Hydrodehalogenation of 1,1-dibromocyclopropanes by Grignard reagents promoted by titanium compounds †

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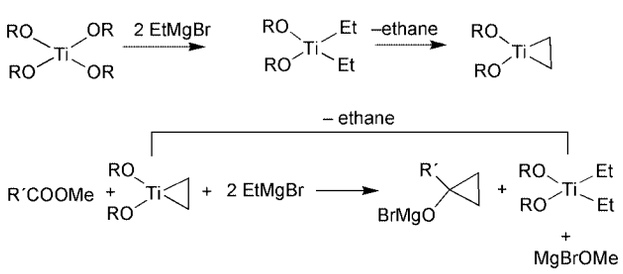
1,1-Dibromocyclopropanes are converted into the corresponding monobromocyclopropanes (as mixtures of stereoisomers where appropriate) by reaction with 1.0–1.3 mol equiv. of ethylmagnesium bromide and 2–10 mol% titanium isopropoxide for <1 h in ether at ambient temperature; in most cases examined, the yields were *ca.* 95%. With an excess of the Grignard reagent, the product is the non-halogenated cyclopropane (>90%). With ethylmagnesium bromide, the reaction occurs very slowly in the absence of catalyst; with methylmagnesium bromide, the reaction does occur in the absence of catalyst, but is only slightly promoted in the presence of titanium isopropoxide. Reactions with a number of other Grignard reagents are also discussed. In the case of phenethylmagnesium bromide, the major product containing the phenethyl-group is ethylbenzene, together with small amounts of styrene and ethyl 4-phenyl-2-butyl ether, a product of trapping of the solvent, ether. In other cases, relatively large amounts of a diether, formally derived by hydrogen abstraction adjacent to the ether oxygen followed by dimerisation, are isolated. No products were identified incorporating the cyclopropane and either the Grignard alkyl group or the solvent. Labelling studies indicate that the hydrogen introduced into the cyclopropane is not derived from either the α- or β-positions of the Grignard reagent. When the reduction is carried out with phenethylmagnesium bromide in d_8-tetrahydrofuran both monobromides contain deuterium.

1-Bromocyclopropanes have proved to be valuable precursors of a range of acyclic, carbocyclic and heterocyclic systems through reactions such as ring-opening, ring-enlargement and metallation. However, access to such monobromides is limited as few methods for the addition of monobromocarbene to alkenes are known.[1] Instead the monobromides are generally accessed either by Hunsdieker type reactions on cyclopropanecarboxylic acids or, generally more effectively, by hydrodebromination of readily available 1,1-dibromocyclopropanes.[2,3] This reduction of 1,1-dibromocyclopropanes to the corresponding monobromides has been known for many years and methods are available which allow the selective formation of either *exo*- or *endo*-monobromides.[3] One of the most frequently used reactions is the radical reduction using tri-*n*-butyltin hydride at about 40 °C;[4] where isomers are possible, the predominant monobromide is normally the *cis*- or *endo*-isomer. Other reagents such as, *e.g.*, zinc–ethanol–potassium hydroxide,[5,6] zinc–copper couple,[7] zinc–acetic acid,[8] *O*,*O*′-diethyl α-lithiomethylphosphonate,[9] photochemical[10] and electrochemical,[11,12] complex hydrides,[13] butyllithium followed by methanol,[14] and hydrogen and a catalyst[15] have also been reported. Reduction with sodium methyl sulfoxide in DMSO is also effective, but leads predominantly to *exo*-isomers.[16] Although these methods are all effective, they do suffer from disadvantages. For example, reduction with zinc in ethanol requires a rather tedious work-up, tri-*n*-butyltin hydride requires the removal of toxic organotin residues, and sodium methyl sulfoxide uses a reagent which is tedious to make and reaction conditions which require careful control. A recent method using low-valent vanadium and diethyl phosphonate or triethyl phosphite at room temperature can lead to very high stereoselectivities when isomeric monobromides can be produced; however, absolute isolated yields are rather variable and reaction times are quite long.[17]

A simple preparative method for hydrodebromination of dibromocyclopropanes

The cyclopropanation of esters by reaction with titanium isopropoxide and ethylmagnesium bromide discovered by Kulinkovich has proved to be extremely valuable.[18] This reaction has been explained in terms of a catalytic cycle involving the loss of ethane from the diethyltitanium species (Scheme 1).



