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C–O cleavage via In^{III} alkoxide intermediates: In situ ^{13}C NMR analysis of the mechanism of an enantioselective in-mediated cyclopropanation reaction

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ABSTRACT

The mechanism of asymmetric cyclopropanation of dibenzylideneacetone and benzylideneacetone by in situ generated allyl indium reagents in the presence of methyl mandelate as a chiral modifier has been studied by in situ $^{13}C\{^1H\}$ NMR in conjunction with $^{13}C/^2H$ labelling and mass spectrometry. Two indium alkoxides were identified, the first arising from indium mediated allylation of the ketone, the second arising from reaction of an in situ liberated homoallylic via a LiI mediated reaction with excess allyl indium reagent. On acidification, protonation at oxygen induces C–O rather than In–O cleavage and the incipient tertiary allylic cation is stereoselectivly allylated with approximately 90% *si* selectivity, via what is assumed to be a mandelate-chelated indium allyl reagent.

1. Introduction

Pioneering work by Butsugan and co-workers [1] around three decades ago, led to allyl indium reagents ($\mathbf{1_X}$), prepared in situ from allyl halides (allyl-X) and In metal [2], becoming popular reagents for organic synthesis [3,4]. Although a rather ill-defined mixture of species ($\mathbf{1_X}$) is generated, comprising In^I and In^{III} μ-halide-bridged dimers and aggregates [3], the reagents effect a range of mild and chemoselective allylation processes. For example, they undergo highly [1,2]-selective addition to α,β-unsaturated ketones (**2**), affording the corresponding allylic alcohols (**3**) in good yield after acid work-up (aq. HCl) [1]. In 1998 we reported that if enone **2a** (R = β-styryl, Scheme 1) is added to an excess of $\mathbf{1_{Br}}$, and the work-up modified by addition of LiBr then aq. HCl, then instead of alcohol **3a** being isolated, the reaction affords homoallyl vinylcyclopropane **4a** [5]. In other words there is an overall deoxygenative addition of two allyl units to the enone **2a** to generate a cyclopropane [6,7]. By screening a range of simple enantiopure chiral additives, we identified methyl mandelate (**5**(H)), readily available in both *R* and *S* forms, to be an effective modifier for the process [8]. After optimisation of the conditions, enone **2a** could be converted into cyclopropane **4a** with up to 94/6 *er*. Three factors were found to be essential for efficient and selective cyclopropanation of **2a**: i) generation of the allyl indium mixture ($\mathbf{1_I}$) from allyl iodide, ii) use of ≥2 equiv. of **5**(H), and iii) addition of LiI prior to the aqueous HCl work-up. By coupling the homoallyl vinylcyclopropanation with Ru-catalysed ring closing metathesis [9], the methodology provided an enantioenriched bicyclo[4.1.0]hept-2-ene (**6a**) from a simple enone subtrate [8].

For further development of this intriguing asymmetric reaction (**2a**→**4a**), mechanistic insight is pivotal. However, many aspects of the process were unclear, including i) the sequence of generation of bonds *A*, *B* and *C* (Scheme 1), ii) the roles of the modifier **5**(H), the LiI, and the acid, and the requirement for their addition in the specified order, and iii) why two equivalents [10], of **5**(H) and an excess of $\mathbf{1_x}$ are required. Herein we report on a $^{13}C/^2H$-labelling/in situ ^{13}C NMR/MS study that allows rationalisation of these prior observations [8], and reveals that homoallylic alcohols (**3**) are key reaction intermediates. This in turn allows us to elucidate the stereochemistry attending generation of bonds *B* and *C*; a process in which modifier **5**(H) is shown to act intermolecularly. These insights will be of utility for design of new In^{III}-mediated, C-X bond-

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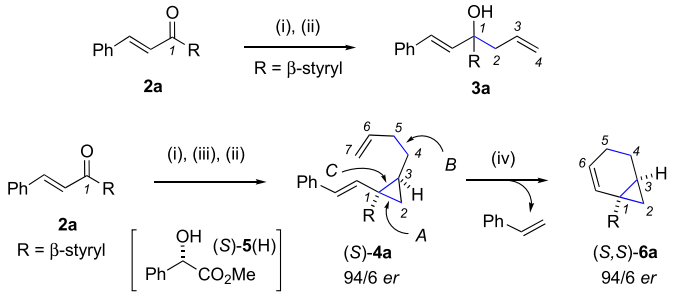


