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A novel atom-transfer cyclisation catalysed by indium metal in halogenated solvents

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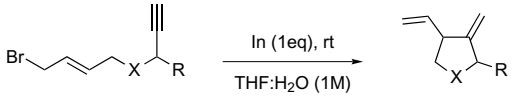
Abstract—Treatment of tethered alkyne–allyl halides **1a–d** with indium metal in halogenated solvents affords carbocyclic vinyl halides (**3a–d**) via a novel atom-transfer reaction. The reactions are operationally facile and proceed smoothly at room temperature even with sub-stoichiometric quantities of the metal. Use of a halogenated solvent containing a different halide than that contained in the substrate affords a mixture of products arising from intramolecular halide transfer and abstraction of a halide atom from solvent.

In recent years, use of indium in organic synthesis has attracted a great deal of attention.[1] As well as indium-mediated Barbier reactions of allyl- and propargyl indium reagents with a wide range of C=O and C=NR derived functional groups,[2] Reformatsky[3] reactions, Michael additions[4] and the addition of allyl indium species to alkynes[5] and nitriles[6] have been reported. Additionally, the low first ionisation potential of indium (5.8 eV) has led to the metal being used in dissolving metal reductions,[7] and to promote SET addition reactions[8] and atom-transfer reactions.[9]

We recently disclosed the first example of an intramolecular carboindination reaction of alkynes by allyl halides with indium metal in aqueous solvent systems to give unsaturated carbocycles and heterocycles (Scheme 1).[10]



1 **2**

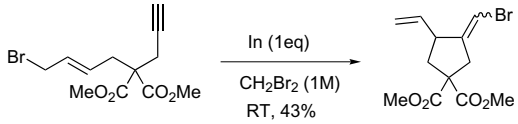
X=O, NR, $C(CO_2Me)_2$, $C(CN)_2$
R=H, ^{n}Pr, ^{n}Pent

49-74%

Scheme 1.

We now report a novel atom-transfer cyclisation reaction of alkynes and allyl halides mediated by indium metal in halogenated solvents, which leads to the formation of carbocyclic and vinyl halides.

As part of our investigations into cyclisation reactions mediated by metallic indium, we examined the fundamental reactivity of tethered alkyne–allyl halides **1** in a wide range of aqueous and nonaqueous solvent systems. During these studies we found that stirring a mixture of (*E*)-2-(4-bromobut-2-enyl)-(2-prop-2-ynyl)-malonic acid dimethyl ester **1a** and indium powder[11] in dibromomethane[12] at room temperature for 16 h followed by work-up and purification, afforded dimethyl 3-(bromomethylene)-4-vinylcyclopentane-1,1-dicarboxylate **3a** smoothly in 43% yield as an inseparable mixture approximately 6.5:1 of (*E*) and (*Z*) isomers[13] (Scheme 2).[14] Inspection of the ^{1}H NMR spectrum of the crude reaction mixture did not reveal the presence of any other organic products.[15]



1a **3a**

(*E*):(*Z*) 6.5:1

Scheme 2.

Keywords: Indium metal; Atom transfer; Cyclisation reaction; Halogenated solvent.
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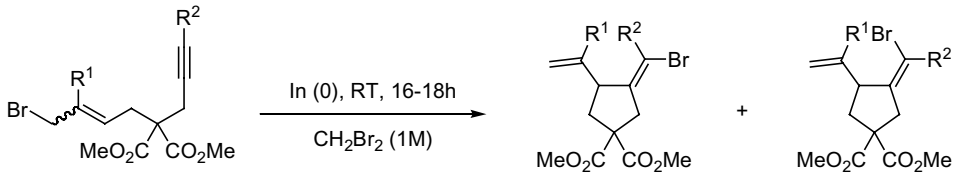
Table 1. Scope of the atom-transfer carbocyclisation reaction mediated by indium



1a-d **3a-d** (*E*) **3a-d** (*Z*)

