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Regioselectivity and Diastereoselectivity in the Indium-mediated Homoallyl-Cyclopropanation of Dibenzylidene Acetone (dba)

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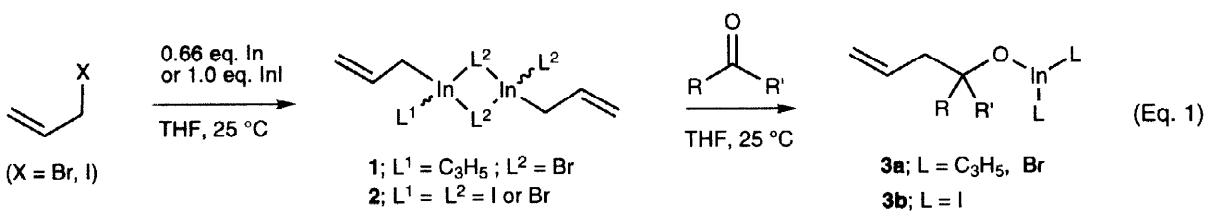
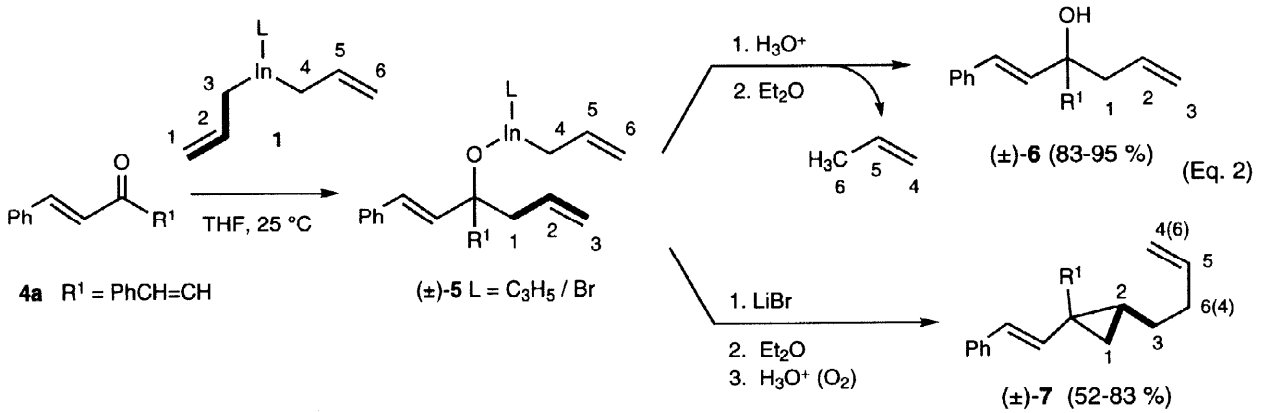
Abstract: Indium mediated reaction of dibenzylidene acetone (dba) with [$^2H_2$]-allyl bromide affords 1,1-distyryl-2-(but-3-enyl) cyclopropane **7** (a triene) as a mixture of four isotopomers. Whilst this reaction is not regiospecific, the analogous reaction employing crotyl bromide in place of allyl bromide is highly regioselective and somewhat selective for the *cis* cyclopropane isomer. When the reaction is performed with dimethylallyl bromide, cyclopropanation fails and tetraene products are obtained instead.

There is a rapidly increasing number of examples of the potential of organoindium reagents in organic synthesis.[1] In particular, allyl indium sesqui- (**1**) and di- (**2**) halides have been extensively developed as practical organometallic reagents. They are conveniently prepared[2] by reaction of In metal or InI with allylic bromides, iodides or phosphates and mediate highly efficient Barbier-type allylations[3] of ketones and aldehydes, often under aqueous conditions, to give homoallylic alcohols[4] *via* hydrolysis of **3** [Eq. (1)].



(Eq. 1)

Usefully, reagents **1** and **2** undergo clean [1,2] addition to α,β-unsaturated ketones **4** to afford allylic-homoallylic alcohols **6**[5] after hydrolysis of intermediate **5** [Eq. (2)]. We are currently engaged in the development of organoindium-mediated deoxygenative methodologies and as part of this program we recently reported that intermediate **5** can also be induced to afford **7** in good yield.[6]



(Eq. 2)