Scheme 1. Preparation of bicyclo[4.1.0]hept-2-ene (*S,S*)-**6a** via asymmetric indium-mediated homoallyl cyclopropanation (**2a**→(*S*)-**4a**; R = β-styryl) then ring-closing metathesis [8]. Conditions: (i) In (4 equiv.), allyl iodide (6 equiv), (*S*)-**5**(H) (2.0 equiv), THF, RT; ii) Et_2O, 1 M HCl, RT; iii) LiI (1 equiv.), 40 min, RT; (iv) 5 mol % $RuCl_2(PCy_3)_2$]CHPh, CH_2Cl_2, RT. Overall yield 44%.

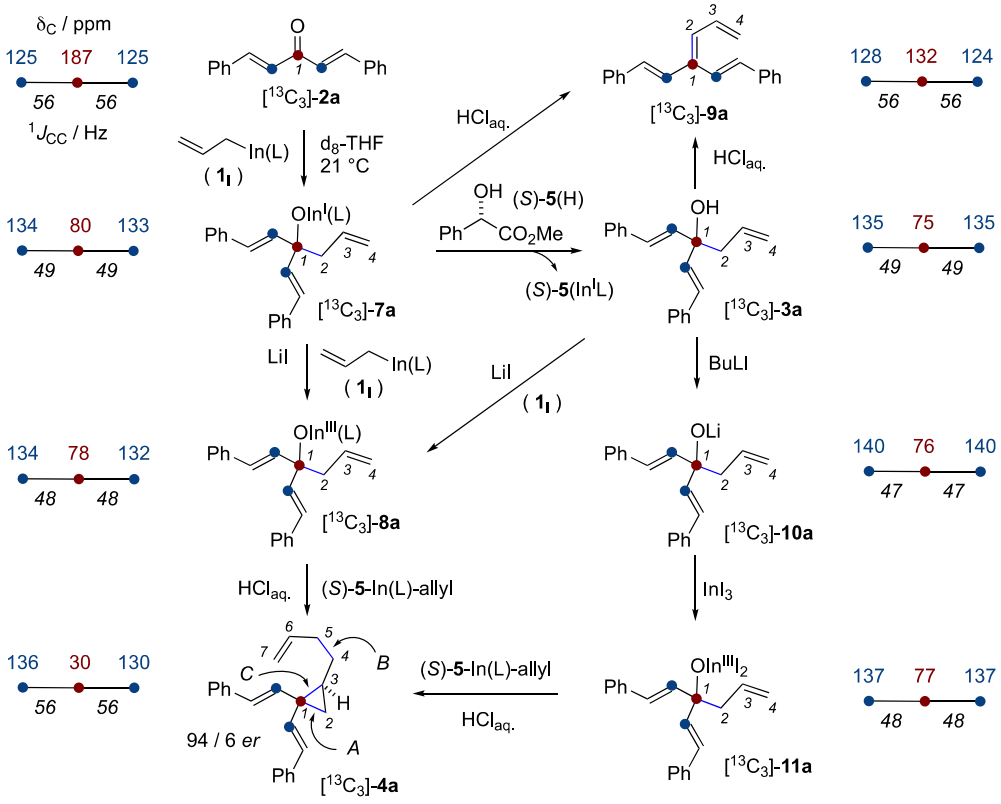
cleaving, and C—C bond-forming reactions.

