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New indium-mediated cyclisation reactions of tethered haloenynes in aqueous solvent systems

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Dedicated with great respect to Professor Steven V. Ley on the occasion of his 60th birthday

Abstract—The intramolecular cyclisation of tethered allyl bromides onto terminal alkynes mediated by metallic indium proceeds smoothly and cleanly in mixtures of THF and H_2O to give unsaturated carbocycles and heterocycles in good yield. Alternatively, the cyclisation may be carried out in anhydrous THF with the aid of acid catalysis. The reaction is also mediated by a range of indium salts and proceeds with substoichiometric quantities of indium in the presence of a co-reductant. Deuteration studies show that the reaction proceeds via a concerted *syn* carboindination of the carbon–carbon triple bond to give an intermediate, which is protonated in situ.

1. Introduction

In recent years there has been a great deal of interest in the application of indium to organic synthesis.[1] Indium-mediated Barbier[2] and Reformatsky-type[3] reactivity of organoindium reagents derived from allylic and propargylic precursors with a wide range of C=O and C=NR derived functional groups[4] are well-documented, and the synthetic utility of these methods has been demonstrated in the synthesis of a number of pharmaceutical and natural products.[5] The addition reactions of allylic indium reagents to carbonyl-derived electrophiles proceed with high diasteroselectivity via predominantly γ-addition of the organometallic, although the ratio of α:γ-addition has been found to be dependent on solvent.[6] Additionally, indium-mediated methodology has also been extended to take in a wide range of transformations including Michael additions,[7] indium hydride[8] and dissolving metal reductions,[9] and Pd(0) catalysed cross-coupling reactions of organoindium reagents.[10] Additionally, indium reagents have been used to facilitate radical cyclisation[11] and atom transfer cyclisation reactions.[12]

In view of the obvious importance of indium-mediated reactions, it is therefore surprising that the reactions of organoindium reagents with carbon–carbon and carbo-heteroatom triple bonds have received comparatively little attention. In early work, Araki et al. reported the addition reactions of allylic indium sesquihalides with alkynols[13] and allenols[14] to give (*E*)-2,5-hexadien-1-ols and (*E*)-2,6-heptadien-1-ols, respectively. They showed that the addition of the organoindium reagent occurs regioselectively in the anti-Markovnikov mode, which it was proposed arose as a result of coordination of the intermediate organometallic species by the hydroxyl group, which directs addition to the terminal carbon of the alkyne. Subsequently the carboindination of unactivated terminal alkynes,[15] which do not bear an adjacent hydroxyl group, to give 1,4-dienes via Markovnikov addition and the carboindination of nitriles to give enamines[16] was reported. Thus, while the synthetic scope and mechanistic aspects of the intermolecular carboindination of alkynes and nitriles have received attention, the corresponding intramolecular carboindination of alkynes with allyl halides remains is much less well understood.

In the intramolecular reaction manifold, a number of potential reaction pathways may be considered. For example, it may be reasoned that exposure of tethered haloenynes **1** (X=O, NR, CR^1R^2) to indium metal would give the corresponding allylindium species **2a** which could exist in equilibrium with the *endo* isomer **2b**. Furthermore,

Keywords: Indium; Cyclisation; Aqueous; Enyne; Carbocycle; Heterocycle.
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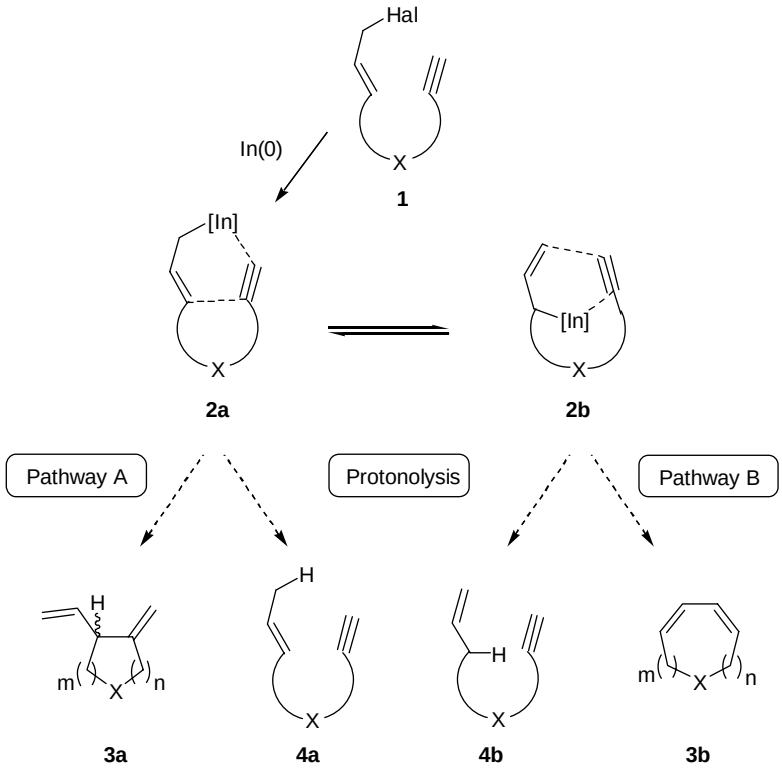
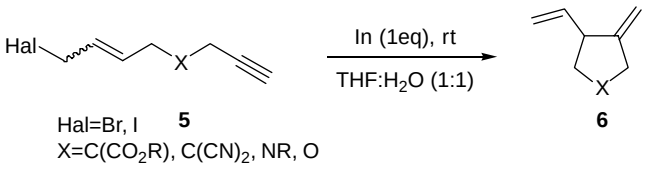


Scheme 1. Possible pathways for the reaction between indium and haloallylalkynes.

such intermediates could be expected to react by (i) a process of carboindation of the alkyne triple bond by either a Markovnikov (pathway A) or *anti*-Markovnikov (pathway B) route to give the corresponding *exo* 1,4-dienes **3a** or *endo* 1,3-dienes **3b**, respectively[17] or (ii) proteodebromination of the organometallic (for example, on workup) to give either the crotyl **4a** or allylic species **4b**. At the outset of our work, it was not clear whether the cyclisation reaction was possible or whether the pathway of proteodebromination would predominate (Scheme 1).

We herein report[18] that a broad range of bromooct-6-en-1-ynes **5** undergo smooth cyclisation at room temperature in the presence of indium metal via pathway A to give *exo*-1,4 carbocyclic and heterocyclic dienes **6** cleanly (Scheme 2). Whilst the cyclisation of enynes to five-membered carbocycles and heterocycles under the influence of a range of transition metals has been previously demonstrated[19] these procedures often necessitate the use of expensive catalysts and/or ligands, which are often moisture and air sensitive or must be prepared in situ immediately prior to use. In contrast, not only is the method discussed in the current submission robust, operationally simple and relatively inexpensive, in fact the efficiency of the reaction



Scheme 2. Indium-mediated cyclisation of tethered terminal haloallylalkynes.

is greatly enhanced by the addition of water to the reaction solvent.

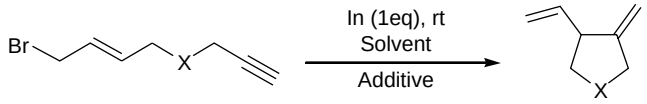
2. Results and discussion

2.1. Initial approaches to the indium-mediated cyclisation reaction

The first substrate chosen for investigation was the parent bromoenyne, (*E*)-1-bromobut-2-ene-4-ol propargyl ether **7a**, which may be readily synthesized from propargyl alcohol and *trans*-1,4-dibromobut-2-ene. In a typical procedure **7a** and indium powder (1 equiv) were suspended in the appropriate solvent and stirred at room temperature or reflux for 12–21 h, before being subjected to standard aqueous acidic workup (Table 1).

Initial results using these conditions were not encouraging. Neither stirring an equimolar mixture of **7a** and indium powder in dry THF (entry 1) or dry DMF (entry 2) under an N_2 atmosphere at room temperature led to the formation of the desired cyclised product but only to recovery of unchanged starting material. Heating the reaction to reflux in dry THF in line with the protocol reported for the corresponding intermolecular reaction[15] also failed to yield any of the cyclised product **8a** (entry 3). However, to our delight when the reaction was carried out in a 1:1 mixture of THF/H_2O overnight, followed by mild protolytic workup, the desired 3-vinyl-4-methylenetetrahydrofuran **8a** was obtained in 62% yield (entry 4) as a single product. This result represents the first example of an intramolecular carboindination of alkynes, and is testament to the profound effect that the addition of water is known to have on

Table 1. Initial approaches to the In-mediated cyclisation



7 or 9 **8 or 10**

Entry	Haloenyne	X	Solvent	Additive	*t*/h	Product	Conversion/%[a]
1	**7a**	O	THF (dry)	—	14	—	0
2	**7a**	O	DMF (dry)	—	12	—	0
3	**7a**	O	THF (dry)[b]	—	14	—	0
4	**7a**	O	THF/H_2O[c]	—	16	**8a**	>95 (62)
5	**9a**	$C(CO_2Me)_2$	THF (dry)[b]	—	21	—	Trace
6	**9a**	$C(CO_2Me)_2$	THF/H_2O[c]	—	17	**10a**	>95 (74)
7	**9a**	$C(CO_2Me)_2$	THF (dry)	TFA (0.1 equiv)	4.5	**10a**	>95 (80)
8	**9a**	$C(CO_2Me)_2$	THF (dry)	AcOH[d] (0.2 equiv)	16	**10a**	72 (35)
9	**9a**	$C(CO_2Me)_2$	THF (dry)	$PhCO_2H$ (0.15 equiv)	20	**10a**	65 (–)[e]
10	**9a**	$C(CO_2Me)_2$	THF (dry)	10-CSA[f] (0.15 equiv)	17	**10**	15 (–)

[a] Conversion estimated from ^{1}H NMR. Isolated yields given in parentheses.
[b] Reaction heated at reflux.
[c] 1:1 ratio.
[d] GPR glacial acetic acid.
[e] Product not isolated.
[f] Dried by azeotroping from toluene.

the rate,[20] as well as the stereo-[21] and regioselectivity[22] of indium-mediated reactions.[23]

Encouraged by this result we decided to examine the possibility of using a substrate bearing a geminal diester group in the hope of utilising the Thorpe–Ingold effect[24] to promote the cyclisation. To this end we prepared dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(prop-2-ynyl)malonate **9a** in one step from commercially available dimethyl-2-(propynyl)malonate. Unsurprisingly, heating this new substrate with indium metal in dry THF at reflux gave only a trace of the desired heterocycle (entry 5). Gratifyingly however, exposure of **9a** to indium metal in THF/H_2O (1:1) at room temperature afforded the corresponding carbocyclic *exo*-1,4 diene **10a** with >95% conversion and in 74% isolated yield (entry 6). Interestingly, it was found that the cyclisation could be effected in dry THF by the addition of a catalytic amount of an anhydrous organic acid to the reaction mixture (entries 7–10). Although most common laboratory acids promoted the reaction to some degree, the efficiency of the cyclisation was related to the strength of the acid added, best results being obtained with TFA (80% yield, 4.5 h). The exact function of the acid in the reaction is still unclear although it is possible that, at the very least, the acid acts to remove any oxide on the surface of the indium thus rendering it more reactive.

The cyclisation reactions in THF/H_2O were extremely clean. Inspection of the ^{1}H NMR spectrum of the crude reaction mixture shows only peaks corresponding to the desired cyclic compound along with those of small amounts of residual starting material. The success or failure of the reactions in THF/H_2O can be conveniently assessed by observing the state of the crude reaction mixture prior to work-up. Appearance of a thick white precipitate of $In(OH)_3$ is normally indicative that the transformation has proceeded smoothly. Typically the reaction mixture also contains a metallic residue, which is approximately 25–30% of the weight of the indium added to the reaction.