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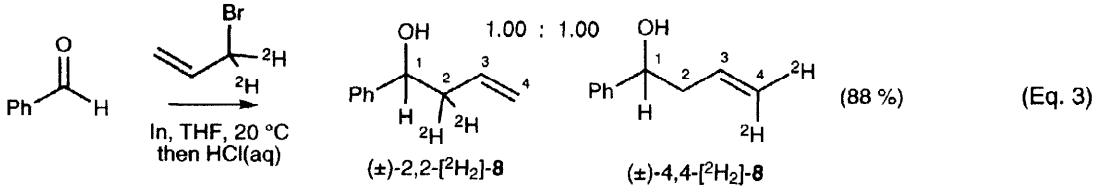
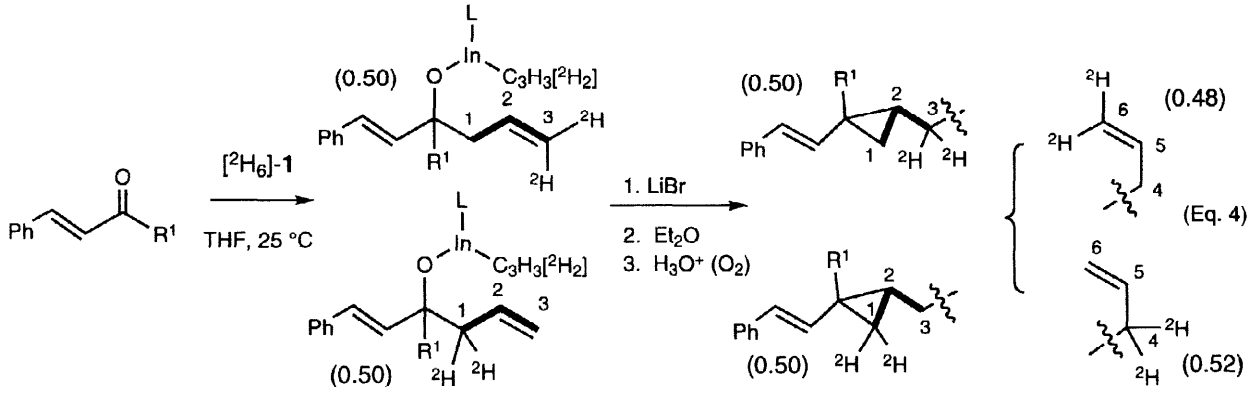
During our studies of this reaction, we employed ^2H labelled allyl bromide[7] to probe the regiochemistry of both the allylation and subsequent rearrangement. Reaction of a slight excess of 1,1-[$^2H_2$]-allyl bromide with In powder and with InI afforded ^2H-labelled allyl indium reagents [$^2H_6$]-**1** and [$^2H_4$]-**2** respectively. ^2H NMR spectroscopy clearly demonstrated that the ^2H label is completely and equally scrambled between C(1) and C(3) during the formation of both reagents.[8] Residual 1,1-[$^2H_2$]-allyl bromide was not scrambled. Addition of ca. 2 equiv. benzaldehyde to the THF solutions resulted in complete consumption of [$^2H_6$]-**1** and [$^2H_4$]-**2** within 1-2 minutes and, after addition of 1 M HCl, signals corresponding to a 1 : 1 mixture of 2,2-[$^2H_2$]- and 4,4-[$^2H_2$]-**8** were observed. Preparative In-mediated reaction of benzaldehyde with 1,1-[$^2H_2$]-allyl bromide afforded [$^2H_2$]-1-phenylbut-3-en-1-ol **8**. Analysis by ^1H, ^2H and $^{13}C\{^1H\}$ NMR indicated that **8** consisted of an equal distribution of the 2,2-[$^2H_2$]- and 4,4-[$^2H_2$]- isotopomers,[9] [Eq. (3)].



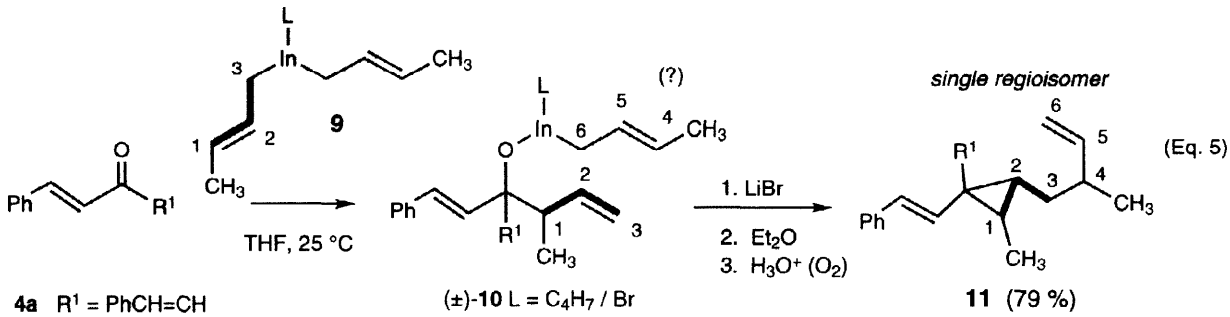
(Eq. 3)