Entry	Substrate	R[1a]	R[2]	In (equiv)	Ratio (*E*):(*Z*)	Isolated yield[c] (%)
1	**1a**	H	H	1	6.5:1	42
2	**1b**	H[b]	H	1	10:1	46
3[b]	**1a**	H	H	0.1	5.1:1	43
4	**1a**	H	H	0	—	0
5	**1a**	H	H	Zn metal (1 equiv)	—	0
6	**1c**	H	Me	1	>20:1	50
7	**1c**	H	Me	0.1	>20:1	43
8	**1d**	Me	H	1	3:1	8

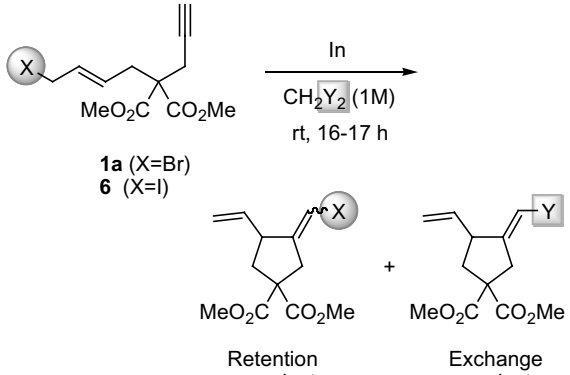
[a] Allyl halide (*E*) geometry unless otherwise stated.
[b] Allyl halide (*Z*)/(*E*) ratio (10:1).
[c] Combined yield of both regioisomers.

Under these conditions therefore, activation of the substrate with In(0) results in ring closure to the carbocycle with concomitant transfer of the bromine atom. The reaction proceeds equally efficiently in the light or with light excluded. To the best of our knowledge this reaction represents the first reported example of an atom-transfer cyclisation of allylic halides onto alkynes.[16] We next probed the scope of the reaction by the synthesis of a range of tethered allyl alkynes **1a**–**d** and submitted them to the reaction conditions (Table 1). It was found that varying the geometry of the allylic bromide from *E* (entry 1) to *Z* (entry 2) had little discernable effect on the efficiency of the reaction, although the stereoselectivity of product formation was slightly improved. More significantly, use of sub-stoichiometric quantities of indium (entry 3) did not have any deleterious affect on yield, although the reaction did not proceed in the absence of indium (entry 4) or with powdered zinc metal (entry 5). Furthermore, the atom-transfer cyclisation reaction still proceeds smoothly with simple nonterminal alkynes in the presence of stoichiometric (entry 6) or sub-stoichiometric quantities of indium (entry 7). However, use of trisubstituted allyl bromides dramatically reduced the efficiency of the reaction (entry 8).[17] Thus the reactions proceed to give a single class of organic product with good levels of and the same sense of stereoselectivity of Br incorporation. They are convenient and operationally simple to set up, and are distinguished by the fact that they proceed very cleanly. Therefore the relatively modest chemical yield obtained is somewhat surprising. However, it was observed that a considerably quantity of polymeric material is produced in the reaction in addition to the organic products. This could be easily separated from the crude product mixture but could not be characterised.

We next investigated whether the atom-transfer reaction would proceed in other halogenated solvents. Accordingly, a mixture of **1a** and indium (1 equiv) in CH_2Cl_2 was stirred at room temperature (16–17 h) and then worked-up in accordance with the general method (Table 2). Inspection of the ^1H NMR spectrum of the crude reaction mixtures of these reactions revealed the presence of two different chemical products bearing either a Br atom **3a** or a Cl atom **4** on the newly-formed trisubstituted alkene in a 1:3 ratio (entry 2). In addition to NMR data, formation of the mixture of products was confirmed by mass spectrometry (FAB), which clearly showed peaks corresponding to **3a** (*m*/*z* = 322, 320 $[MNH_4]^+$) and **4** (278, 276 $[MNH_4]^+$).