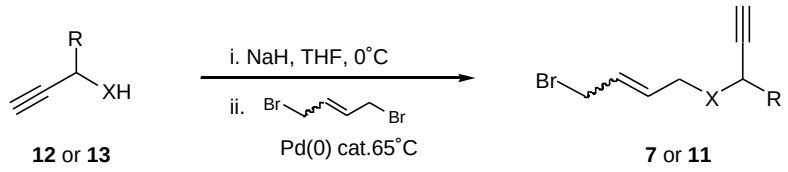
We also screened a number of aqueous and non-aqueous solvent systems for the cyclisation of **9a** to the carbocycle **10a** and the conversion of the reaction was established by inspection of the ^{1}H NMR spectra of the crude reaction mixture. These studies showed that the cyclisation reaction proceeds to some extent in most common laboratory solvents ($THF > DMF > H_2O \approx MeOH \gg Et_2O \approx EtOAc$,) but that in all cases the conversion was improved by conducting the reaction in a 1:1 mixture of the organic solvent and H_2O. The best conversions and yields of the carbocycle were obtained in THF/H_2O (1:1), although it was possible to reduce the amount of THF to approximately 9% (THF/H_2O 1:10) without serious detrimental effect on the conversion of **9a** to **10a**. The reaction was also found to proceed in pure H_2O although the conversion dropped to 75–80%, which may in part be due to the insolubility of the substrate in a completely aqueous environment.

2.2. Synthesis of other haloallyl alkyne cyclisation precursors

The initial results described above prompted us to probe further the scope of the indium-mediated cyclisation of terminal haloenynes. To this end, we prepared three groups of substrates in which the allylic halide and alkyne were linked by an oxygen, nitrogen or carbon atom. The heteroatom-tethered substrates **7a–d** (Table 2, X=O) and **11a–e** (Table 2, X=NR) were prepared as shown below from common starting materials in moderate yields by allylation of the sodium salt of propargyl alcohols **12a–d** or *N*-protected propargyl amines **13a–e** with (*E*)- or (*Z*)-1,4-dibromo-2-butene in moderate yields (Table 2). In some cases, the reaction was promoted using a Pd(0) catalyst in accordance with literature protocols.[25]

The carbon-tethered cyclisation substrates **9a–h** were synthesised in a similar manner, either from commercially available active methylene compounds **14a–e** (Table 3) or,

Table 2. Synthesis of heteroatom-centered cyclisation precursors



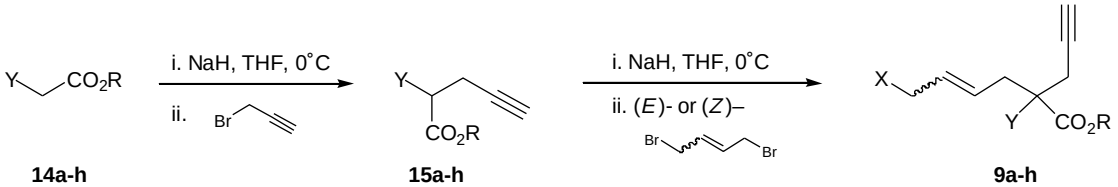
12 or **13** **7** or **11**

Entry	**12/13**[a]	X	R	Product/(% yield)
1	**12a**	O	H	**7a** (34)
2	**12b**	O	Ph	**7b** (30)
3	**12c**	O	^{n}Pr	**7c** (38)
4	**12d** (*E*)	O	^{n}Pen	**7d** (*E*) (37)
5	**12d** (*Z*)	O	^{n}Pen	**7d** (*Z*) (33)[b]
6	**13a**	NTs	H	**11a** (34)[c]
7	**13b**	NTs	^{n}Pen	**11b** (35)[c]
8	**13c**	NBoc	H	**11c** (46)
9	**13e**	NCbz	H	**11d** (63)
10	**13g**	NBn	H	**11e** (37)

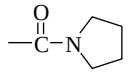
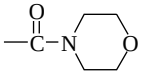
[a] (*E*)-geometry unless otherwise stated.
[b] >97% (*Z*).
[c] Reaction carried out in the presence of 5 mol% $Pd^{2}(dba)_3$ + 5 equiv (wrt Pd) PPh_3 prepared by stirring in degassed reaction solvent for 1 h at rt then added via cannular to the reaction mixture.

in the case of mixed ester/amide substrates **14f–h**, from the corresponding amide, which was in turn prepared in good yield by treatment of commercially available ethyl malonyl chloride with the appropriate amine in CH_2Cl_2–H_2O. *gem* Dinitrile substrate **9i** which was synthesised from propargyl malononitrile **16** which itself was prepared by dehydration of diamide **17**, prepared from commercial dimethylpropargyl malonate **15a** (Scheme 3).[26]

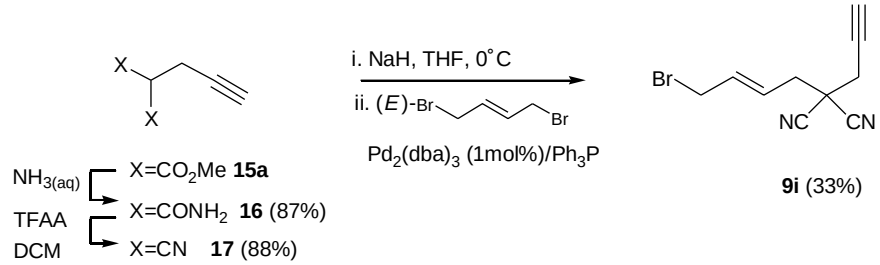
Table 3. Synthesis of carbon-centred terminal haloallylalkynes



14a-h **15a-h** **9a-h**

Entry	**14**[a]	R	Y	**15**/(%)	**9**/%[a]
1	**14a**	Me	CO_2Me	**15a**[b]	**9a** (*E*) (53)
2	**14a**	Me	CO_2Me	**15a**[b]	**9a** (*Z*) (47)[c]
3	**14b**	Et	CO_2Et	**15b** (–)	**9b** (18)[d]
4	**14c**	^{t}Bu	CO_2Me	**15c** (–)	**9c** (17)[d]
5	**14d**	^{t}Bu	^{t}Bu	**15d** (–)	**9d** (27)[d]
6	**14e**	Me	SO_2Ph	**15e** (–)	**9e** (49)[d]
7	**14f**	Et	$CONMe_2$	**15f** (32)	**9f** (37)
8	**14g**	Et		**15g** (52)	**9g** (38)
9	**14h**	Et		**15h** (48)	**9h** (32)

[a] (*E*)-isomer unless otherwise stated.
[b] Purchased from commercial sources.
[c] (*Z*)/(*E*) ratio 94:6.
[d] Yield from **14** over 2 steps.



9i (33%)

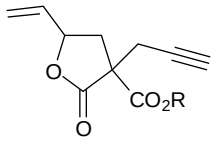
Scheme 3. Synthesis of 2-(4-bromobut-2-enyl)-2-(prop-2-ynyl)malononitrile **9i**.

2.3. Investigation of the scope of the indium-mediated cyclisation reaction

Having synthesised the desired substrates, our attention turned to establishing the scope of the intramolecular carboindination reaction. To this end the heteroatom-tethered haloallylalkynes **7a–d** and **13a–e** were stirred with indium powder (1 equiv) in THF/H_2O (1:1) at room temperature for 15–18 h before being submitted to mild acidic work up and purification. As shown in Table 4, the oxygen-tethered substrates **7a–d** underwent smooth cyclisation to give the corresponding *exo*-diene tetrahydrofurans **8a–d** in moderate to acceptable yield and with a small preference for the *syn* diastereomer[27] in the case of substrates bearing a substituent in the α-position (entries 2–5). The (*E*)/(*Z*) geometry of the allylic fragment exerts little influence on the stereochemical course of the reaction, as both the (*E*)- and (*Z*)-allyl bromide of **7d** undergo smooth cyclisation to give *exo* diene tetrahydrofuran **8d** (entries 4 and 5). It is noteworthy that although the diastereoselectivity of this reaction was modest, the degree of selectivity and the sense of selectivity (i.e., *syn* rather than *anti*) was the same regardless of the geometry of the allylic group in the starting material.

Nitrogen-tethered substrates **13a–e** bearing common protecting groups the such as 4-toluenesulfonyl (**13a–b**, X=NTs, entries 6 and 7), *tert*-butoxycarbonyl (**13c**, X=NBoc, entry 8) and benzyloxycarbonyl (**13d**, X=NCbz, entry 9) also underwent smooth, clean cyclisation to afford the corresponding pyrrolidines in relatively good yield. One exception was the *N*-benzyl derivative (**13e**, X=NBn, entry 10), which decomposed under the reaction conditions, possibly by intramolecular S_N2' attack of the nucleophilic nitrogen at the allylic position assisted by Lewis acidic nature of the allylindium intermediate.

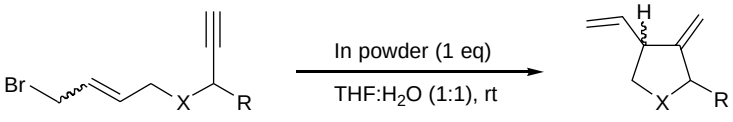
The cyclisation reaction of the carbon-centred substrates was also investigated using the precursors described above (Table 5). Gratifyingly it was found that in nearly all cases the substrates **9a–9i** also underwent smooth indium-mediated cyclisation in aqueous THF to give the corresponding cyclopentyl dienes **10a–10i** in moderate to good yield. The only exception was the geminal di-*tert*-butyl enyne **9d** which did not give the expected carbocycle on treatment with indium. In this case, a complex reaction mixture was obtained from which two compounds, tentatively assigned as the lactones **19** and **20**, were isolated in low yield.[28] In all other cases the cyclisation of the substrates proceeded very cleanly without the need for any additives to give the corresponding hetero- or carbocycle as essentially the only organic product.[29] As with the oxygen and nitrogen-tethered series, the cyclisation reaction proceeded equally efficiently starting with either **9a**(*E*)- (entry 1) or **9a**(*Z*)- (entry 2), or a mixture of both isomers of **9a** (entry 3).



19 (R=^{t}Bu)
20 (R=H)

In contrast to the heterocyclic series, the stereoselectivity of the cyclisation of substrates that gave diastereomeric products was poor (entries 5, 7–11) and it was generally not possible to separate the individual diastereomers or assign their *syn* or *anti* character with certainty by NOESY spectroscopy. However, unambiguous confirmation of the structure of the carbocyclic products was obtained by single-crystal X-ray analysis of **9h** (Fig. 1)[30] which was one of of the few cyclic products obtained as a microcrystalline solid, the remainder being isolated as clear, viscous oils.

Table 4. Cyclisation of heteroatom-tethered haloenynes

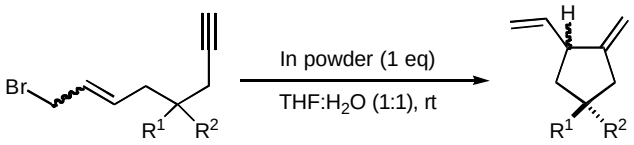


7 or **11** **8** or **18**

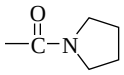
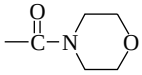
Entry	Haloenyne[a]	X	R	*t*/h	Product/(%)[b]	*syn*/*anti*[c]
1	**7a**	O	H	16	**8a** (62)	—
2	**7b**	O	Ph	16	**8b** (50)	2:1[d]
3	**7c**	O	^{n}Pr	17	**8c** (56)	3.5:1[d]
4	**7d** (*E*)	O	^{n}Pen	17	**8d** (52)	3:1[d]
5	**7d** (*Z*)[e]	O	^{n}Pen	17	**8d** (45)	3.6:1
6	**13a**	NTs	H	16	**18a** (62)	—
7	**13b**	NTs	^{n}Pen	17	**18b** (83)[c]	dr 14:1[f]
8	**13c**	NBoc	H	16	**18c** (69)	—
9	**13d**	NCbz	H	15	**18d** (66)	—
10	**13e**	NBn	H	17	**18e** (0)[g]	—

[a] (*E*)-isomer unless otherwise stated.
[b] Isolated yields after chromatography.
[c] Isomers assigned by analogy to **8d**.
[d] *syn*/*anti* ratios provisionally assigned by ^{1}H NOESY spectral analysis of mixture of diastereomers.
[e] 95:5 (*Z*)/(*E*) ratio of isomers.
[f] *syn*/*anti* isomers could not be identified.
[g] Decomposition/polymerisation only observed.

