Stereoselective insertion of cyclopropenes into Mg–Mg bonds†

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The reaction of cyclopropenes with compounds containing Mg–Mg bonds is reported. 1,2-Dimagnesiation occurs exclusively by syn-addition to the least hindered face of the alkene forming a single diastereomeric product. DFT calculations support a concerted and stereoselective mechanism. These findings shed new light on the stereochemistry of reactions involving magnesium reagents.

The direct functionalisation of alkenes is an essential component of modern organic chemistry. Since the pioneering contribution of Markovnikov,1 it has been clear that controlling the selectivity of this reaction is of vital importance. While the regioselectivity of alkene functionalisation can be determined by assignment of the reaction products, for simple linear alkenes the stereoselectivity (syn- vs. anti-addition) is often a hidden consideration. In this regard, cyclic alkenes − specifically cyclopropenes − offer an opportunity to study the stereochemistry of alkene functionalisation.

Protocols for the hydroelementation and carboelementation of cyclopropenes have been reported. For example, a number of selective catalytic methods for the hydroboration,2,3 hydrostannation,4 and hydrosilylation5 of cyclopropenes have emerged in the recent years. Similarly, selective catalytic carbozincation6,7 and carbomagnesiation8 reactions of cyclopropenes have been achieved. These reactions typically employ organozinc or organomagnesium compounds in combination with a transition metal catalyst. In almost all cases, exclusive syn-addition to the cyclopropene occurs to give a single diastereomer, suggestive of a concerted and stereospecific transition state for carbometallation. Direct isolation and structural characterisation of the organometallic intermediates in these reactions is, however, uncommon; they are usually subjected to subsequent synthetic transformations without isolation.

Very recently the scope of main group reagents that can be used to functionalise alkenes has been expanded to compounds that contain reactive Mg–Mg bonds.9–11 Both Jones and coworkers12–14 and our group15 have demonstrated the 1,2-dimagnesiation of alkenes. In specific cases the reaction has been shown to be reversible. Despite the importance of these findings, the stereochemistry of addition remains unknown. In this paper, we report the 1,2-dimagnesiation of cyclopropenes. For the cases investigated, the reaction is stereoselective and occurs by syn-addition to the least hindered face of the cyclopropene. DFT calculations support a concerted reaction mechanism. We also investigate the stereointegrity of the resulting organomagnesium compounds. Despite the known propensity of stereocentres adjacent to Mg to undergo epimerisation,16–26 the syn-addition products are stable up to 60 °C.

Reaction of 1a with cyclopropene 2a, at 25 °C in C6D6 led to the rapid formation of the 1,2-dimagnesio cyclopentyl complex 3a. Similar reactivity was observed between 1a and 2b (15 min at 25 °C) or 2c (4 h at 60 °C), leading to the corresponding species 3b and 3c. The slowest reaction occurs with the most sterically hindered substrate. In all cases, the selective syn-insertion of the alkene into the Mg–Mg bond was observed. For 2a and 2b, attack of 1a occurs on the least hindered face of the ring system leading to the formation of a single diastereomer of the product (Scheme 1).

Isolation and characterisation of 3a-c was possible by further reaction with either DMAP or THF to form 3a(DMAP)2, 3b(THF)2, and 3c(THF)2. NMR spectroscopic data are consistent with symmetric structures. The most salient NMR data are the 1H and 13C signals observed for methine position directly linked to the Mg centre, which are observed in the following ranges: δH = –0.19 to –0.70 ppm and δC = 33.1 to 35.1 ppm. The structure of 3a(DMAP)2 was confirmed by X-ray diffraction analysis (Fig. 1a). The extremely long Mg–Mg separation...

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† Electronic supplementary information (ESI) available: Experimental procedures, details of calculations and characterization data (PDF). Coordinates for DFT calculations (xyz). Crystallographic data for 3a(DMAP)2, and 4c(DMAP)2 ( cif). CCDC 2173920 and 2173921. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2cc02931f

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The Mg–C bonds of 2.02(1) and 2.20(1) Å are in the normal range for magnesium alkyls. Additional support for the proposed structure being retained in solution was obtained through in situ generation of an asymmetric analogue of 3a (with different ligands on each Mg centre). In this case, the two protons of the cyclopropane moiety become inequivalent. Analysis of the 1H NMR spectrum of the crude reaction mixture indicates a mutual JHH = 13.6 Hz coupling for the cyclopropane protons which is consistent with known literature values for syn-stereochemistry.27

Addition of 2a-c (2 equiv.) to 1b, a less sterically hindered analogue of 1a, also proceeded extremely rapidly at 25 °C in C6D6 solution to form a single diastereomeric product. In these cases, however, a double insertion reaction occurred, forming 4a-c (Scheme 2). This reaction likely proceeds by two sequential steps: (i) a syn-selective insertion of the cyclopropane into the Mg–Mg bond of 1b and (ii) a syn-selective carbomagnesiation of a second equivalent of cyclopropane from the intermediate 1,2-dimagnesiocyclopropyl complex. This type of reactivity has already been reported by Jones and co-workers for reaction of 1b with ethylene in the presence of an N-heterocyclic carbene ligand.14 In the case of 2c, an intermediate 3d could be spectroscopically observed. Addition of a further equiv. of cyclopropane to this intermediate led to 4c.

The isolation of 4a-c was again achieved by reaction with DMAP. 4a-c (DMAP)2 were isolated as yellow powders by precipitation in n-hexane in 50–75% yield. Spectroscopic data are consistent with their formulation. For example, for 4c (DMAP)2, is characterised by two sets of doublets in the high field region of the 1H NMR spectrum at δ = 0.22 (2H, JHH = 10.5 Hz) and δ = 1.30 (2H, JHH = 10.5 Hz) ppm. The mutual coupling between these resonances was confirmed by a COSY NMR experiment. Clear evidence for the syn-selective double insertion is also evident from single-crystal X-ray diffraction of 4c (DMAP)2 (Fig. 1b).