2. Results and discussion

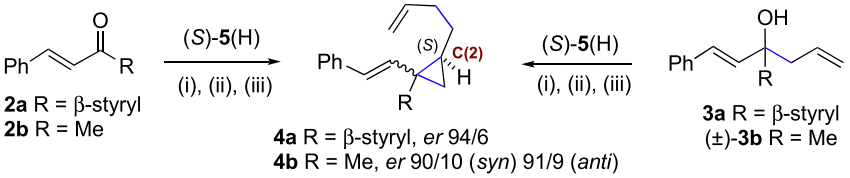
In situ ^{1}H NMR spectroscopic analysis of the mechanism of the cyclopropanation reaction (**2a**→**4a**) was not productive, due to very broad and uninformative signals arising from the dynamic aggregation of indium intermediates. We thus switched to $^{13}C\{^1H\}$ NMR spectroscopy and employed triply-^{13}C-labelled enone [$^{13}C_3$]-**2a**, readily prepared from commercially-available [$^{13}C_3$]-acetone, to allow selective analysis of the enone-derived component throughout the reaction. Using this technique we were able to unambiguously track the carbonyl carbon, C(1), in **2a** as a triplet, that migrates a remarkable 157 ppm upfield on conversion of **2a** to **4a**, Scheme 2. The three contiguous ^{13}C labels also provide information regarding changes in hybridisation and electronegativity of the substituents at C(1) (via modulation of $^1J_{CC}$) [11], as well as identifying intermediates in which coordination to indium induces the two ^{13}C-labelled carbons adjacent to C(1) to become diastereoisotopic.

$^{13}C\{^1H\}$ NMR spectroscopic analysis (see SI) of a D_8-THF solution of allyl indium reagent $\mathbf{1_I}$, immediately after addition of enone $^{13}C_3$-**2a** (C(1), *t*, 187 ppm, $^1J_{CC}$ = 56 Hz) directly to the NMR tube under N_2, the showed that enone **2a** is completely converted to a new species (C(1), *t*, 80 ppm, $^1J_{CC}$ = 49 Hz) in which C(1) is sp^3 hybridised and bound to an electronegative atom, i.e. oxygen. This first intermediate ($^{13}C_3$-**7a**) is thus assigned as an indium alkoxide, arising from a standard In-mediated [1,2]-allylation [1] of the enone [12]. Addition of LiI to indium alkoxide $^{13}C_3$-**7a** led to a second indium alkoxide intermediate $^{13}C_3$-**8a** (C(1), *t*, 78 ppm, $^1J_{CC}$ = 48 Hz). In both $^{13}C_3$-**7a** and $^{13}C_3$-**8a**, the carbons adjacent to C(1) are inequivalent ($\Delta\delta_C$ = 1 and 2 ppm, respectively), indicative of diastereotopicity at these sites, induced by the other ligands (allyl, I, THF) present on indium [13]. On addition of 1 M HCl (aq), intermediate $^{13}C_3$-**8a** immediately generated the cyclopropane $^{13}C_3$-**4a** (C(1), *t*, 30 ppm, $^1J_{CC}$ = 56 Hz), by acid-mediated reaction with the excess indium allyl reagent $\mathbf{1_I}$.

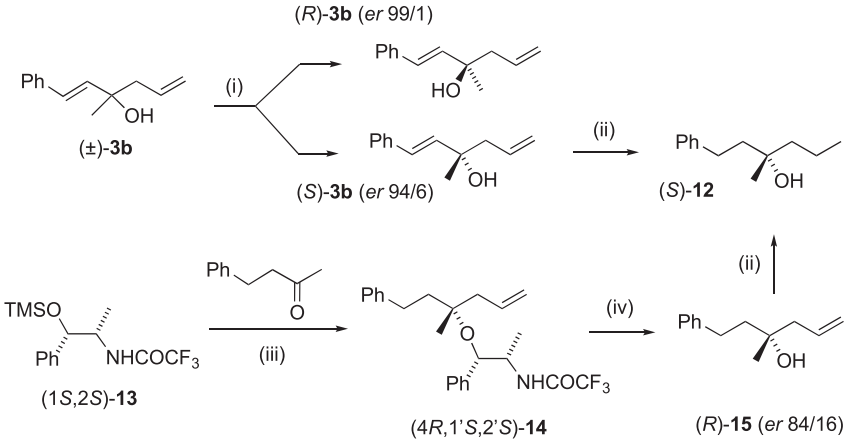
$^{13}C\{^1H\}$ NMR spectroscopic analysis of the same sequence, but conducted in the presence of modifier (*S*)-**5**(H) revealed that a different species ($^{13}C_3$-**3a**) is generated immediately after addition of the allyl indium reagent $\mathbf{1_I}$. In this new species, C(1) is 5 ppm upfield (*t*, 75 ppm, $^1J_{CC}$ = 49 Hz) of indium alkoxide $^{13}C_3$-**7a** and the adjacent carbons are not diastereotopic, suggesting that the oxygen at C(1) is not bound to indium. In a subsequent step, that was markedly accelerated by the LiI, $^{13}C_3$-**3a** reacted with excess allyl