It is clear that in this case, activation of the substrate by indium followed by carbocyclisation produces an intermediate, which may further react to give the retention

Table 2. Cyclisation in other halogenated solvents



Entry	X	Y	Retention:exchange	Yield[a] (%)
1	Br	Br	— (**3a**)	42
2	Br	Cl	1:3.00 (**3a**:**4**)	76
3	Br	I	1:3.25 (**3a**:**5**)	43
4	I	Br	1:5.25 (**5**:**3a**)	75
5	I	I	— (**5**)	46

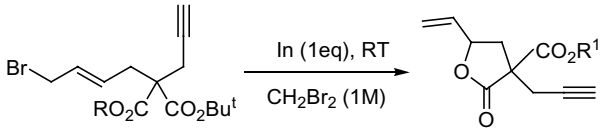
[a] Combined isolated yield of both regioisomers.

product in which the original Br is conserved by either intramolecular or intermolecular Br atom transfer; or which abstracts a Cl atom from the solvent to give the corresponding chlorinated exchange product. Gratifyingly the analogous reaction of **3a** and indium in CH_2I_2 gave a corresponding inseparable mixture of brominated retention product **3a** and iodinated exchange product **5** in 1:3.25 ratio (entry 3). The presence of the retention product **3a** in the crude reaction mixture was confirmed by ^{1}H NMR by adding an authentic sample of **3a**, which resulted in a clear rise in intensity in the peaks corresponding to the retention product. In analysing the product mixtures obtained from these reactions it is important to consider not only the ratio of retention and exchange products, but also to note the (*E*):(*Z*) ratio in which they are formed. As far as can be ascertained from the inspection of ^{1}H NMR spectra the *exchange products* **4** and **5** (entries 2 and 3) were obtained only as the (*E*) isomer (assigned by NOESY spectroscopy) whereas the *retention product* **3a** was produced as a mixture of (*E*):(*Z*) isomers. Furthermore the retention products were observed to be present in approximately (*E*):(*Z*) 1.5:1 ratio, which is in sharp contrast to the 6.5:1 ratio typically observed when the reaction was carried out in dibromomethane. One possible explanation is that the (*E*) halogenated products arise from (i) intermolecular abstraction of halogen from solvent (exchange product) and (ii) intermolecular capture of Br from a mixed dihalide species such as CH_2ClBr generated during the reaction (retention product (*E*) isomer); whereas the (*Z*) isomer of the retention product arises from *intramolecular* transfer of Br atom within a molecule of starting material.

We also examined the effect of halide precursor on the fate of the reaction. To this end we stirred (*E*-2-(4-iodobut-2-enyl)-(2-prop-2-ynyl)-malonic acid dimethyl ester **6** (prepared by treating **3a** with potassium iodide in acetone) with 1 equiv of indium metal in CH_2Br_2 and obtained a 1:5.25 mixture of iodinated retention product **5** and brominated exchange product **3a** in 75% total yield (entry 4). The retention product **5** was obtained as a mixture of (*E*) and (*Z*) isomers (2.10:1 ratio assigned by NOESY spectroscopy), however only the (*E*) version of the exchange product was formed. Mass spectrometry (CI) confirmed the formation of both iodo- and bromocarbocycles with peaks corresponding to **5** (m/z = 368 $[MNH_4]^+$) and **3a** (320 $[MNH_4]^+$). In an analogous reaction, stirring a mixture of **5** and indium metal (1 equiv) in diiodomethane (1 M) followed by work-up and chromatography gave the expected iodomethylene carbocycle **5** as a 26:1 mixture of (*E*) and (*Z*) isomers (as determined by ^{1}H and NOESY spectroscopy) (entry 5), along with a trace of the (*Z*) bromomethylene carbocycle arising, presumably, from cyclisation of small residual amounts of **3a** present in the allyl iodide starting material.