Table 5. Cyclisation of carbon-tethered haloenynes



9a-h **10a-h**

Entry	Haloenyne[a]	R^1	R^2	*t*/h	Product/(%)[b]	dr[c]
1	**9a**	CO_2Me	CO_2Me	17	**10a** (74)	—
2	**9a** (*Z*)[d]	CO_2Me	CO_2Me	16	**10a** (75)	—
3	**9a** (*E*)/(*Z*)[e]	CO_2Me	CO_2Me	17	**10a** (74)	—
4	**9b**	CO_2Et	CO_2Et	18	**10b** (71)	—
5	**9c**	CO_2Me	CO_2^tBu	16	**10c** (56)	1:1
6	**9d**	CO_2^tBu	CO_2^tBu	17	**10d** (0)	—
7	**9e**	SO_2Ph	CO_2Me	16	**10e** (44)	4.5:1
8	**9f**	$CONMe_2$	CO_2Et	18	**10f** (84)	1.3:1
9	**9g**		CO_2Et	17	**10g** (77)	1:1
10	**9h**		CO_2Et	17	**10h** (63)	1.3:1
11	**9i**	CN	CN	17	**10i** (49)	—

[a] (*E*)-isomers (>99%) unless otherwise stated.
[b] Isolated yields after chromatography.
[c] *syn* and *anti* diastereomers could not been conclusively distinguished by NOESY NMR.
[d] 94:6 (*Z*)/(*E*) mixture of alkene isomers.
[e] 67:33 (*E*)/(*Z*) mixture of alkene isomers.

2.4. Effect of the allylic precursor on the cyclisation reaction

We also investigated the influence of the nature of the allylic precursor on the course of the reaction. Although the (*E*)-allyl bromides were used as the precursors of choice due to their ready availability we found that the (*E*)-iodo analogue **21**, which could be prepared in 79% yield from dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(prop-2-ynyl)malonate **9a** by treating it with NaI (5 equiv) in acetone, also underwent efficient indium-mediated cyclisation under standard conditions to give carbocycle **10a** in >95% conversion and 73% isolated yield (Table 6, entry 1). By contrast, the (*E*)-chloro analogue **22** was almost completely inert to the reaction conditions[31] (entry 2) even in the presence of NaBr (entry 3), although NaI (entry 4) or KI (entry 5) were more effective in promoting the reaction. The corresponding allyl mesylate **23** (3:2 *cis*/*trans* mixture) was similarly inert (entry 6) but could also be made to undergo smooth cyclisation in aqueous THF by the addition of KI (entry 7).

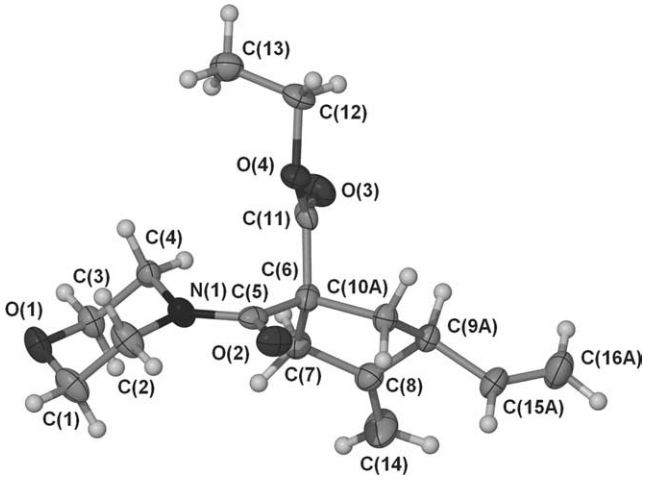


Figure 1. X-ray structural analysis of carbocycle **9h**.

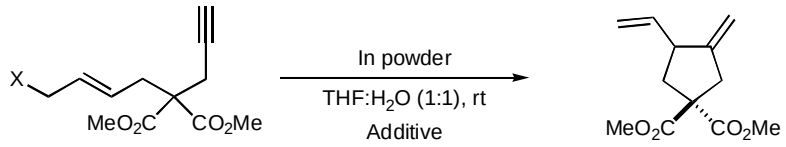
2.5. Influence of the nature of the indium reagent on the cyclisation reaction

Having demonstrated the viability of the indium mediated cyclisation of terminal haloallylalkynes we wished to investigate the scope of the reaction with respect to the indium reagent. Accordingly a number of indium reagents were screened for their efficiency in promoting the cyclisation of **9a**.

In a typical procedure the indium was added as In(0) powder (1 equiv, 99.99 atom% In) (Table 7, entry 1), a procedure which afforded the carbocyclic product in 75%. We found that the amount of indium could be reduced to 0.67 equiv without compromising yield (entry 2) but that the use of smaller amounts (entries 3 and 4) led to a reduction in the efficiency of reaction, giving lower conversions in direct proportion to the amount of indium added. A combination of sub-stoichiometric indium metal and excess manganese failed to turn the reaction over (entry 5).[32]

It was found that presenting the indium as wire (entry 6), 2–5 mm shot (entry 7) or 0.5 mm foil (entry 8) had a marginally detrimental effect on yield presumably due to the greatly reduced surface area of these forms relative to

Table 6. Scope of the allylic precursor

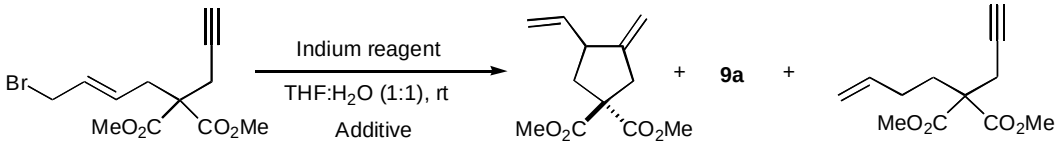


21-23 **10a**

Entry	Haloenyne	X	Additive	Conversion **10a**/(%)[a]
1	**21**	I	—	>95 (75)
2	**22**	Cl	—	17 (–)[b]
3	**22**	Cl	NaBr (2 equiv)	12 (–)[b]
4	**22**	Cl	NaI (5 equiv)	80 (–)[b]
5	**22**	Cl	KI (5 equiv)	50 (14)
6	**23**	OMs	—	0[c]
7	**23**	OMs	KI (5 equiv)	97 (71)

[a] Isolated yield in parentheses.
[b] Product not isolated.
[c] Approx. 8% of the corresponding allyl alcohols arising from hydrolysis of the starting mesylate was observed.

Table 7. Use of different indium sources for the cyclisation reaction



9a **10a** **24**

Entry	In source	Mol% In	Additive	*t*/h	Yield **10a**/%	Ratio **10a**:**9a**:**24**[a]
1	In(0) powder	100	—	17	75	95:5:0
2	In(0) powder	67	—	16	73	75:25:0
3	In(0) powder	50	—	18	—[b]	51:49:0
4	In(0) powder	10		18	—[b]	10:90:0
5	In(0) powder	10	Mn (5 equiv)	18	—[b]	<5:95:0
6	In(0) wire[c]	100	—	15	50	64:36 (21)[d]:0
7	In(0) shot[e]	100	—	17	71	94:6:0
8	In(0) foil[f]	100		17	63	80:20:0
9	None	—	Ga (1 equiv)	18	0	0:100 (90)[g]:0
10	InBr[h]	100	—	17	53	69:21(18)[i]:0
11	InI[h]	100	—	18	34	66:34 (15)[i]:0
12	$InBr_3$	100	—	17	0	0:100 (95)[g]:0
13	$InCl_3$	100	—	16	0	0:100 (80)[g]:0
14	$In(OH)_3$	100	—	17[j]	0	0:100:0
15	$InBr_3$	100	Zn (5 equiv)	17	72	87:0:13
16	$InBr_3$	10	Zn (5 equiv)	17	44	13:77:0
17	$InBr_3$	10	Zn (2 equiv)	18	17	24:0:76 (79)[k]
18	$InBr_3$	10	Zn (1 equiv)	16	—[b]	50:0:50
19	$InBr_3$	10	Mn (5 equiv)	16	0	0:100:0
20	$InBr_3$	10	Mg (5 equiv)	17	0	0:100:0
21	$InBr_3$	10	Ga (3 equiv)	17	0	0:10 0:0[l]
22	$InBr_3$	10	Al (3 equiv)	18	0	0:100:0
23	$InBr_3$	10	Fe (3 equiv)	18	0	0:100:0
24	$InCl_3$	100	Zn (5 equiv)	16	62	64:0:36

[a] Estimated from ^{1}H NMR.
[b] Not isolated.
[c] 99.99% In cut into approx. 1 mm lengths.
[d] Isolated yield in parentheses.
[e] 2–5 mm shot (99.99+% In).
[f] 99.99% In cut into 1–2 mm squares.
[g] Recovered starting material yield in parentheses.
[h] 99.99% InX beads crushed to powder.
[i] Starting material recovered as 2:1 mixture of iodo- and bromo isomers (16% total recovery).
[j] Dry THF only used as solvent.
[k] Isolated yield in parentheses.
[l] Some hydrolytic decomposition observed.

indium powder. In addition, the comparative softness of indium metal also meant that adding it in any form other than a fine powder (which is light enough to be suspended in the solvent) often resulted in it being flattened into a 'mirror' on the inside of the flask. The same problem was experienced with gallium metal, which did not promote the reaction at all (entry 9).

In addition to elemental indium, the reaction was found to proceed in the presence of indium salts. Use of InBr (entry 10) and InI (entry 11) in aqueous THF promoted the cyclisation but under these conditions the reaction was more capricious than with In(0) and proceeded with lower conversions and in poorer chemical yield. Additionally in the case of InI the product mixture also contained 2-((*E*)-4-iodobut-2-enyl)-2-(prop-2-ynyl)malonate **19** as well as the carbocyclic product and unreacted allyl bromide starting material. It should be noted that when using indium(I) salts, it was essential to crush the reagent to a powder before addition due to the poor solubility of In(I) in the reaction medium.

More highly oxidised In(III) salts such as $InBr_3$ (entry 12), $InCl_3$ (entry 13) or $In(OH)_3$ (entry 14) did not promote cyclisation; the unreacted starting bromide being the only species present in the crude reaction mixture as determined by ^1H NMR spectroscopy. Whilst InX_3 salts alone were not effective reagents for the transformation, the use of a co-reductant such as zinc (entry 15) with $InBr_3$ (1 equiv) to generate a reduced indium species in situ afforded the carbocyclic product smoothly and cleanly in essentially the same yield as that obtained with In(0) powder. Significantly, it was found that under these conditions the reaction could be made to turn over even in the presence of substoichiometric quantities of $InBr_3$ (0.1 equiv)[33] (entries 16–18) although both the conversion and isolated yield of the carbocycle was dramatically reduced. In all cases where $InBr_3$ was used to mediate the reaction, proteodebrominated product **24** was also generated in varying amounts. A number of co-reductants in addition to zinc were screened (entries 20–23) but none were found to be effective in promoting the reaction. Use of the cheaper $InCl_3$ as the In(III) source in the presence of zinc dust (5 equiv) did facilitate the cyclisation reaction, however, whilst conversion of the starting allylbromoalkyne was in line with other methods much higher quantities of the proteodebrominated by-product **24** was generated.