We then studied the formation of cyclopropane [$^2H_4$]-**7**. Reaction of **4a** with [$^2H_6$]-**1** in THF at 25 °C, for 24 h followed by 1 equiv. LiBr and then aerobic work-up with Et_2O / 1M HCl(aq) afforded [$^2H_4$]-**7** (78 %) as a mixture of all four [$^2H_4$]-isotopomers. ^1H, ^2H and $^{13}C\{^1H\}$ NMR analysis of [$^2H_4$]-**7** indicated an equal distribution of [$^2H_2$] between C(1) and C(3) and thus no observed secondary kinetic isotope effect, [Eq. (4)]. This is consistent with the ^2H distribution observed in the allylation of benzaldehyde, [Eq. (2)], and supports the intermediacy of a species of type [$^2H_4$]-**5** as a 1.00 : 1.00 ratio of C(1)-[$^2H_2$] and C(3)-[$^2H_2$] isotopomers which arise *via* a "normal" In-mediated [1,2]-allylation of the carbonyl C=O of **4a**.



In stark contrast, the ^2H-distribution at C(4) and C(6) in [$^2H_4$]-**7** demonstrated a net secondary kinetic isotope effect of 1.09 (± 0.01) in favour of [$^2H_2$] at C(4) over C(6). Since the ^2H-distribution in the In-allyl group C(4,5,6) in [$^2H_4$]-**5** is likely to be very similar to that in the In-allyl groups of the reagent [$^2H_6$]-**1**, this suggests that the mechanism for the transfer of the second allyl unit to the methylene carbon of the cyclopropane is quite different in charge distribution and extent of rehybridisation during the transition state to that involved in the initial allylation step of the carbonyl.

Reaction of crotyl indium sesquibromide (**9**) with **4a** also proceeded smoothly to afford **11** - the product arising from transfer of two crotyl units [Eq. (5)]. The reaction was readily scaled up to afford multigram quantities of **11** (79 %). There are four possible regioisomers arising from the reaction, however, the DEPT ^{13}C NMR spectrum indicated that all terminal allyl carbons (C(6)) and all homoallylic carbons (C(3)) were $\underline{C}H_2$, with no evidence of $\underline{C}H(Me)$.



The reaction thus proceeds with excellent regio-selectivity (> 98 %) to yield **11** with the two CH_3 exclusively at C(1) and C(4). This regioselectivity further supports the intermediacy of **10** since the regioselectivity is consistent with that observed for the In-mediated crotylation of aldehydes and ketones where an *E*-crotyl-indium reagent is assumed to react *via* Zimmermann-Traxler type transition state. On rearrangement of **10** this regioselectivity places the CH_3 at C(1) rather than at the homoallylic (C(3)) position. Assuming that the preferred isomer of the In-crotyl unit in **10** is the same as in **9**, i.e. *E*-CH_3-CH=CH-CH_2-In, then the regioselective formation of **11** with a CH_3 at C(4) would suggest that the rearrangement of **11** proceeds *via* a closed, e.g. cyclic, transition state hence delivering the terminus (C(4)) of the crotyl unit in **10** to C(3).

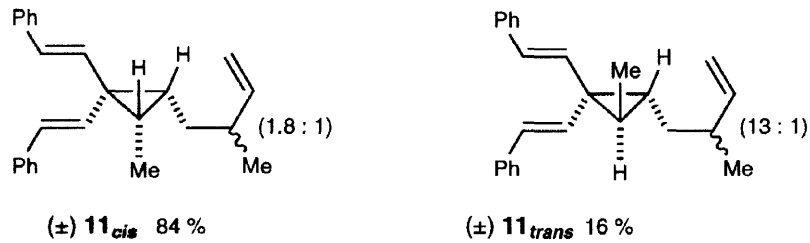
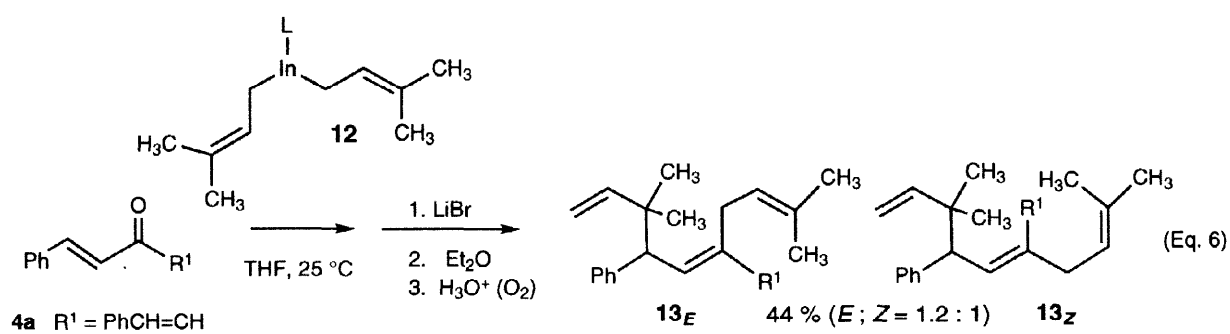


Figure 1. Diastereomer ratios of *cis* and *trans* **11** - assignments based on NOESY ($^1H,^1H$, 500 MHz) spectrum of mixture.