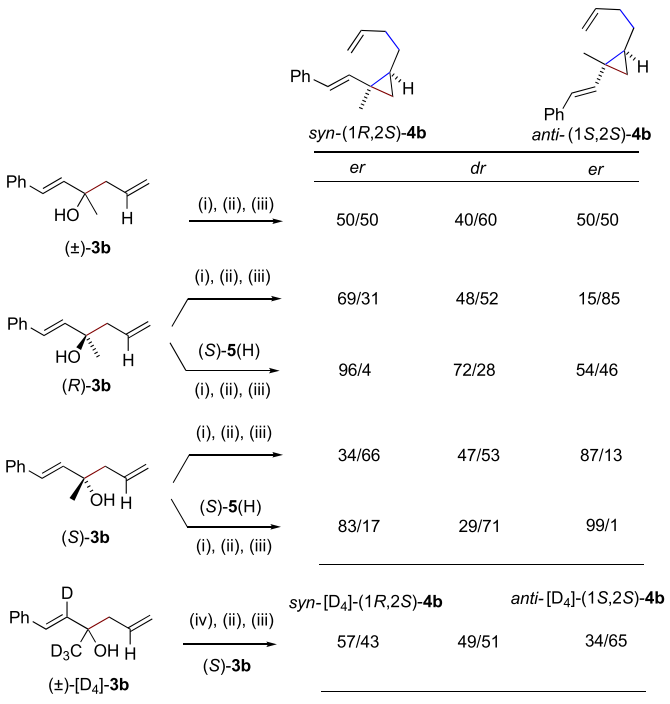
Scheme 2. In situ $^{13}C\{^1H\}$ NMR spectroscopic study of the reaction of dienone [$^{13}C_3$]- **2a** with allyl indium species ($\mathbf{1_I}$) to generate cyclopropane **4a** and tetraene **9a**, with addition of two equivalents of enantiopure methyl mandelate (*S*)-**5**(H) as a chiral modifier. The allyl indium reagent, $\mathbf{1_I}$, is generated in situ from In (4 equiv.) + allyl iodide (6 equiv) and is a mixture of In^I/In^{III} species; L = unspecified ligands: iodide/μ-iodide, allyl, alkoxide, solvent (D_8-THF).



Scheme 3. Comparison of the asymmetric cyclopropanation of enones **2a,b** and homoallylic alcohols **3a** and (±)-**3b**. Conditions (i) In (4 equiv.), allyl iodide (6 equiv), (*S*)-**5**(H) (2.0 equiv), THF, RT; ii) LiI (1 equiv.), 40 min, RT; iii) Et_2O, 1 M HCl, RT.



Scheme 4. Resolution of (±)-**3b** and assignment of configurations by convergent synthesis. The *relative* configuration of intermediate **14** established by X-ray crystallography [17]. Conditions: (i) preparative chiral HPLC, Chiralcel OD; (ii); **3b**/**15**, EtOH, Pd/C, H_2; 85% yield. (iii) allyl-TMS, DCM, −78 °C, TfOH, 48h, then NEt_3; 50% yield; (iv) **14**, THF, −78 °C, NH_3, N_2, Na (2.5 equiv.); then MeOH; 94% yield.



