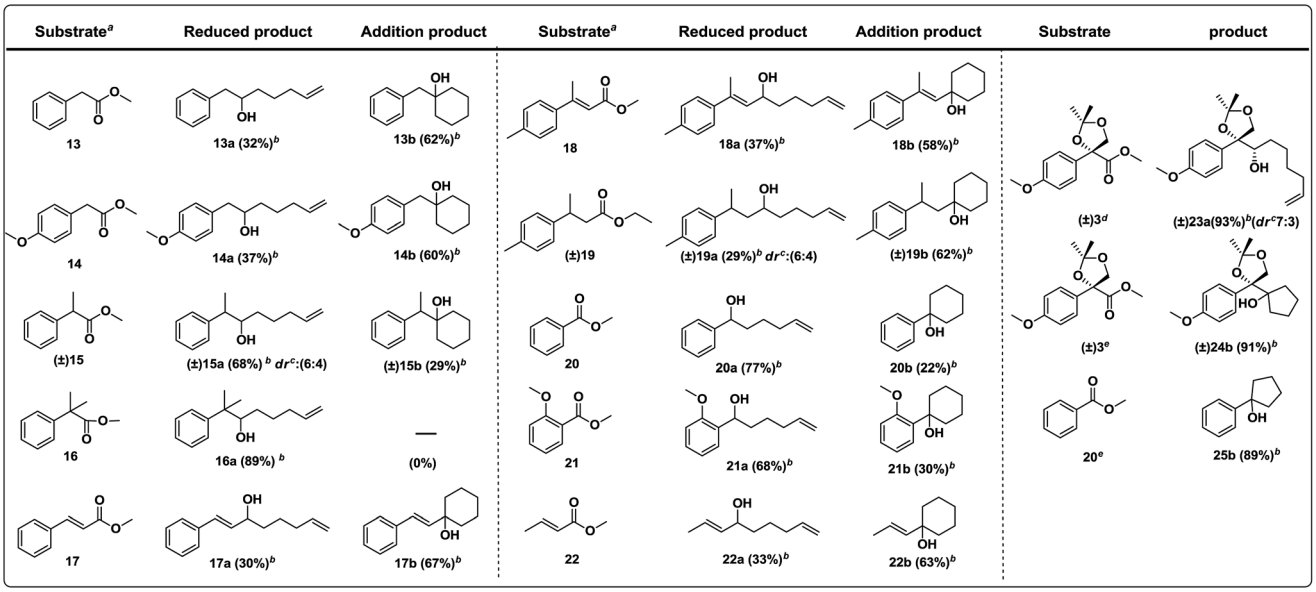
Table 1 Unusual Grignard reaction of acetonide protected ester substrates




[a] Reaction conditions: 1,5-dibromopentane, Mg, THF, 0 °C–RT, 5 h. [b] Product yields calculated after column chromatography purification. [c] Unable to separate two alcohols using column chromatography so acetate protection of the secondary alcohol, separation of it from the respective cycloalkanol and subsequent deprotection was carried out, and thus pure products were isolated in order to obtain data. [d] Yield and dr calculated over two steps. [e] dr: diastereomeric ratio determined by $^1$H-NMR analysis. [f] Relative stereochemistry of **4a** to **9a** was determined by extensive chemical transformations of **3a** into known compound.[17]

resulted in product **16a** being obtained in 89% yield with the absence of cycloalkanol **16b**. Thus formation of **16a** highlights the importance of the presence of a tertiary carbon alpha to the carboxylic ester. It is evident from the above study that the absence of an acetonide steric bias does affect the yield and diastereoselectivity. Furthermore, when α,β-unsaturated esters **17** and **18** were reacted under similar reaction conditions, they led to the formation of **17a** and **18a** in reduced yields due to a decrease in the steric bulk. In order to study the scope and limitations of the method using an acetonide group, some of the esters were subjected to treatment with terminal di(bromomagnesio)alkanes of varying chain lengths. Thus, acetonide

Table 2 Exploration of the unusual Grignard reaction



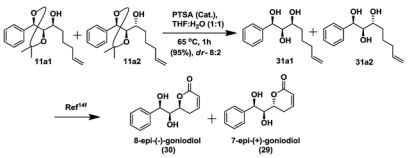

[a] Reaction conditions: 1,5-dibromopentane, Mg, THF, 0 °C–RT, 5 h. [b] Product yields calculated after column chromatography purification. [c] dr: diastereomeric ratio determined by $^1$H-NMR analysis. [d] Reaction conditions: 1,6-dibromohexane, Mg, THF, RT, 5 h. [e] Reaction conditions: 1,4-dibromobutane, Mg, THF, 0 °C–RT, 5 h.

protected ester **3**, on reaction with 1,6-di(bromomagnesio) hexane, in THF as a solvent at room temperature furnished reduced product **23a** in 93% yield. Interestingly, it was observed that the reaction of 1,4-di(bromomagnesio)butane with esters **3** and **20** always resulted in the formation of the usual addition products, cyclopentanol **24b** and **25b** respectively, with good yields.