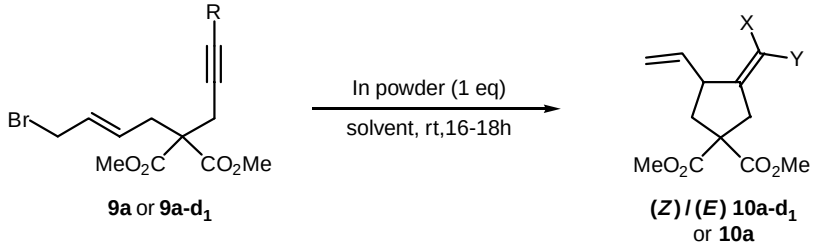
The failure of more highly oxidised salts alone to facilitate the cyclisation is unsurprising in view of the likely sesquihalide nature of the organoindium intermediate which may be assumed to develop in this type of reaction.[34] The generation of such an intermediate from the allyl halide would require formal oxidative addition of the indium reagent to the substrate, which would be possible for both In(0) and In(I) but would not be possible for In(III) species.

2.6. Deuteration studies aimed at elucidating the mechanism of the cyclisation reaction

Whilst the synthetic scope of the indium-mediated cyclisation had been established, a number of the mechanistic aspects of the reaction remained unexplored. For example, it was still not known whether the addition of the allyl bromide fragment to the alkyne proceeded by regioselective *syn* or *anti* carboindination of the carbon–carbon triple bond or by another, non-regioselective, pathway. Furthermore, it was also unclear whether the protonation of the organindium intermediate generated on cyclisation of the precursor takes place during the reaction, or occurs on acidic work-up. In order to investigate the protonation process a deuteration study of the indium-mediated cyclisation reaction of (*E*)-**9a** was carried out (Table 8).

Firstly, **9a** was allowed to react with indium in a mixture of dry THF/H_2O (1:1) under a N_2 atmosphere for 16 h whereupon the reaction mixture was evaporated to dryness in vacuo. The resulting milky-white solid was suspended in diethyl ether and treated with 18% DCl in D_2O (99.99 atom% D), stirred at room temperature for 5 min and then the mixture was partitioned between diethyl ether and water, and the organic layer was washed with brine and then dried ($MgSO_4$). The ^1H NMR spectrum of the residue obtained on

Table 8. Deuterium labling studies



9a or **9a-d$_1$** → **(*Z*) / (*E*) 10a-d$_1$** or **10a**

Entry	R	Solvent[a]	Work-up	Conversion (%)[b]	X	Y
1	H	THF/H_2O	18% DCl/D_2O	>95 (65)	H	H
2	H	THF/D_2O	15% $HCl_{(aq)}$	>95 (50)	D[c]	H
3	D[d]	THF/H_2O	15% $HCl_{(aq)}$	>97 (86)	H	D[d]
4	H	d_8-THF/H_2O	15% $HCl_{(aq)}$	>95 (73)	H	H

[a] (1:1) mixture of solvents.
[b] Estimated from ^1H NMR. Isolated yield in parentheses.
[c] 90% incorporation.
[d] 50% incorporation.

filtration and removal of solvent showed that cyclisation had occurred as expected but that no deuterium had been incorporated into the product (Table 8, entry 1). The procedure was repeated using dry THF/D_2O (1:1) as solvent and the reaction was worked up according to the method described above except that 15% HCl in H_2O was used to quench the reaction. Significantly, the cyclised product generated under these conditions contained an atom of deuterium at the terminal end of the 1,1-disubstituted exocyclic alkene generated by carboindination of the alkyne moiety (entry 2). The geometry of the newly-formed double bond in (*Z*)-**10a–d$_1$** was established by NOESY spectroscopy. No incorporation into the (*E*) position was observed. Interestingly, deuterated haloallylalkyne **9a–d$_1$** in which the acetylinic proton has been replaced with deuterium (50%) also underwent smooth reaction with In(0) in THF/H_2O to give the cyclised product (*E*)-**10a–d$_1$** with essentially quantitative conversion and in 86% isolated yield with no loss of deuterium (entry 3). No scrambling of the deuterium into the (*Z*)-position was observed. Unsurprisingly, the use of d_8-THF/H_2O as the solvent followed by $HCl_{(aq)}$ work-up did not lead to the incorporation of deuterium into the product (entry 4).

These results indicate that the protonation (deuteration) event in the cyclisation occurs as the reaction cycle is turning over and not at the time of the protolytic (deuterolytic) work-up. It follows therefore that an organic and/or inorganic indium hydroxide (deuteroxide) species is present in the mixture during the reaction cycle. Furthermore, the exclusive (*Z*)-geometry of the newly-formed exocyclic alkene strongly suggests that the reaction proceeds via a *syn*-selective concerted carboindination of the alkyne, a postulate that is reinforced by the observation that the d_1-alkyne substrate undergoes cyclisation to give exclusively the (*E*)-deuterated carbocylic product. The fact that this latter transformation proceeds without the integrity of the alkynic deuterium atom being compromised rules out the possibility that the reaction proceeds via an acetylinic indium species, an observation that is consistent with the mechanism for the intermolecular addition of organoindium reagents to aliphatic terminal alkynes.[16b]

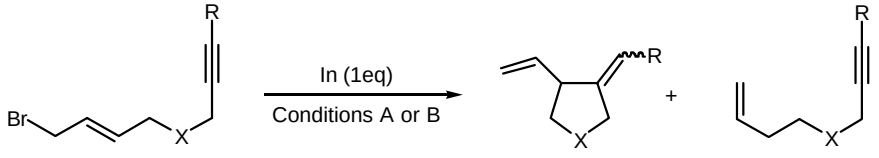
2.7. Cyclisation of non-terminal haloallyl alkynes in THF/H_2O (1:1)

Whilst terminal haloenynes undergo indium-mediated cyclisation under mild conditions in aqueous solvent systems without the need for additives, attempts to extend this methodology to the cyclisation of non-terminal haloallyl alkynes were largely unsuccessful. Exposure of non-terminal *gem*-diester haloallylalkyne **25** or **26** to indium metal in THF/H_2O (1:1) at room temperature did not lead to the generation of either of the desired carbocyclic products **30** or **31** but instead gave the corresponding proteodebrominated materials (Table 9, entries 1 and 2) as the major product of the reaction. Attempts to effect the cyclisation of **25** by generation of a more active indium species by in situ reduction of $InBr_3$ (1 equiv) with Zn (5 equiv) also met with failure (entry 3). Addition of KI either in THF/H_2O (1:1) or DMF/H_2O (1:1) did not improve matters. Indeed, it was necessary to move to much more forcing conditions (DMF, 100 °C, entry 5) to effect the cyclisation of non-terminal alkyne systems **25**, **26** (entries 4 and 5).[35]

2.8. Intramolecular carboindination of non-terminal haloenynes

Although unactivated non-terminal alkynes proved inert to cyclisation using the aqueous protocol, electron-poor haloallyl alkyne **27** underwent smooth and clean cyclisation to give the corresponding carbocycle **32** in good yield (Table 9, entry 6). It is reasonable to suggest that the greatly altered electronic nature of **27** compared with that of **25** or **26** in which the alkyne triple bond is essentially unpolarised, shifts the mechanism of the reaction from an

Table 9. Cyclisation of non-terminal bromoenynes



25-29 **30-34** Cyclic product Alkene product

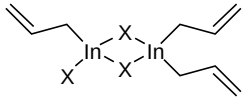
Entry	Enyne	X	R	In source	Conditions[a]	Product	Cyclic/alkene[b]
1	**25**	$C(CO_2Me)_2$	Me	In(0)	A	**30**	0:88(59)[c]
2	**26**	$C(CO_2Me)_2$	Ph	In(0)	A	**31**	0:100(66)
3	**25**	$C(CO_2Me)_2$	Me	$InBr_3$/Zn	A	**30**	0:100(84)
4	**26**	$C(CO_2Me)_2$	Ph	In(0)	B	**31**	91(85):9[d]
5	**25**	$C(CO_2Me)_2$	Me	In(0)	B	**30**	89(65):11
6	**27**	$C(CO_2Me)_2$	CO_2Me	In(0)	A	**32**	95(65)[e]:5
7	**28**	O	Ph	In(0)	A	**33**	40(30):60
8	**29**	O	^{n}Pr	In(0)	A	**34**	—[f]

[a] Conversion estimated from ^{1}H NMR. Isolated yields in parentheses.
[b] Condition A: THF/H^{2}O (1:1), rt. Condition B: DMF (anhydrous), 100 °C.
[c] Ref. 36
[d] Starting material also recovered.
[e] 92:8 (*E*)/(*Z*) mixture of diastereomers.
[f] Decomposition of starting material observed.

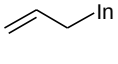
alkyne carbometalation pathway to an intramolecular Michael addition-type pathway. Intriguingly however, the oxygen-centred haloallyl alkyne **28** did undergo indium-mediated cyclisation in THF/H_2O (1:1) at room temperature to a certain extent (entry 7) to give **33** although the major product was still the proteodebrominated material. The contrast in reactivity of the **28** the carbon-centred non-terminal haloenynes may be partially due to the C–O bond in **28** being slightly shorter than the analogous C–C bond in the carbon-centred substrates. However, the failure of propyl-substituted oxygen-centred substrate **29** to undergo cyclisation indicates that the reaction is finely balanced and is governed by both steric and electronic factors.

2.9. Nature of the allyindium intermediate

The difference in the reactivity of non-terminal haloallyl alkynes towards indium in aqueous THF and anhydrous DMF is striking especially in view of the fact that it has been established that the cyclisation does not proceed via a route involving insertion into a C≡C–H bond (vide supra). The explanation of this observation lies in the likely nature of the organoindium intermediate present in each reaction. It is known that reactions of allyindium reagents in highly polar solvents such as DMF or THF proceed via an indium sesquihalide intermediate ($R_3In_2X_3$) **35** but that this structure can be transformed into the corresponding dialkylindium species by the addition of KBr or KI. However under aqueous conditions, the monomeric allylindium species **36** has been shown to be present in the reaction mixture.[37]



35

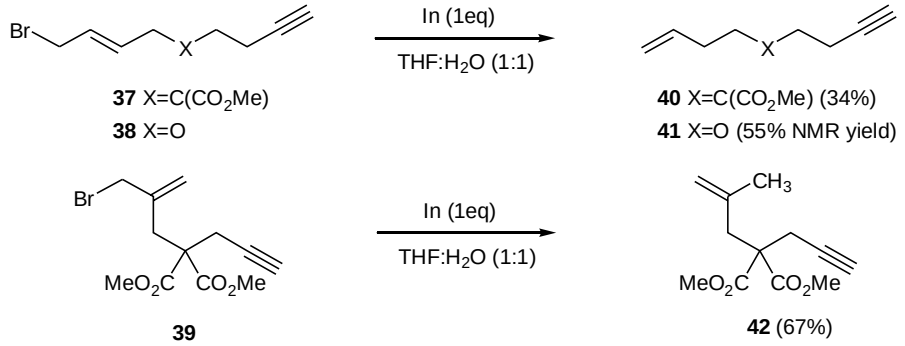


36

In the analogous intermolecular carboindinations of alkynes it has been demonstrated that the two of the three allyl groups are added across the alkyne carbon–carbon triple bond, and the third acts as a ligand for the indium complex in the reaction.[33] Accordingly in the intermolecular case, 0.6 equiv of indium with respect to the alkyne substrate (representing an effective 1.2 fold excess of allylindium reagent over the alkyne) are typically used and one allyl group per molecule of the organoindium complex is sacrificed. However, in the case of intramolecular carboindination the ratio of allyl group to alkyne is necessarily fixed at 1:1. Thus if the organoindium species generated during the cyclisation of tethered terminal haloallyl alkynes in THF/H_2O is an indium sesquihalide, the maximum possible yield for the reaction would be 66% with the remaining 33% of the organic reagent being lost as a ligand for the indium complex generated in the reaction. The fact that the cyclisation in THF/H_2O proceeds without loss of yield with only 0.67 equiv of indium with respect to the substrate (Table 6, entry 2) would appear to support a sesquihalide intermediate. However, this is offset by the observation that the yield of the reaction can exceed 66%, and that the reaction does not proceed in dry THF (which would be expected to lead to the formation of an indium sesquihalide) but only turns over in aqueous solvent systems (which would promote a dimeric or monomeric allylic indium species). Therefore, whilst it is still not possible to identify the exact nature of the intermediate in THF/H_2O, these data suggest that it is most likely composed of a mixture of mono- and dimeric organoindium species which are Lewis acidic enough to undergo addition to a terminal alkyne but not sufficiently reactive to add to more sterically congested non-terminal alkynes, in contrast to the indium sesquihalide intermediate which would likely be present in more polar DMF. Furthermore, the fact that the (*E*)/(*Z*) geometry of the allylic precursor has no effect on the yield or stereoselectivity of the reaction indicates that the cyclisation to a five-membered ring proceeds from a common intermediate.[38]

Something of the constraints placed upon on the cyclisation of this intermediate can be understood by contrasting the smooth cyclisation of the substrates described above with indium in THF/H_2O to give five-membered carbo- and heterocycles with the failure of 1-bromo-2-nonene-8-ynes **37–38** and bromomethallylalkyne **39** to cyclise to the corresponding six-membered analogues (Scheme 4) under them same conditions. These observations indicate that in the presence of a protic solvent mixture,[33] the rate of proteodebromination of substrates **37–39** to give alkenes **40–42** is faster than that of cyclisation, and therefore it seems likely that the reaction proceeds by a cyclic rather than open transition state.