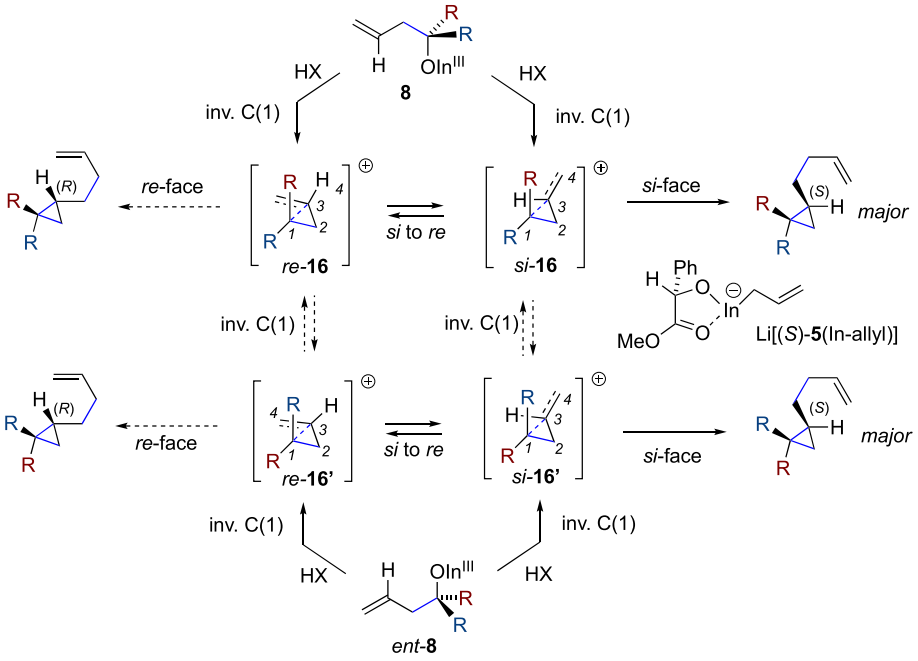
Scheme 5. Match/mismatch selectivity with the modifier (*S*)-**5**(H) in the cyclopropanation of homoallylic alcohol **3a** and chiral modifier effect of (*S*)-(−)-**3b** on the reaction of (±)-$^2H_4$-**3b**. Conditions (i) In (4 equiv.), allyl iodide (6 equiv), THF, RT with (*S*)-**5**(H) (2.0 equiv) *if indicated*; ii) LiI (1 equiv.), 40 min, RT; iii) Et_2O, 1 M HCl, RT.; iv) In (8 equiv.), allyl iodide (12 equiv), (*S*)-(−)-**3b** (1 equiv.) THF, RT, with selective analysis of $^2H_4$-**4b** in presence of **4b** by chiral-HPLC MS.

indium reagent **1** to generate the *same* alkoxide ($^{13}C_3$-**8a**) as is observed in the absence of modifier (*S*)-**5**(H), after reaction with LiI/**1**$_\mathbf{I}$. On addition of HCl (1 M), cyclopropane (*S*)−$^{13}C_3$-**4a** was again immediately generated, and chiral HPLC analysis showed it to be of 94/6 *er*. The intermediate species $^{13}C_3$-**3a**, was subsequently identified as the homoallylic alcohol. This arises from rapid protonation of the incipient and unobserved indium alkoxide ($^{13}C_3$-**7a**) by the alcohol moiety of the modifier (*S*)-**5**(H). Addition of (*S*)-**5**(H) to an in-situ generated sample of indium alkoxide $^{13}C_3$-**7a** confirmed that protonation to generate alcohol **3a** is rapid, and thus the equilibrium between the alkoxides ($^{13}C_3$-**7a** and (*S*)-**5**-In) strongly favours the latter, presumably due to chelation of indium by the α-carbonyl. Both the OH and the ester were previously found to be essential components for selectivity using modifier (*S*)-**5**(H) [8].