The reaction was also found to be sensitive to the type of the ester in the substrate. Whilst the atom-transfer reaction proceeded smoothly in the presence of methyl ester substituents to give the corresponding bromomethylene cyclopentane product **3a**, use of substrates bearing *tert*-butyl esters **7a**–**b**, led cleanly to the formation of lactones **8a**–**b** in good yield (Table 3).[18]

Table 3. Cyclisation of *tert*-butyl ester bearing substrates



7a (R=Me)
7b (R=Bu^t)

8a (R^1=Me)
8b (R^1=H)

Entry	R	R^1	Product	Yield[a] (%)	dr
1	Me	Me	**8a**	68	5.0:1
2	Bu^t	H	**8b**	72	5.5:1

[a] Combined yield of all diastereomers.

Whilst the mechanism of the lactonisation reaction is still not entirely clear, the formation of these products presumably arises from the loss of the *tert*-butyl ester catalysed by the action of a Lewis acidic In(I)/In(III) species produced during the reaction; followed by intramolecular attack of the resultant carboxylate on the allyl bromide functionality in an S_N2' fashion. It is notable that the reaction does not proceed in the absence of indium metal or in the presence of mineral acid alone (**1a**, TFA [50 mol%], CH_2Br_2).

In summary, we have discovered a novel indium-catalysed atom-transfer cyclisation of allyl halides onto alkynes in halogenated solvents. The protocol is convenient and operationally simple and provides rapid access to potentially useful halomethylene cyclopentanes. A detailed investigation of the mechanism of the reaction and efforts to extend this methodology to the synthesis of heterocycles are currently in hand.[19]

Acknowledgements

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11. Indium metal powder was obtained from Aldrich Chemical Co. (99.99% purity).
12. All halogenated solvents were of 99% purity or better and were used as obtained from commercial sources without any further purification or drying.
13. Estimated from ^{1}H NMR spectrum. *E*/*Z* assigned from NOESY spectroscopy.
14. *General procedure for the synthesis of dimethyl 3-(bromomethylene)-4-vinylcyclopentane-1,1-dicarboxylate* **3a**: (*E*-2-(4-bromo-but-2-enyl)-2-prop-2-ynyl-malonic acid dimethyl ester **1a** (303 mg, 1.0 mmol) and indium powder (114 mg, 1.0 mmol, 1 equiv) were placed into a 5 mL round-bottomed flask and dibromomethane (1 mL) was added. The suspension was stirred at room temperature for 16 h and then the reaction mixture was partitioned between Et_2O and 2 N $HCl_{(aq)}$. 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 (SiO_2, hexane–EtOAc, 4:1) to give the cyclised product **3a** (172 mg, 42%) as a clear slightly yellow oil ($R_f = 0.57$). ^{1}H NMR (360.13 MHz, $CDCl_3$) (major isomer): $\delta_H = 1.69$ (1H, dd, $J = 10.4$, 13.4 Hz), 2.39 (1H, dd, $J = 5.4$, 13.4 Hz), 2.75 (1H, d with fine coupling, $J = 17.8$ Hz), 2.85 (1H, br s), 3.03 (1H, br d, $J = 17.8$ Hz), 3.65 (3H, s), 3.69 (3H, s), 5.03 (2H, m), 5.61 (1H, ddd, $J = 7.0$, 10.2, 17.2 Hz), 5.87 (1H, br s) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): $\delta_C = 32.9$, 39.5, 38.8, 53.3, 53.4, 55.2, 115.1, 119.3, 130.6, 139.5, 170.7, 171.2 ppm. IR (thin film): 3470, 3080, 2954, 1737, 1652, 1632, 1434, 1251, 1199, 1139, 1085, 1058, 989, 923, 866, 822, 745 cm^{-1}. MS (FAB): *m*/*z* (%) = 305 (4), 304 (6), 303 (4), 302 (6), 273 (11), 271 (11) 245 (21), 244 (36), 243 (22), 242 (39), 223 (73.0), 185 (71), 183 (72), 163 (100).
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19. We are currently in the process of investigating the analogous reaction of tethered allyl halides and alkenes in halogenated solvents. The results of these studies will be communicated in due course.