Therefore, whilst the exact structure of this intermediate is still unclear, the deuterium labelling results and consideration of the geometries involved in the cyclisation suggests that the reaction most likely proceeds through the (*E*)-form



37 X=C(CO_2Me)
38 X=O

40 X=C(CO_2Me) (34%)
41 X=O (55% NMR yield)

39

42 (67%)

Scheme 4. Attempted extension of the cyclisation reaction to six-membered systems.

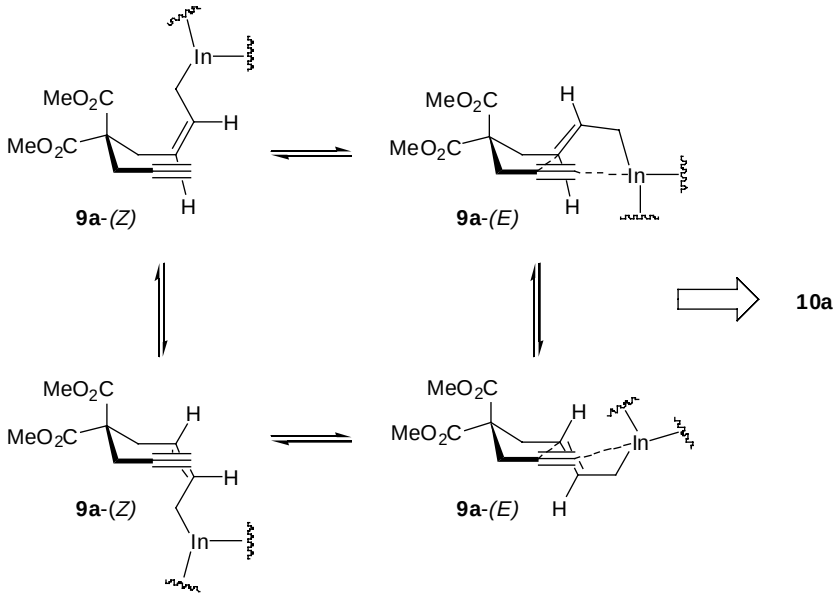


Figure 2. Suggested structures for the cyclisation intermediate.

of the allylindium intermediate, generated either from the action of indium on the (*E*)-allylic halide or from isomerisation of the (*Z*)-allylindium. This then adds across the alkyne in *syn* fashion with complete specificity, a reaction mode which would be accommodated only by a concerted carboindination of the triple bond and would not be consistent with a radical mechanism (Fig. 2).

3. Conclusion

In summary, we have demonstrated a novel indium-mediated cyclisation reaction of terminal haloallyl alkynes which proceeds in THF/H_2O via intramolecular allylindination of the unactivated alkyne C–C triple bond. The reactions, which occur smoothly under extremely mild conditions without the need for the addition of NaI or KI, are operationally simple and provide a quick and convenient route to the synthesis of a variety of five-membered heterocycles and carbocycles.

The reaction was facilitated by both In(0) and In(I) species although not by the addition of either In(III) salts or Ga(0). Generation of indium reagent by in situ reduction of In(III) species with zinc allowed the use of catalytic quantities (10 mol%) of indium. The presence of water in the reaction medium was found to be essential for smooth and efficient cyclization, and although a 1:1 mixture of THF/H_2O was established as the solvent system of choice, the reaction still proceeds in $>90\%$ water without any serious detrimental effect on the reaction.

Deuteration studies demonstrated that alkynylindium intermediate is not involved in the reaction, but that the intramolecular addition of the allylindium reagent to the alkyne occurs via concerted *syn* specific carboindination of the triple bond to generate a putative vinylindium species which is protonated in situ by the aqueous component of the solvent system.

Not only is this protocol very attractive from a synthetic standpoint due to operational simplicity, convenience and cleanliness of the reactions, but is also provides a practical contribution to the field of Green Chemistry. The use of aqueous media for organic synthesis is a field of growing importance[22] and the development of environmentally benign protocols by the minimisation of the use of organic solvents is of considerable interest from both an economic and environmental standpoint. We believe that the current method represents a valuable addition to this important field.

4. Experimental

4.1. General experimental procedure

^1H and ^{13}C NMR data were recorded on a Brucker AM400 or AM360 spectrometer in deuterochloroform, referenced to either TMS or residual $CHCl_3$ as an internal standard. Chemical shifts were measured in ppm and coupling constants (*J*) were measured in Hz. Mass spectra were obtained on a Jeol AX505W spectrometer using EI or CI. IR spectra were recorded neat or from solution, as stated, on a Perkin–Elmer paragon 1000 Fourier transform IR spectrometer. Analytical tlc was carried out on Merck 60 F_{245} plastic backed silica gel plates. Short wave UV (245 nm) or $KMnO_4$, were used to visualise components. Compounds were purified by column chromatography using Merck silica gel 60 (0.040–0.063 mm. Diethyl ether was dried over sodium wire in a septum sealed Winchester under argon. THF was distilled under N_2 from sodium benzophenone ketal NaH was freed of mineral oil by triturating three times with 60–80 °C petroleum ether. Other chemicals were used as obtained from commercial sources. All reactions were carried out in oven dried glassware.

4.2. Representative procedure for the synthesis of carbon-centred haloenynes

4.2.1. Dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(prop-2-ynyl)malonate 9a. Sodium hydride (60% in oil, 2.40 g, 60 mmol) was washed with dry hexane (3×30 mL) and dried in vacuo. The NaH was suspended in dry THF (50 mL) and cooled to 0 °C. To this was added dimethyl-(2-propynyl)malonate dropwise via syringe and after the addition was complete the mixture was stirred and allowed to come to room temperature over 30 min. This was then added via a wide-bore cannula to a solution of (*E*)-1,4-diromo-2-butene (15.67 g, 75 mmol) in THF (75 mL) at 0 °C over 5 min. The mixture was allowed to come to room temperature and stirred for a further 2 h during which time a white precipitate formed. The mixture was quenched with a mixture of diethyl ether and water and then partitioned between diethyl ether and 2 M $HCl_{(aq)}$. The aqueous layer was extracted with diethyl ether (2×50 mL) and the combined organics washed with water (1×50 mL), brine and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography (SiO_2, hexane/EtOAc 5:1) to give the required allyl bromide as a clear, colourless oil (8.10 g, 53%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.05 (1H, brs), 2.81 (2H, m), 2.83 (2H, d, J=7.7 Hz), 3.77 (6H, s), 3.91 (2H, d, J=7.5 Hz), 5.63 (1H, dt, J=7.5, 15.1 Hz), 5.86 (1H, dt, J=7.5, 15.1 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 23.4, 32.5, 35.3, 53.3, 57.3, 72.2, 78.9, 129.3, 131.9, 170.3; IR (thin film): 3291, 2954, 2122, 1736, 1661 cm^{-1}; MS (EI): m/z (%)=320 [MNH_4^+] (100.0), 223 (16.0), 162 (6.0).

4.3. Representative procedure for the synthesis of heteroatom-centred haloenynes

4.3.1. (*E*)-1-Bromo-4-(prop-2-ynyloxy)but-2-ene 8a. Propargyl alcohol, (1.40 g, 1.45 mL, 25 mmol) was added dropwise via syringe to a suspension of NaH (60% in oil which had been removed by washing with dry hexane, 1.00 g, 1 equiv) in dry THF (25 mL) at 0 °C. The mixture was stirred at ice point for 30 min and then (*E*)-1,4-dibromo-2-butene (5.59 g, 1.1 equiv) in dry THF (25 mL) was added via a cannula and the reaction was heated at 50 °C for 15 h. The mixture was allowed to cool and then quenched with a mixture of diethyl ether and water and then poured onto diethyl ether and 2 M $HCl_{(aq)}$. The aqueous layer was extracted with diethyl ether (2×50 mL) and the combined organics washed with water (1×50 mL), brine and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography (SiO_2, hexane/EtOAc 5:1) to give the required propargylic ether as a clear, colourless oil (1.6 g, 34%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.47 (1H, br s), 4.03 (2H, d, J=8.2 Hz), 4.16 (2H, br s), 4.21 (2H, dd, J=1.5, 6.5 Hz), 5.85 (1H, dt, J=5.6, 15.3 Hz), 5.96 (1H, 6.5, 15.3 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 26.3, 57.4, 64.2, 74.9, 17.4, 129.3, 130.1; IR (thin film): 3293, 2853, 2116, 1667 cm^{-1}; MS (CI): m/z (%)=168 (27.0), 151 (100.0).

4.4. Representative procedure for the cyclisation of bromoallyl alkynes

4.4.1. Tetrahydro-3-methylene-4-vinylfuran 8a. To a well-stirred solution of (*E*)-1-bromo-4-(prop-2-ynyloxy)-but-2-ene **7a** (1.89 g, 10 mmol) in dry THF (10 mL) and distilled water (10 mL) at room temperature, was added indium (Aldrich, 99.99%, 1.41 g, 10 mmol, 1 equiv). The mixture was stirred for a further 16 h and then the reaction mixture was poured onto a mixture of Et_2O and 2 M HCl. The aqueous layer was extracted with Et_2O (2×25 mL) and the combined organics were washed with water (2×25 mL), saturated aqueous NaCl (1×25 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography on silica (hexane/Et_2O, 10:1) to give the cyclised product **8a** (680 mg, 62%) as a clear colourless oil: ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 3.24 (1H, m), 3.48 (1H, dd, J=8.5, 8.6 Hz), 4.03 (1H, dd, J=8.0, 8.1 Hz), 4.23 (1H, d, J=13.3 Hz), 4.34 (1H, br d, J=13.1 Hz), 4.85 (1H, br s), 4.94 (1H, br s), 5.58 (1H, ddd, J=8.3, 10.1, 16.9 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 49.5, 71.8, 73.8, 105.6, 117.6, 136.8, 151.0; IR (thin film): 3447, 3079, 2979, 2847, 1665, 1637 cm^{-1}; MS (EI): m/z (%)=110 (20.5) [M^+], 80 (100.0).