To gain a deeper understanding of the stereochemistry a series of plausible mechanisms were investigated by DFT calculations using the B3PW91 functional.28 Prior DFT studies have modelled the addition of ethylene to a derivative of 1b, but stereochemistry was not a consideration in this case.14 The reaction of 1b with cyclopropane 2a is calculated to proceed by an initial formation of a weak van der Waals complex Int-1 followed by a stereoselective syn-addition transition state TS-1 that connects directly to the product Int-2 (Fig. 2). Int-2 (R1 = Me, R2 = Ph) is a direct analogue of the spectroscopically observed intermediate 3d (R1 = R2 = Ph). This reaction is predicted to be exergonic by ΔG‡ (298 K) = −29.0 kcal mol⁻¹ with a readily accessible activation barrier of ΔG‡ (298 K) = 5.7 kcal mol⁻¹. An alternative syn-addition pathway in which 1b approaches the more hindered face of 2a was calculated to proceed by a slightly higher energy transition state TS-2 (ΔG‡ (298 K) = 9.3 kcal mol⁻¹). The concerted anti-addition pathway, while leading to the most thermodynamically stable product, ΔG‡ (298 K) = −34.2 kcal mol⁻¹, is prohibitively high in energy requiring distortion of the reactants into a twisted geometry in TS-3 (ΔG‡ (298 K) = 30.7 kcal mol⁻¹). Hence, the calculations are consistent with the experiments and predict that the reaction of 1b with 2a should be under kinetic control and highly stereo-selective at room temperature (ΔΔG‡ (298 K) = 3.6 kcal mol⁻¹).

Comparison of TS-1, TS-2, and TS-3 explains the origin of syn-selectivity. TS-1 is a four-membered transition state, and its structure determines the syn-addition to the least hindered face of the alkene. The geometry of TS-1 is asymmetric with one short Mg1–C1 (2.48 Å) and one long Mg2–C2 (3.08 Å) bond. TS-2
is similar. NBO calculations are also consistent with asynchronous bond formation occurring in TS-1, as evidenced by analysis of the NPA charges, which develop asymmetrically for both pairs of magnesium and carbon atoms (Fig. 3). The data indicate that the Mg\textsubscript{1}–C\textsubscript{1} bond is formed earlier than the Mg\textsubscript{2}–C\textsubscript{2} bond. In contrast, TS-3 is more symmetric, with almost no difference in two Mg–C bond distances (2.62 Å and 2.67 Å). This closer approach of the Mg–Mg reagent, combined with the required antarafacial bond formation to the \(\pi\)-system strongly disfavour the anti-addition by TS-3.

Further comparison of TS-1 and TS-2 can be used to rationalise the facial selectivity. QTAIM calculations combined with non-covalent interaction (NCI) analysis for reveals that TS-1 is stabilised by a greater number of (\(\pi\)-H–C) non-covalent interactions than TS-2 (Fig. 4). While we have not quantified these, it is likely a balance between these attractive dispersion interactions,\textsuperscript{29} and steric repulsion that favours addition to the face with the methyl substituent. The DFT model was expanded to consider chemoselectivity (see Fig. S30, ESI\textsuperscript{†}). To simplify the possible reaction outcomes the substrate was modified to avoid the complication of facial selectivity. Calculations suggest that the syn-addition of two equiv. of the diphenyl substituted cyclopropene \(2c\) to \(1b\) to form the double insertion product \(4c\) is energetically feasible. The first insertion occurs with a barrier of \(\Delta G^\ddagger\text{(298 K)} = 6.6\) kcal mol\(^{-1}\), the second with a barrier of \(\Delta G^\ddagger\text{(298 K)} = 15.8\) kcal mol\(^{-1}\), the overall reaction is exergonic by \(\Delta G\text{1(298 K)} = -80.5\) kcal mol\(^{-1}\). Hence, while the barrier to the second syn-insertion is higher than the first, both

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**Scheme 2** Sequential 1,2-dimagnesiation and carbometallation of cyclopropenes.

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**Fig. 2** (a) Free energy profile for mechanism of the first insertion. (b) Geometries of first insertion transition states TS1-Me, TS1-Ph and TS1-anti. Computed at the PCM (benzene)/B3PW91-D3(BJ)/def2-TZVP//B3PW91/SDDAll-6-31G(d,p) level.
measured as 11 h at –100 °C. The nitrile-substituted cyclopropyl magnesium reagent has been found, for example, the half-life of racemisation of an enantiopure methyl magnesium reagent is 120 h at 25 °C and then 120 h at 60 °C. Further studies showed that 1Alkyl magnesium reagents bearing cyclopropyl groups are expected to be the most stable derivatives, due to the low p-character of the alkene. 11 12 13 Dange, A. R. Gair, D. D. L. Jones, M. Juckel, S. Aldridge and C. Jones, Nat. Rev. Chem. 2017, 1, 0059.

In summary, we have developed an experimental and computational understanding of the stereochemistry of 1,2-dimagnesiation of cyclopropenes. Key to this understanding is the realisation that the reaction occurs by a concerted syn-addition transition state in which the Mg–Mg bond adds across the most sterically accessible face of the alkene. These findings may have broad implications for the design of stereoselectivity reactions involving the addition of magnesium reagents to unsaturated carbon–carbon and carbon–heteroatom bonds.

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**Conflicts of interest**

There are no conflicts to declare.

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