$^{13}C\{^1H\}$ NMR spectroscopic analysis of the reaction of independently prepared alcohol $^{13}C_3$-**2a** with LiI/**1**$_\mathbf{I}$ confirmed that this also generates indium alkoxide $^{13}C_3$-**8a** (1 h at 60 °C) and then racemic cyclopropane (±)-$^{13}C_3$-**4a**, on addition of 1 M HCl. The same reaction conducted with stoichiometric modifier (*S*)-**5**(H) gave (*S*)−$^{13}C_3$-**4a** in 93/7 *er*, together with a trace of a tetraene, $^{13}C_3$-**9a**. Acidification before conversion of the alcohol $^3C_3$-**3a** to indium alkoxide $^3C_3$-**8a**, resulted solely in elimination to generate the tetraene $^{13}C_3$-**9a** and no cyclopropane $^{13}C_3$-**4a**; confirming that it is the indium alkoxide **8a**, not the alcohol **3a**, that is the active intermediate for cyclopropane generation.

The above experiments establish that the first stage in the overall cyclopropanation process is generation of bond *A* (Scheme 1), through a conventional indium-mediated [1,1,2]-allylation of the enone (**2a**). Indium(I)-allyl species are generally accepted as being the most active for carbonyl allylation [3,14], implying that intermediate **7a** is an indium(I) alkoxide, as well as the modifier-derived alkoxide (*S*)-**5**(In^I).

Both the indium (I) alkoxide **7a** and alcohol **3a** undergo LiI-accelerated reaction with allyl indium reagents **1**$_\mathbf{I}$ to generate an



Scheme 6. Generic scheme to account for the stereochemical outcomes on indium mediated homoallyl-cyclopropanation of **1 ab** and **3 ab**, proceeding via indium(III) alkoxide **8 ab**, via intermolecular allyation by (*S*)-**5**-modified indium allyl reagent.

intermediate (**8a**) that, based on $^{13}C\{^1H\}$ NMR is structurally similar to **7a**, but shows profoundly different behaviour on acidification: indium alkoxide **8a** gives cyclopropane **4a**, whereas indium alkoxide **7a** gives tetraene **9a**, presumably via alcohol **3a** [12]. The difference can be ascribed to In(I) versus In(III) oxidation state in the alkoxide, in which the greater oxophilicity of In(III) results in fission of the C—O rather than O—In bond upon protonation at oxygen. This conclusion is supported by the observation that sequential reaction of homoallylic alcohol **3a** with *n*-BuLi (1.0 equiv.); InI_3, (1.0 equiv.); allyl indium reagent $\mathbf{1_I}$; modifier (*S*)-**5**(H), and then acidification (1 M HCl) efficiently generated cyclopropane **4a** (80%, 93/7 *er*), whereas the analogous process with InI gave mostly tetraene **9a**, and ≤15% **4a** [15]. $^{13}C\{^1H\}$ NMR spectroscopic analysis of the same sequence, but using alcohol $^{13}C_3$-**3a**, confirmed that the stable [16] lithium alkoxide $^{13}C_3$-**10a** (C(1), *t*, 76 ppm, $^1J_{CC}$ = 47 Hz) reacted cleanly with the InI_3 to generate an In^{III} alkoxide $^{13}C_3$-**11a** (C(1), *t*, 77 ppm, $^1J_{CC}$ = 48 Hz) in which the adjacent carbons were equivalent, consistent with solely iodide ligands (L = I) at indium. Overall this suggests that the function of the LiI in the reaction is to accelerate $In^I \rightarrow In^{III}$ exchange of the alkoxide (**7a**) with the allylating reagent ($\mathbf{1_I}$) or other indium species generated in situ, so that the key C—O—In(III) intermediate (**8a**) is generated. An alternative interpretation is that LiI changes the aggregation state [17] of **7a** versus **8a**. However the ^{13}C NMR chemical shift for C(1) in series **3a** (ROH, 75 ppm); **10a** (ROLi, 76 ppm); **11a** ($ROIn^{III}$, 77 ppm); **8a** (ROIn(L), 78 ppm); and **7a** (ROIn(L′), 80 ppm) suggests a progressive decrease in covalency at oxygen, with the difference between **7a** and **8a** ($\Delta\delta_C$ = 2 ppm) larger than expected for a change in aggregation state. Moreover, in situ ^1H NMR analysis (see SI) of the chemical shifts[1bc,3c] of the methylene unit in the mixture of allylindium reagents remaining after generation of **7a** from **2a** indicate they are predominantly of the form $[(allyl)_{3\text{-}n}In^{III}I_n]_m$ (*n*,*m* = 1,2; δ_H CH_2—In = 2.12 and 2.06 ppm, d, $^3J_{HH}$ = 8 Hz).[1bc] After addition of LiI and conversion of **7a** to **8a**, the allylindium reagents are predominantly of the form allyl-In^I (δ_H CH_2—In = 1.71 ppm, d, $^3J_{HH}$ = 8 Hz).[3bc,14].