4.4.2. Tetrahydro-3-methylene-2-phenyl-4-vinylfuran 8b. 1-(1-((*E*)-4-Bromobut-2-enyloxy)prop-2-ynyl)benzene **7b** (226 mg, 1 mmol), indium powder (114 mg, 1 mmol) in 1:1 THF/H_2O (2 mL) were reacted and worked up according to the general procedure. Chromatography on silica (hexane/Et_2O 10:1) gave the cyclised product **10b** as 2:1 mixture of diastereomers as a clear colourless oil (82 mg, 50%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 3.52 (1H, m, two diastereomers), 3.64 (1H, dd, J=8.3, 10.2 Hz, major), 3.88 (1H, dd, J=6.7, 8.6 Hz, minor), 4.12 (1H, m, two diastereomers), 4.15 (1H, dd, J=8.6, 15.2 Hz, minor), 4.31 (1H, dd, J=8.1, 16.1 Hz, major), 4.75 (1H, s, minor), 4.85 (1H, s, major), 4.97 (1H, s, major), 5.03 (1H, s, minor), 5.1–5.3 (2H, m, two diastereomers), 5.68 (1H, ddd, J=8.3, 10.4, 16.1 Hz, major), 5.79 (1H, ddd, J=8.2, 10.4, 16.2 Hz, minor); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 49.5 (minor), 49.9 (major), 72.6 (minor), 72.9 (major), 83.9 (minor), 84.1 (major), 106 (major), 109.2 (minor), 117.2 (minor), 118.2 (major), 127.3, 127.7, 128.2, 128.3, 128.7, 128.8, 136.4, 137.6, 141.6 (minor), 141.9 (major), 154.3 (minor), 154.7 (major); IR (thin film): 3079, 2929, 2851, 1718, 1663, 1637 cm^{-1}; MS (CI): m/z (%)=204 [MNH_4^+] (100.0), 190 (6.8), 187 [MH^+] (5.5), 173 (6.3).

4.4.3. Tetrahydro-3-methylene-2-propyl-4-vinylfuran 8c. 3-((*E*)-4-Bromobut-2-enyloxy)hex-1-yne **7c** (345 mg, 1.5 mmol), indium powder (180 mg, 1.57 mmol) in 1:1 THF/H_2O (1.5 mL) were reacted and worked up according to the general procedure. Chromatography on silica (hexane/Et_2O 10:1) gave the cyclised product **10b** as 3.5:1 mixture of diastereomers as a clear colourless oil (128 mg, 56%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 0.94 (3H, m, two diastereomers), 1.40–1.70 (4H, m), 3.31 (1H, m), 3.44 (1H, dd, J=8.5, 8.6 Hz, major), 3.63 (1H, dd, J=8.6, 8.7 Hz, minor), 3.97 (1H, dd, J=7.6, 8.6 Hz, minor), 4.12 (1H, dd, J=8.0, 8.1 Hz, major), 4.31 (1H, m, major), 4.35 (1H, m, minor), 4.88 (1H, br s, two diastereomers), 4.91 (1H, br s, two diastereomers), 5.12 (2H, m, two diastereomers), 5.61

(1H, ddd, J=8.3, 9.7, 16.3 Hz, major), 5.65 (1H, m, minor); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.1, 19.6 (major), 19.1 (minor), 37.1 (minor), 37.8 (major), 49.5 (minor), 49.7 (major), 71.1 (minor), 71.9 (major), 80.7 (minor), 81.2 (major), 105.2 (major), 105.6 (minor), 116.4 (minor), 117.5 (major), 136.3 (major), 137.6 (minor), 154.4 (major), 154.5 (minor); IR (thin film): 3309, 2958, 2871, 1663, 1640 cm^{-1}; MS (CI): m/z (%)=151 (40.1) [MH$^+$], 137 (20.1), 123 (23.0), 111 (35.0), 97 (62.0), 83 (63.0), 69 (67.0), 57 (100.0).

4.4.4. Tetrahydro-3-methylene-2-pentyl-4-vinylfuran 8d. 3-((*E*)-4-Bromobut-2-enyloxy)oct-1-yne **7d** (213 mg, 0.83 mmol), indium powder (94 mg, 0.83 mmol) in 1:1 THF/H_2O (2 mL) were allowed to react and then worked up according to the general procedure. Chromatography on silica (hexane/EtOAc 5:1) gave the desired carbocycle **8b** as 3.6:1 mixture of diastereomers as a clear colourless oil (77 mg, 52%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 0.88 (3H, m, two diastereomers), 1.26–1.66 (8H, m), 3.30 (1H, m, two diastereomers), 3.42 (1H, dd, J=8.5, 9.8 Hz, major), 3.61 (1H, dd, J=6.9, 8.7 Hz, minor), 3.96 (1H, dd, J=7.5, 7.6 Hz, minor), 4.10 (1H, dd, J=8.0, 8.1 Hz, major), 4.30 (1H, m, two diastereomers), 4.86 (1H, br s, two diastereomers), 4.90 (1H, s, two diastereomers), 5.16 (2H, m, two diastereomers), 5.58 (1H, ddd, J=8.6, 10.5, 16.2 Hz, major), 5.78 (1H, ddd, J=8.2, 10.3, 16.1 Hz, minor); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 13.0, 21.5 (minor), 21.6 (major), 24.0 (major), 24.58 (minor), 30.8 (minor), 30.9 (major), 33.9 (minor), 34.5 (major), 48.5 (minor), 48.7 (major), 70.1 (minor), 70.9 (major), 79.9 (minor), 80.4 (major), 104.1 (minor), 104.6 (major), 115.4 (minor), 116.5 (major), 135.3 (major), 136.6 (minor), 153.3 (minor), 153.5 (minor); IR (thin film): 3079, 2932, 2859, 1663, 1641 cm^{-1}; MS (EI): m/z (%)=180 (10.0) [M$^+$], 150 (19.0), 124 (45.0), 109 (100.0).

4.4.5. 3-Methylene-1-tosyl-4-vinylpyrrolidine 18a. (*E*)-4-Bromo-*N*-(prop-2-ynyl)-*N*-tosylbut-2-en-1-amine **13a** (105 mg, 0.31 mmol), indium powder (35 mg, 0.31 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react and then worked up according to the general procedure. Chromatography on silica (hexane/EtOAc 5:1) gave the pyrrolidine **18a** as a clear colourless oil (50 mg, 62%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.44 (3H, s), 2.86 (1H, dd, J=8.9, 9.2 Hz), 3.25 (1H, m), 3.62 (1H, dd, J=8.0, 9.3 Hz), 3.72 (1H, br d, J=14.2 Hz), 3.99 (1H, br d, J=14.2 Hz), 4.86 (1H, br s), 4.97 (1H, br d), 5.07–5.13 (2H, m), 5.50 (1H, ddd, J=8.2, 10.4, 16.5 Hz), 7.33 (2H, d, J=8.0 Hz), 7.71 (2H, d, J=8.0 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.9, 48.1, 52.3, 53.6, 108.7, 118.5, 128.2, 130.1, 133.1, 135.9, 144.1, 147.0; IR (thin film): 3272, 3081, 2984, 2923, 2851, 1736, 1667, 1597, 1348, 1163 cm^{-1}; MS (EI): m/z (%)=263 (27.9), 222 (15.5), 155 (28.0), 108 (100.0).

4.4.6. 3-Methylene-2-pentyl-1-tosyl-4-vinylpyrrolidine 18b. *N*-((*E*)-4-Bromobut-2-enyl)-*N*-tosyloct-1-yn-3-amine **13b** (206 mg, 0.5 mmol), indium powder (57 mg, 0.5 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react and then worked up according to the general procedure. Chromatography on silica (hexane/EtOAc 4:1) gave the desired pyrrolidine **18b** as a 14:1 mixture of diastereomers as a clear colourless oil (139 mg, 83%). *Data for major isomer*. ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 0.86 (3H, t, J=6.8 Hz), 1.16–1.80 (8H, m), 2.42 (3H, s), 2.63 (1H, br dd, J=6.5, 10.1 Hz), 3.05 (1H, dd, J=10.3, 12.2 Hz), 3.74 (1H, dd, J=8.4, 12.2 Hz), 4.25 (1H, br m), 4.80 (1H, s), 4.88 (1H, s), 4.93 (1H, d, J=17.3 Hz), 5.07 (1H, d, J=10.2 Hz), 5.45 (1H, ddd, J=8.1, 10.2, 17.3 Hz), 7.28 (2H, d, J=8.2 Hz), 7.71 (2H, d, J=8.2 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.5, 21.9, 22.9, 24.7, 32.2, 36.0, 47.9, 52.6, 63.8, 108.4, 118.3, 127.7, 130.1, 136.3, 136.5, 143.8, 152.1; IR (thin film): 3080, 2953, 2929, 1653, 1640 cm^{-1}; MS (CI): m/z (%)=351 (32.5) [MNH$_4^+$], 334 [MH$^+$] (100.0).

4.4.7. *N*-*tert*-Butoxycarbonyl(3-methylene-4-vinylpyrrolidine) 18c. *N*-(*tert*-Butoxycarbonyl)-(*E*)-4-bromobut-2-enylprop-2-ynylamine **13c** (864 mg, 3 mmol), indium powder (342 mg, 3 mmol) in 1:1 THF/H_2O (6 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/EtOAc 10:1) gave the *N*-protected pyrrolidine **18c** as a clear colourless oil (430 mg, 69%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.45 (9H, s), 3.13 (1H, m), 3.30 (1H, br m), 3.75 (1H, m), 4.01 (1H, br d, J=18.7 Hz), 4.08 (1H, br d, J=18.3 Hz), 4.90 (1H, s), 5.00 (1H, br s), 5.14 (2H, m), 5.65 (1H, ddd, J=8.6, 10.3, 16.3 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.7 (rotamer), 47.5 (rotamer), 48.2 (rotamer), 50.6 (rotamer), 50.9 (rotamer), 51.2 (rotamer), 51.7 (rotamer), 79.8, 107.6 (rotamer), 107.8 (rotamer), 117.9, 136.8, 147.9 (rotamer), 148.8 (rotamer), 154.8; IR (thin film): 3466, 3081, 2977, 2868, 1701, 1644 cm^{-1}; MS (EI): m/z (%)=209 (2.2) [M$^+$], 154 (22.1), 108 (43.5), 79 (30.2), 57 (100.0).

4.4.8. *N*-(Benzyloxycarbonyl(3-methylene-4-vinylpyrrolidine)) 18d. *N*-(Benzyloxycarbonyl)-(*E*)-4-bromobut-2-enylprop-2-ynylamine **13d** (626 mg, 1.94 mmol), indium powder (221 mg, 1.94 mmol) in 1:1 THF/H_2O (3 mL) were reacted together and worked up according to the general procedure. Chromatography on silica (hexane/EtOAc 5:1) gave the *N*-protected pyrrolidine **18d** as a clear colourless oil (310 mg, 66%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 3.24 (1H, bs dd, J=8.6, 10.2 Hz), 3.34 (1H, m), 3.85 (1H, br dd, J=8.7, 9.7 Hz), 4.08 (2H, m), 4.95 (1H, br s), 5.06 (1H, br d, J=14.9 Hz), 5.16 (4H, m), 5.68 (1H, br m),7.35 (5H, br m); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 47.4 (rotamer), 48.2 (rotamer), 50.7 (rotamer), 51.1 (rotamer), 51.5 (rotamer), 51.7 (rotamer), 67.2 (rotamer), 67.5 (rotamer), 108.2, 118.2 (rotamer), 119.1 (rotamer), 128.3 (rotamer), 123.4 (rotamer), 128.8 (rotamer), 128.9 (rotamer), 136.5 (rotamer), 137.2 (rotamer), 155.1; IR (thin film): 3080, 2979, 2948, 2867, 1953, 1704, 1542 cm^{-1}; MS (EI): m/z (%)=242 (14.8), 230 (6.5), 198 (8.6), 152 (48.7), 91 (100.0).