As a part of our ongoing program towards the total synthesis of bioactive natural products, we quickly realised that this methodology could be very useful for the synthesis of styryl lactones[8] *viz.* 7-*epi*-(+)-goniodiol **29** and 8-*epi*-(−)-goniodiol **30**, isolated by Mu and co-workers.[10] By virtue of the strong cytotoxic activity exhibited by these styryl lactones,[11] they have been the most sought after phytochemicals worldwide, due to their promising role in oncopharmacology.[9] 7-*epi*-(+)-Goniodiol **29** with a 25 mM MIC value against *Listeria denitrificans*[9a] is the stereoisomer, amongst all the other stereoisomers of styryl lactones, which showed the highest activity against Gram positive bacteria.[14b] Various synthetic approaches for styryl lactones have been reported in the literature, highlighting synthesis of goniodiol,[12a–d] as it is the source of a variety of it's natural analogues.[13,14] In light of the results obtained in the case of ester **11** (Table 1), the diastereoselectivity observed from the unusual Grignard reaction is noteworthy. Since the diastereomers could not be separated by normal column chromatography, it was decided to proceed towards the synthesis of **29** and **30** (Scheme 2).

Oxidative cleavage of **11a** (dr 7 : 3, ee 98%),[15] resulted in the formation of lactol **26**, which was further oxidised using tetrapropylammonium perruthenate in the presence of *N*-methylmorpholine-*N*-oxide to furnish lactone **27** in 87% yield. Lactone **27** was alkylated at −78 °C using phenylselenyl bromide and employing LDA, and subsequent oxidation–elimination in the presence of hydrogen peroxide and pyridine provided compound **28** in good yield, which after acetonide deprotection furnished 7-*epi*-(+)-goniodiol **29** and 8-*epi*-(−)-goniodiol **30**. The spectral data of **29** and **30** thus obtained are in agreement with those reported in the literature.[14] One of the diastereomers became enriched during chromatographic purification, at the lactol step. Hence, the diastereomeric ratio of the final compounds was observed to be 8 : 2 with respect to **29** and **30**.

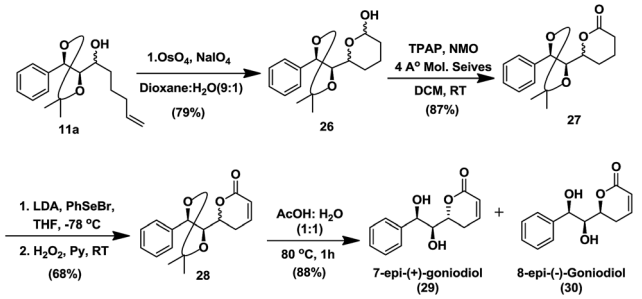
On the other hand, a mixture of **11a1** and **11a2** (dr 7 : 3), when subjected to acetonide deprotection, produced the corresponding triols **31a1** and **31a2** (dr 8 : 2), which have been reported as intermediates in the total synthesis of Goniodiol and 8-*epi*-(−)-goniodiol **30** by Prasad *et al.*[14f] (Scheme 3) and thus this also constitutes an alternative route for the formal synthesis of styryl lactones **29** and **30.**



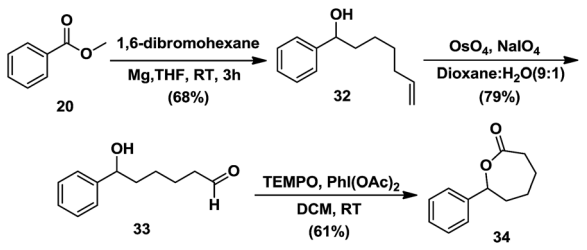

Scheme 3 Formal synthesis of **30** and **29**.

Using the above protocol for the unusual Grignard reaction, a regioselective route for the preparation of substituted ε-caprolactone in a reduced number of steps was developed. Accordingly, when methyl benzoate **20** was treated under Grignard reaction conditions in the presence of 1,6-di(bromomagnesio)hexane with THF as a solvent at room temperature, this afforded a seven carbon long chain alcohol **32** containing a terminal double bond, which proved to be an immensely important intermediate for the facile synthesis of seven membered lactones.[16] As shown in Scheme 4, alcohol **32** was treated under Lemieux–Johnson oxidation conditions to furnish aldehyde **33** in 79% yield, which was then subjected to TEMPO catalyzed oxidative lactonization in the presence of (diacetoxyiodo)benzene to afford lactone **34** in 61% yield.

In summary, an unusual diastereoselective Grignard reaction has been explored using diverse and synthetically important substrates. The presence of an acetonide protecting group, and its orientation and position in the starting ester, determines the fate of the product formation as well as the diastereoselectivity of the intramolecularly reduced product. As an application, the diastereoselective synthesis of styryl lactones 7-*epi*-(+)-goniodiol (**29**) and 8-*epi*-(−)-goniodiol (**30**) was accomplished in a reduced number of steps. Also, the synthesis of 7-membered lactones can be achieved, exemplified by the preparation of lactone **34**. The exploration and investigation of the unusual Grignard reaction with a wide range of aliphatic and aromatic substrates demonstrates the potential scope of this protocol and its applicability for the total synthesis of structurally challenging natural products, which will be reported in future.[17]




Scheme 2 Diastereoselective synthesis of **29** and **30**.




Scheme 4 Synthesis of caprolactone **34**.

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17 As an application of this methodology, the enantioselective synthesis of venlafaxine is actively in progress and it will be reported in due course.

18 For further details of the computational method, please see the ESI file.†

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