Enone **2b**, and the corresponding homoallylic alcohol **3b**, also underwent enantioselective cyclopropanation using (*S*)—**5**H (see Scheme 2). Although **4b** is generated as a mixture of *syn*/*anti* diastereomers, there is a similar level of stereocontrol at C(2) (*ca.* 90:10) to that in **4a** generated from **2a**/**3a**, Scheme 3, suggesting that the same prochiral face of the homoallyl unit reacts with C(1) on generation of bond C. On this basis, the C(2) stereocentres in *syn*/*anti* **4b** are assigned by analogy to (*S*)-**4a**; the latter having previously been definitively assigned via a convergent asymmetric synthesis from hex-1-ene [7].

The stereochemistry at C(1) during the pathway(s) leading to generation of bond B was probed by cyclopropanation of the enantiomers of **3b**, resolved from (±)-**3b** by preparative chiral HPLC. The configurations of (*R*)-**3b** and (*S*)-**3b** were assigned by convergent synthesis involving alcohols (*S*)-**12** and (*R*)-**15**, Scheme 4. The diastereoselective allylation procedure of Tietze [18] employing pseudoephedrine-derived reagent **13**, was used to prepare (*R*)-**15**, via intermediate **14**, for which the relative configurations have been unambiguously established by X-ray crystallography [18].

Cyclopropanation of alcohol **3b** under the conditions of Scheme 3, results in *syn*/*anti* selectivity that depends on match/mismatch with the modifier (*S*)-**5**(H), Scheme 5. For example, reaction of (*R*)-**3b** with $\mathbf{1_I}$/(*S*)-**5**(H) gave 72% *syn*-1*R*,2*S*-**4b** (96/4 *er*) whereas the enantiomer (*S*)-**3b** gave 71% *anti*-1*S*,2*S*-**4b** (99/1 *er*). Moreover, cyclopropanation of (*S*)-**3b** and (*R*)-**3b**, in the *absence* of modifier (*S*)-**5**(H), gave **4b** in non-racemic form, with the C—C unit being predominantly formed via inversion at C(1), ruling out fully-developed carbocation intermediates [19,20]. Curiously, the reaction of (±)-**3b** in the absence of modifier (*S*)-**5**(H) gave a different ratio of diastereomers (40/60 syn/anti) to the net product from individual reactions of (*S*)-**3b** and (*R*)-**3b** (48.5/52.5). This suggested that alcohol **3b** acts as a chiral modifier for its own cyclopropanation reaction. This was tested by co-reaction of (*S*)-**3b** with racemic (±)-$^2H_4$-**3b**, in the absence of modifier (**5**(H)). MS analysis of the isotope distribution in each of the four stereoisomers after physical separation by iterative analytical chiral HPLC confirmed that cyclopropanation product $^2H_4$-**4b** is indeed generated in non-racemic form due to the presence of co-reacting (*S*)-**3b**.

Despite extensive efforts, we were not able to isolate or identify the reagent generated from $\mathbf{1_I}$ and **5**(H) (see Scheme 5). Reactions with analogous modifiers in which the α-hydroxy group is protected −e.g. (*S*)-**5**(Ac) and (*S*)-**5**(Me) give no enantioselectivity (50/50 *er*) [7], suggesting that the allylindium is chelated [21], e.g. as an indate, Li[**5**((*S*)−In-allyl)]. The consistent level of stereoselectivity (approximately 90/10 *er*) induced by (*S*)-**5**(H) and the identical ^{13}C chemical shifts for all intermediates generated from **4a** in the presence/absence of **5**(H), suggest that the allyl is delivered intermolecularly by an alkoxide-modified allyl indium reagent to a carbocationoid (**16**); a generic scheme that accounts for the stereochemical outcomes at C(1) and C(2) is shown in Scheme 6.