4.4.9. Dimethyl 3-methylene-4-vinylcyclopentane-1,1-dicarboxylate 10a. (*E*)-2-(4-Bromobut-2-enyl)-(2-prop-2-ynyl)-malonic acid dimethyl ester **9a** (451 mg, 1.5 mmol), indium powder (171 mg, 1.5 mmol) in 1:1 THF/H_2O (1.5 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/EtOAc 3:1) gave the cyclised product **10a** as a clear colourless oil (249 mg, 74%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.01 (1H, dd, J=11.0, 13.0 Hz), 2.57 (1H, dd, J=8.0, 13.0 Hz), 2.95

(1H, ddd, J=3.0, 6.0, 18.0 Hz), 3.08 (1H, br d, J=18.0 Hz), 3.17 (1H, m), 3.73 (3H, s), 3.75 (3H, s), 4.82 (1H, s), 4.98 (1H, s), 5.05 (1H, br s), 5.08 (1H, m), 5.64 (1H, ddd, J=8.0, 10.5, 13.0 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 40.7, 48.1, 53.2, 53.2, 58.9, 108.6, 116.5, 139.4, 150.8, 172.4, 172.6; IR (thin film): 3660, 3471, 3078, 2953, 1731, 1714, 1659, 1642 cm^{-1}; MS (FAB): m/z (%)=225 (73.2) [MH$^+$], 193 (36.5), 165 (65.1), 154 (74.3), 137 (68.1), 136 (61.7), 105 (100), 91 (49.7), 77 (49.1).

4.4.10. Diethyl 3-methylene-4-vinylcyclopentane-1,1-dicarboxylate 10b. (*E*)-2-(4-Bromobut-2-enyl)-(2-prop-2-ynyl)-malonic acid diethyl ester **9b** (660 mg, 2 mmol), indium powder (228 mg, 2 mmol) in 1:1 THF/H_2O (2 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/Et_2O 10:1) gave the cyclised product **10b** as a clear colourless oil (360 mg, 71%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.25 (3H, m), 2.05 (1H, dd, J=10.8, 12.9 Hz), 2.58 (1H, dd, J=8.0, 12.9 Hz), 2.93 (1H, ddd, J=2.9, 6.0, 17.8 Hz), 3.09 (1H, br d, J=17.8 Hz), 3.18 (1H, m), 4.19 (2H, m), 4.83 (1H, s), 4.99 (1H, s), 5.06 (1H, br s), 5.11 (1H, m), 5.64 (1H, ddd, J=8.0, 10.3, 12.9 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.4, 40.6, 48.1, 58.9, 61.9, 108.4, 116.4, 139.6, 151.0, 171.9, 172.2; IR (thin film): 3079, 2982, 1732, 1658, 1640 cm^{-1}. MS (FAB): m/z (%)=253 (2.3) [MH$^+$], 252 (4.5), 207 (10.1), 178 (57.8), 105 (100.0).

4.4.11. Ethyl-*tert*-butyl 3-methylene-4-vinylcyclopentane-1,1-dicarboxylate 10c. (*E*)-Ethyl-*tert*-butyl-2-(4-bromobut-2-enyl)-(2-prop-2-ynyl)-malonate diethyl ester **9c** (344 mg, 1 mmol), indium powder (114 mg, 1 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/Et_2O 10:1) gave the cyclised product **10b** as a 1:1 mixture of diastereomers in the form of a clear colourless oil (150 mg, 56%). ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.45 (4.5H, s, diastereotopic), 1.46 (4.5H, s, diastereotopic), 1.98 (1H, m, two diastereomers), 2.53 (1H, m, two diastereomers), 2.96 (1H, ddd, J=3.0, 5.9, 17.8 Hz, two diastereomers), 3.11 (1H, br d, J=17.8 Hz, two diastereomers), 3.16 (1H, br m, two diastereomers), 3.73 (1.5H, s, diastereotopic), 3.75 (1.5H, s, diastereotopic), 4.81 (1H, s, two diastereomers), 4.98 (1H, s, two diastereomers), 5.06 (1H, br s, two diastereomers), 5.09 (1H, m, two diastereomers), 5.66 (1H, ddd, J=7.9, 8.2, 13 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.17, 28.19, 40.51, 40.55, 48.03, 48.15, 52.88, 52.93, 59.58, 59.76, 82.14, 108.22, 116.25, 116.33, 139.65, 151.15, 151.19, 170.84, 171.08, 172.76, 173.00; IR (thin film): 3079, 2980, 1731, 1658, 1640 cm^{-1}. MS (FAB): m/z (%)= 284 (52.7) [MNH$_4^+$], 267 (14.4), 228 (100.0), 211 (12.1).

4.4.12. Methyl 3-methylene-1-(phenylsulfonyl)-4-vinylcyclopentanecarboxylate 10e. (*E*)-Methyl 6-bromo-2-(phenylsulfonyl)-2-(prop-2-ynyl)hex-4-enoate **9e** (258 mg, 0.67 mmol), indium powder (100 mg, 0.87 mmol) in 1:1 THF/H_2O (1.5 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/EtOAc 3:1) gave the cyclised product **10b** as a 4.5:1 mixture of diastereomers in the form of a clear colourless oil (91 mg, 44%):^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.23 (1H, m, minor), 2.29 (1H, dd, J=12.2, 12.3 Hz, major), 2.59 (1H, ddd, J=1.6, 7.2, 12.5 Hz, major), 2.80 (1H, dd, J=8.6, 14.4 Hz, minor), 2.99 (1H, br m, major), 3.08 (1H, br d, J=18.7 Hz, minor), 3.14 (1H, br d, J=18.2 Hz, major), 3.21 (1H, d, J=18.7 Hz, major), 3.23 (1H, br d, J=18.2 Hz, minor), 3.39 (1H, m, minor), 3.62 (3H, s, minor), 3.66 (3H, s, major), 4.84 (1H, br s two diastereomers), 5.00 (1H, br s, two diastereomers), 5.04 (1H, br s, two diastereomers), 5.07 (1H, m, two diastereomers), 5.54 (1H, ddd, J=8.2, 9.9, 15.9 Hz, minor), 5.64 (1H, ddd, J=8.1, 10.2, 13.0 Hz, major), 7.54 (2H, dd, J=7.5, 8.0 Hz, two diastereomers), 7.67 (1H, dd, J=7.4, 7.6 Hz, two diastereomers), 7.82 (2H, dd, J=7.2, 7.5 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 38.1 (major), 38.3 (two diastereomers), 38.5 (minor), 47.6 (minor), 48.1 (major), 53.6 (minor), 53.8 (major), 77.3 (major), 77.7 (minor), 109.3 (minor), 109.8 (major), 129.3 (major), 130.0 (major), 130.3 (minor), 134.6 (major), 134.7 (minor), 136.6 (minor), 137.2 (major), 138.5 (major), 138.8 (minor), 148.5 (major), 149.3 (minor), 168.8 (major), 169.1 (minor); IR (thin film): 3077, 2952, 1977, 1910, 1737, 1658, 1639 cm^{-1}; MS (FAB): m/z (%)=324 (100.0) [MNH$_4^+$].

4.4.13. Ethyl 1-(dimethylcarbamoyl)-3-methylene-4-vinylcyclopentanecarboxylate 10f. (*E*)-Ethyl 2-(dimethylcarbamoyl)-6-bromo-2-(prop-2-ynyl)hex-4-enoate **9f** (330 mg, 1 mmol), indium powder (114 mg, 2 mmol) in 1:1 THF/H_2O (1.5 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/Et_2O 3:1 gradient to 1:1) gave the cyclised product **10e** as a 1.3:1 mixture of diastereomers as a clear colourless oil (210 mg, 84%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.23 (3H, t, J=7.2 Hz, diastereotopic), 1.92 (1H, dd, J=11.3, 12.6 Hz, major), 2.23 (1H, dd, J=11.5, 13.2 Hz, minor), 2.40 (1H, dd, 7.7, 13.2 Hz, minor), 2.58 (1H, dd, J=7.8, 12.6 Hz, major), 2.80 (3H, br s, two diastereomers), 2.85 (1H, m), 2.94 (3H, br s, two diastereomers), 3.20 (1H, m, two diastereomers), 4.19 (2H, q, J=7.0 Hz, two diastereomers), 4.77 (1H, br s, two diastereomers), 4.92 (1H, br s, two diastereomers), 5.06 (1H, br s, two diastereomers), 5.09 (1H, m, two diastereomers), 5.66 (1H, ddd, J=8.5, 10.5, 13.3 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.6 (minor), 15.6 (major), 37.2 (broad, two diastereomers), 41.1 (minor), 41.5 (minor), 41.6 (major), 41.8 (major), 47.7 (minor), 48.6 (major), 57.7 (major), 58.0 (minor), 60.8 (major), 61.9 (minor), 107.4 (major), 107.6 (minor), 116.4 (minor), 116.6 (major), 139.4 (major), 139.6 (minor), 151.4 (minor), 151.6 (major), 170.6 (minor), 172.2 (major), 173.9 (major), 174.3 (minor); IR (thin film): 3501, 3077, 2980, 2934, 1729, 1650 cm^{-1}. MS (FAB): m/z (%)=269 (3.2) [MNH$_4^+$], 252 (100.0) [MH$^+$].

4.4.14. Ethyl 1-(pyrrolidinylcarbamoyl)-3-methylene-4-vinylcyclopentanecarboxylate 10g. (*E*)-Ethyl 2-(pyrrolidinylcarbamoyl)-6-bromo-2-(prop-2-ynyl)hex-4-enoate **9g** (355 mg, 1 mmol), indium powder (114 mg, 2 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react and worked up in accordance with the general procedure. Purification by chromatography on silica (hexane/EtOAc 3:2) gave the cyclised product **10f** as a 1:1 mixture of diastereomers as a clear colourless oil (212 mg, 77%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.26 (3H, m, diastereotopic), 1.88 (4.5H, m, two

diastereomers), 1.96 (1H, dd, $J=11.0$, 12.9 Hz, diastereomer), 2.21 (1H, dd, $J=11.6$, 13.1 Hz, diastereomer), 2.47 (1H, dd, $J=7.3$, 12.9 Hz, diastereomer), 2.62 (1H, dd, $J=8.0$, 13.0 Hz, diastereomer), 3.00 (1H, dd, $J=2.2$, 16.8 Hz, diastereomer), 3.25 (3H, m, diasteromers), 4.21 (2H, m, two diastereomers), 4.79 (1H, br s, two diastereomers), 4.95 (1H, br s, two diastereomers), 5.06 (1H, br s, two diastereomers), 5.12 (1H, m, two diastereomers), 5.66 (1H, ddd, $J=8.5$, 10.5, 13.1 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.6 (two diastereomers), 26.0 (rotamer), 28.93 (rotamer), 42.6 (diastereomer), 42.9 (diastereomer), 43.2 (diastereomer), 43.3 (diastereomer), 48.5 (diastereomer and rotamer), 48.6 (diastereomer and rotamer), 49.5 (diastereomer and rotamer), 49.6 (diastereomer and rotamer), 49.9 (diastereomer), 50.6 (diastereomer), 60.6 (diastereomer), 61.0 (diastereomer), 63.9, 109.4 (diastereomer), 109.7 (diastereomer), 118.3 (diastereomer), 118.6 (diastereomer), 141.6 (diastereomer), 141.8 (diastereomer), 153.6 (diastereomer), 153.9 (diastereomer), 171.1 (diastereomer), 171.5 (diastereomer), 176.1 (diastereomer); IR (thin film): 3076, 2977, 2877, 1730, 1637 cm^{-1}; MS (FAB): m/z (%)=278 (100.0) [MH$^+$], 179 (5.6).