A mixture of all four diastereoisomers of **11** are observed. The relative geometry about the cyclopropane rings was determined by examination of the 500 MHz NOESY spectrum in d_6-acetone.[10] Promising selectivity (84 %) is observed for a *cis* arrangement of the substituents about the cyclopropyl ring (Fig 1). Moderate ($\mathbf{11}_{cis}$ 1.8 : 1) and high ($\mathbf{11}_{trans}$ 13 : 1) diastereoselectivity was also observed for the generation of the non-cyclopropane stereogenic centre on the pendant 2-(but-3-enyl) chains.[11]



When the steric hindrance of the allylation step was increased, cyclopropanation failed. Thus 3,3-dimethyl allyl indium sesquibromide **12** gave the terpene-like product **13** (44 %) solely as the "head-tail" isomer and as a 1.2 : 1.0 mixture of *E* : *Z* isomers according to n. O. e experiments, [(Eq. 6)]. Clearly intermediates analogous to **10** and **5** are too strained for the cyclopropane formation to occur. We currently cannot explain the regioselectivity of formation of **13**, but note that whilst all **4a** was consumed in the reaction, **13** is the sole hydrocarbon product (44 %).

In conclusion, ^{2}H-labelling demonstrates that the homoallyl-cyclopropanation of dba (**4a**) is not regiospecific. However, crotyl indium sesquibromide **9** displays promising selectivity: **11** is the sole regioisomer and there is 84 % selectivity for $\mathbf{11}_{cis}$. Synthetic and mechanistic studies are in train.

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6. H. A. F. Höppe, G. C. Lloyd-Jones, M. Murray, T. M. Peakman, K. E. Walsh, *Angew. Chem.* **1997**, submitted.
7. Labelled allyl bromide (CH_2=CH-C[$^2H_2$]Br) was prepared by modification of a published procedure (M. Solomon, W. Hoekstra, G. Zima, D. Liotta, *J. Org. Chem.* **1988**, *53*, 5058-5062): i. LiAl[$^2H_4$], acroyl chloride, Et_2O, 0 °C; ii. CBr_4, PPh_3, CH_2Cl_2, distil (bp 69-70°C). The ^{2}H incorporation in the 1,1-[$^2H_2$]-allyl bromide was >99%, and the regioselectivity of the bromination >90 % (^{1}H, ^{2}H and ^{13}C NMR).
8. Studies on the dynamic behaviour of allyl indium reagents in solution will be reported in due course: G. C. Lloyd-Jones, M. Murray, T. M. Peakman, T. Russell and K. E. Walsh, *manuscript in preparation.*
9. There is thus no *observable* secondary kinetic isotope effect (2°KIE) on the product distribution for this reaction. However, this could arise from two equal but opposite 2°KIE. For example, a 2°KIE of magnitude 1.1. in favour of an equilibrium distribution of 1,1,1',1'-[$^2H_4$]-**2** over 3,3,3',3'-[$^2H_4$]-**2** coexistent with a 2°KIE of 1.1 on the relative rates of reaction of 3,3,3',3'-[$^2H_4$]-**2** over 1,1,1',1'-[$^2H_4$]-**2** with PhCHO *via* a Zimmerman Traxler transition state would lead to an equimolar isotopomer distribution in [$^2H_2$]-**8**.
10. The use of d_6-acetone as NMR solvent proved crucial in obtaining sufficient resolution of diastereomers. In other deuterated solvents ($CDCl_3$, CD_2Cl_2, d_6-benzene, d_8-toluene, d_5-pyridine, d_3-acetonitrile, d_3-nitromethane and d_6-dmso) nearly all the peaks arising from all four diastereomers were coincident.
11. Due to free rotation of the 2-(but-3-enyl) chain in both $\mathbf{11}_{cis}$ and $\mathbf{11}_{trans}$ at the NMR timescale we have thus far been unable to determine relative configuration of these stereogenic centres. Full spectrocopic data and assignment of diastereoisomers by chemical derivatisation will be reported in full in due course.