3. Conclusions

We have used in situ $^{13}C\{^1H\}$ NMR in conjunction with $^{13}C/^2H$ labelling and mass spectrometry to study the asymmetric homoallyl-cyclopropanation of enone **2a** (Scheme 1) using a mixture of in situ generated allylindium reagents ($\mathbf{1_I}$) and chiral modifier (*S*)-**5**(H) [7]. A key outcome is the identification of acid-labile In(I) alkoxide **7a** as a primary intermediate from In(I)-mediated allylation of the ketone **2a**. In the absence of the modifier **5**(H), the In(I) alkoxide **7a** undergoes LiI mediated In(I/III) exchange with excess reagent ($\mathbf{1_I}$), leading to the key In(III) alkoxide intermediate **8a**. In the presence of (*S*)-**5**(H), the In(I) alkoxide **7a** is rapidly protonated, leading to homoallylic alcohol **3a** and consuming 1 equivalent of the modifier, to generate (*S*)-**5**-In(L); where L are unspecified ligands. Alcohol **3a** also undergoes LiI mediated reaction with excess reagent ($\mathbf{1_I}$) to generate indium (III) alkoxide **8a**. On acidification of the solution of **8a**, protonation at oxygen induces C−O rather than In(III)−O cleavage [20]. This is undoubtedly assisted by stabilisation of the incipient tertiary allylic cation by the homoallyl chain to give a highly charge-delocalised system (**16**). Allylation of the homoallyl terminus in transient cation **16** by (*S*)-**5**(In-allyl) is stereoselective, proceeding with approximately 90% *si* selectivity, and presumably involving a mandelate-chelated indium reagent [21]. In the case of a cation derived from a chiral precursor (e.g. **3b**), racemization in the homoallyl-cation is slower than its trapping by the allylating species, leading to cyclopropane generation with substantial net inversion (76%) of the C−O bond. Overall the results suggest that In(III) reagents may provide considerable utility for the selective cleavage of other C−O or C-X units in the presence of nucleophilic reagents.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131786.

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[11] Typical ranges for one bond carbon−carbon coupling constants are: sp^2-sp^2 $^1J_{CC}$ 75−80 Hz, sp^2-sp^3 $^1J_{CC}$ 35−60 Hz, and sp^3-sp^3 $^1J_{CC}$ 25−55 Hz, see Hansen, P. E.; Wray, V. Org. Magn. Reson 15 (1981) 102−103.

[12] Careful Aqueous Work-Up of an Independent Identically Prepared Solution of **7a** Afforded the Corresponding Alcohol **3a**. Acidification of **3a** (HCl) Generates Tetraene **9a**.

[13] Diastereotopicity Can Be Induced by the Presence of a Stereocentre at the

Indium Bound to Oxygen in the Alkoxide, or to Presence of a Stereocentre at an Indium that Is μ-halide Bridge to the Indium Alkoxide.

[14] There Has Been Considerable Debate Regarding the Active Species in the Mixture of Reagents Generated - See Reference [3]. A Small Amount of Residual Indium Metal Present after Generation of ($\mathbf{1_I}$) Was Found to Improve Yields of the Cyclopropane Products (4). LiI May Possibly Induce Comproportionation with In(III), or Further Reaction with Excess Allyliodide.

[15] $InBr_3$ Functioned Equally as Well as InI_3; $\leq$ 3% **4a** Was Obtained with $InCl_3$.

[16] There was no anionic oxy-Cope rearrangement of the lithium alkoxide 13C3-10a at these temperatures, even when the analogous potassium alkoxide was generated using KH. The reaction requires heating to reflux - see: S.K. Mandal, Sk R. Amin, W.E. Crowe J. Am. Chem. Soc. 123 (2001) 6457–6458.

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