4.4.15. Ethyl 1-(morpholinocarbamoyl)-3-methylene-4-vinylcyclopentanecarboxylate 10h. (*E*)-Ethyl 2-(morpholinocarbamoyl)-6-bromo-2-(prop-2-ynyl)hex-4-enoate **9h** (323 mg, 0.868 mmol), indium powder (100 mg, 0.877 mmol) in 1:1 THF/H_2O (0.8 mL) reacted and worked up following the general procedure. Purification by on silica (hexane/EtOAc 2:1) gave the carbocyclic product **10g** as a 1:1 mixture of diastereomers as a clear colourless oil (159 mg, 63%) which crystallised on standing (mp 87.7–89.4 °C): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.28 (3H, m, diastereotopic), 1.95 (1H, dd, $J=11.4$, 12.4 Hz, major), 2.27 (1H, dd, $J=11.4$, 13.2 Hz, minor), 2.42 (1H, dd, $J=7.6$, 13.2 Hz, minor), 2.62 (1H, dd, $J=7.8$, 12.6 Hz, diastereomer), 3.00 (1H, dd, $J=2.2$, 16.8 Hz, diastereomer), 3.21 (1H, br m, diastereomers, 3.30 (3H, br m, diastereomers), 3.66 (6H, br s, diasteromers), 4.23 (2H, m, two diastereomers), 4.81 (1H, br s, two diastereomers), 4.96 (1H, br s, two diastereomers), 5.08 (1H, br s, two diastereomers), 5.13 (1H, m, two diastereomers), 5.66 (1H, ddd, $J=8.3$, 10.7, 15.0 Hz, two diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 14.6 (two diastereomers), 41.1 (diastereomer), 41.4 (diastereomer), 41.6 (diastereomer), 41.8 (diastereomer), 47.6 (diastereomer), 48.6 (diastereomer), 57.6 (diastereomer), 57.9 (diastereomer), 62.2 (two diastereomers), 66.0–68.0 (broad peak, diasteromers and rotamers), 107.8 (diastereomer), 107.9 (diastereomer), 116.6 (diastereomer), 116.8 (diastereomer), 139.2 (diastereomer), 139.4 (diastereomer), 151.0 (diastereomer), 151.2 (diastereomer), 169.6 (diastereomer), 169.9 (diastereomer), 173.8 (diastereomer), 174.2 (diastereomer); IR (thin film): 3076, 2978, 2919, 2856, 1730, 1653 cm^{-1}; MS (EI): m/z (%)=293 (47.8) [M$^+$], 239 (64.2), 220 (100.0, 205 (25.1), 179 (13.8), 133 (28.4).

4.4.16. 3-Methylene-4-vinylcyclopentane-1,1-dicarbonitrile 10i. 2-((*E*)-4-Bromobut-2-enyl)-2-(prop-2-ynyl)-malononitrile **9i** (236 mg, 1 mmol), indium powder (114 mg, 1 mmol) in 1:1 THF/H_2O (1 mL) were allowed to react according to the general procedure. Mild acidic work-up and purification by chromatography on silica (hexane/EtOAc 10:1) gave the carbocyclic product **10i** as a light yellow oil (78 mg, 49%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.25 (3H, m), 2.22 (1H, dd, $J=10.7$, 13.1 Hz), 2.76 (1H, dd, $J=7.7$, 13.1 Hz), 3.11 (1H, d $J=17.9$ Hz), 3.25 (1H, br d, $J=17.9$ Hz), 3.42 (1H, m), 5.08 (1H, br s), 5.23 (1H, m), 5.67 (1H, ddd, $J=8.2$, 9.3, 16.5 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 32.6, 44.2, 44.7, 47.0, 112.7, 116.1, 116.3, 118.7, 136.8, 145.2; IR (thin film): 3084, 2985, 2252, 1849, 1660, 1640 cm^{-1}; MS (FAB): m/z (%)=158 (100) [M$^+$], 143 (30.4), 130 (56.9), 116 (66.0), 104 (21.5), 79 (85.5).

4.4.17. (*E*)-Dimethyl 3-ethylidene-4-vinylcyclopentane-1,1-dicarboxylate 30. Dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(but-2-ynyl)malonate **25** (316 mg, 1 mmol) and indium powder (114 mg, 1mmol) were placed in a round-bottomed flask under N_2 and dry DMF (1 mmol) was added. The mixture was heated at 100 °C for 1.25 h and then allowed to cool. The mixture was partitioned between 2 M HCl and diethyl ether and the aqueous layer was extracted with Et_2O (2×10 mL) and the combined organics were washed with water (2×10 mL), saturated aqueous NaCl (10 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography on silica (hexane/EtOAc, 6:1) to give the carbocyclic product **30** (154 mg, 65%) as a clear colourless oil as essentially a single diastereomer: ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.60 (3H, d, $J=6.7$ Hz), 1.95 (1H, dd, $J=11.5$, 12.8 Hz), 2.53 (1H, ddd, $J=1.6$, 8.7, 12.9 Hz), 2.84 (1H, d, $J=17.2$ Hz), 3.02 (1H, d, $J=17.3$ Hz), 3.09 (1H, m), 3.73 (3H, s), 3.75 (3H, s), 5.01 (2H, m), 5.2 (1H, m), 5.56 (1H, ddd, $J=8.3$, 11.2, 15.8 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 15.0, 37.2, 40.9, 48.2, 53.2, 53.2, 59.0, 116.3, 118.4, 140.0, 141.6, 172.6, 172.7; IR (thin film): 2954, 1716, 1661, 1644 cm^{-1}; MS (CI): m/z (%)=256 (100.0) [MNH$_4^+$], 239 [MH$^+$] (48.0).

4.4.18. (*E*)-Dimethyl 3-benzylidene-4-vinylcyclopentane-1,1-dicarboxylate 31. Dimethyl 2-((*E*)-4-bromobut-2-enyl)-2-(3-phenylprop-2-ynyl)malonate **26** (379 mg, 1 mmol) and indium powder (114 mg, 1 mmol) were placed in a round-bottomed flask and placed under a nitrogen atmosphere, Dry DMF (1 mmol) was added and the mixture was heated at 100 °C for 70 min and then allowed to cool. The mixture was partitioned between 2 M HCl and diethyl ether and the aqueous layer was extracted with Et_2O (2× 10 mL) and the combined organics were washed with water (10 mL), saturated aqueous NaCl (10 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave a residue which was purified by chromatography on silica (hexane/EtOAc, 5:1) to give the carbocyclic product **31** (258 mg, 85%) as a clear colourless oil as a 3.6:1 mixture of diastereomers: ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 1.94 (1H, d, $J=11.6$, 12.7 Hz, major), 2.15 (1H, dd, $J=4.4$, 8.7 Hz, minor), 2.54 (1H, ddd, $J=1.5$, 10.4, 12.8 Hz, major), 2.65 (1H, dd, $J=8.7$, 13.2 Hz, minor), 3.14 (1H, br d, $J=2.7$, 17.8 Hz, two diastereomer), 3.26 (1H, m, two diastereomers), 3.33 (1H, br d, $J=17.8$ Hz, major), 3.65 (3H, s, minor), 3.66 (6H, s, two diastereomers), 3.68 (3H, s, major), 4.92–5.10 (3H, m, two diastereomers), 5.62 (1H, ddd, $J=8.3$, 9.4, 17.6 Hz, major), 5.74 (1H, m, minor), 6.13 (1H, br s, major), 6.41 (1H, br s, minor), 7.18–7.28 (5H, m, two

diastereomers); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 39.1 (major), 40.0 (minor), 41.3 (minor), 43.2 (major), 44.4 (minor), 50.0 (major), 53.1 (minor), 53.2 (two diastereomers), 53.3 (major), 58.2 (minor), 60.0 (major), 115.4 (diastereomer), 15.6 (diastereomer), 117.1 (diastereomer), 124.3 (diastereomer), 125.1 (diastereomer), 126.7 (diastereomer), 126.8 (diastereomer), 128.4 (diastereomer), 128.5 (diastereomer), 128.6 (diastereomer), 128.8 (diastereomer), 132.0 (diastereomer), 138.0 (major), 138.8 (minor), 139.5 (major), 142.3 (minor), 143.5 (major), 172.2 (diastereomers), 172.3 (diastereomer); IR (thin film): 2952, 2843, 1732, 1635 cm^{-1}; MS (EI): *m/z* (%)=300 (30.6) [M^+], 240 (100.0), 181 (93.7).

4.4.19. (*E*)-Dimethyl 3-((methoxycarbonyl)methylene)-4-vinylcyclopentane-1,1-dicarboxylate 32. (*E*)-Trimethyl 8-bromooct-6-en-1-yne-1,4,4-tricarboxylate **27** (114 mg, 0.32 mmol) and indium powder (36 mg, 0.32 mmol) in THF/H_2O (1:1) were allowed to react together and worked up in accordance with the general procedure. Purification of the crude reaction mixture on silica (hexane/EtOAc 2:1) gave the desired cyclic triester **32** as a clear, colourless oil (58 mg, 65%) as essentially a single diastereomer. *Data for major diastereomer*. ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 2.01 (1H, dd, J=12.6, 12.7 Hz),2.59 (1H, dd, J=7.3, 12.9 Hz), 3.34 (2H, m), 3.69 (3H, s), 3.74 (3H, s), 3.75 (3H, s), 5.16 (2H, m), 5.57 (1H, ddd, J=8.2, 10.1, 16.9 Hz), 5.67 (1H, s); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 39.7, 40.6, 50.1, 51.5, 53.3, 53.4, 59.1, 114.4, 118.7, 137.5, 165.0, 167.2, 172.0, 172.3; IR (thin film): 2998, 2953, 1737, 1659, 1640 cm^{-1}; MS (EI): *m/z* (%)=282 (8.9) [M^+], 250 (98.7), 223 (47.5), 188 (100.0), 162 (47.9), 131 (22.7), 102 (36.5).

4.4.20. 3-Benzylidene-tetrahydro-4-vinylfuran 33. 1-(3-((*E*)-4-Bromobut-2-enyloxy)prop-1-ynyl)benzene (264 mg, 1 mmol) and indium powder (114 mg) in THF/H_2O (1:1) were reacted together and worked up in accordance with the general method. Purification of the crude reaction mixture on silica (hexane/EtOAc 10:1) gave the desired vinylic furan **33** as essentially a single diastereomer as a yellowish oil (56 mg, 30%): ^{1}H NMR (360.13 MHz, $CDCl_3$) δ 3.32 (1H, m), 3.93 (1H, dd, J=1.9, 11.2 Hz), 4.00 (1H, dd, J=1.9, 11.2 Hz), 4.32 (1H, dd, J=2.3, 16.1 Hz), 4.42 (1H, dd, J=2.1, 16.1 Hz), 4.94 (1H, d, J=17.2 Hz), 5.01 (1H, d, J=10.3 Hz), 5.79 (1H, ddd, J=7.8, 10.3, 17.2 Hz), 7.30 (5H, m); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 47.7, 59.6, 71.3, 117.8, 118.9, 127.9, 128.5, 128.8, 128.9, 132.2, 136.6, 137.7, 139.9; IR (thin film): 3400, 3057, 2851, 1954, 1883, 1725, 1693, 1659 cm^{-1}; MS (CI): *m/z* (%)=228 (100.0) [$MNaNH_4^+$], 193 (26.3), 165 (54.1).

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Supplementary data

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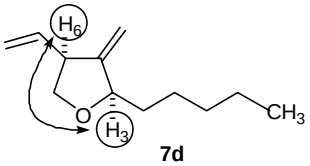

7d

28. It is postulated that these products occur from attack of one of the esters at the S_N2' site of the bromoallyl fragment followed by $A_{AL}1$-type, and/or similar loss of the *tert*-butyl group mediated by Lewis acidic indium salts generated in the reaction.
29. The crude reaction mixtures from the carbocyclisation reactions typically contained 5–10% of the corresponding proteodebrominated product.
30. Full crystallographic data is presented in the Supporting Information supplied with the present paper. Alernatively, crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 279213. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or deposit@ccdc.cam.ac.uk].
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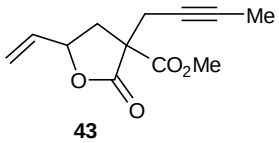

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