Scheme 1

During the course of a study of this reaction with 2,2-dibromocyclopropanecarboxylates we found that the same combination of reagents is also extremely effective in bringing about the simple, clean and efficient conversion of 1,1-dibromo- and 1,1-dichlorocyclopropanes into the corresponding monohalides and of 1,1,2-tribromides into 1,2-dibromides;[19] we now present in full the results for the reduction of dibromides.

Reaction of dibromide **1a** with 1.3 mol equiv. of ethylmagnesium bromide and 2 mol% of titanium isopropoxide in

† Expanded versions of Tables 3, 4 and 6; Tables 7–10, 12; Scheme A; experimental details for a number of the syntheses and reactions described in the text; and additional spectroscopic data for known compounds are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/a9/a910317l/

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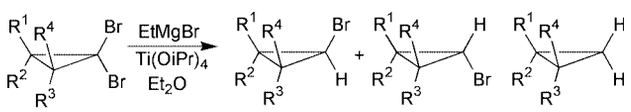
Table 1 Reduction of dibromocyclopropanes with EtMgBr and $Ti(O^iPr)_4$ in ether at ambient temperature

N[a]	Starting material	EtMgBr/ mol equiv.[b]	$Ti(O^iPr)_4$/ mol%	Time/min		GLC control[f]			Isolated yield (%)[c]		Ratio
				Addition	Stirring	**1**	**2** + **3**	**4**	**2** + **3**	**4**	**2**:**3**
1	**1a**	1.3	2	10	10	2	98	0	**94**		2.0:1
2	**1a**	1.2	22	30	10	6	90	0			2.0:1
		1.3		10	10	0	99	1	**92**		2.0:1
3	**1a**	1.3	2	10	10	1	98	<1	**92**[d]		2.0:1
4	**1a**	1.3	0.5	10	10	78	18	0			2.0:1
5	**1a**	2.0	10	40	10	0	56	40			—
		3.0		20	20	0	0	97		**93**	
6	**1b**	1.0	2	10	10	19	77	0			
		1.25		2	10	3	93	0	**90**		1:1.1
7	**1c**	1.0	5	20	10	18	82	[e]			—
		1.3		10	10	0	99	[e]	**85**		
8	**1d**	1.2	10	20	10	14	86	<1			
		1.4		5	10	0	99	<1	**90**		1:3.8
9	**1e**	1.0	2	20	50	26	65	1			
		1.4			30	4	88	1			
		1.5			10	0	88	1	**96**		1:2.5
10	**1f**	1.2	5	20	25	16	78	0			
		1.4			25	4	92	0			
		1.45			10	1	95	<1	**97**		1:1.7
11	**1g**	1.0	10	10	10	1	89	0	**96**		3.5:1
12	**1h**	1.0	2	10	10	0	97	0	**95**		3.5:1
13	**1i**	1.05	10	10	10	3	92	4	**95**		—

[a] Number of experiment (cross-referenced to Experimental section or to Supplementary Information). [b] Total Grignard reagent added within a single experiment number. [c] Monohydrodebrominated products after chromatography. [d] Distilled yield. [e] The percentage of **4c** could not be determined by GLC in this solvent. [f] GLC ratios are relative peak areas uncorrected for different responses; only products derived directly from **1a** are recorded.

ether for 20 min at 20 °C followed by quenching with water led to a 92% distilled yield of a 2:1 mixture of monobromides **2a** and **3a** respectively (see Table 1, entry 3).

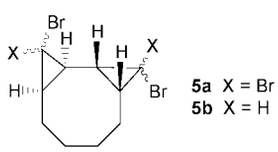


1 **2** **3** **4**

	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)
R^1	Me	H	Me	H	H	H	Octyl	Butyl	Br
R^2	Ph	Ph	Me	$-(CH_2)_2$	$-(CH_2)_3$	Hexyl	Br	Br	Br
R^3	H	H	H	$-(CH_2)_2$	$-(CH_2)_3$	H	H	H	Me
R^4	H	H	H	H	H	H	H	H	Me

Under these conditions, GLC showed 1% unreacted dibromide **1a**, and <1% of the completely reduced cyclopropane **4a**. However, 0.5 mol% of catalyst led to only an 18% reduction of the dibromide under the same conditions. Moreover with 10 mol% of catalyst and 3 mol equiv. of EtMgBr, complete debromination occurred in 90 min at 20 °C and **4a** was isolated (93%). Although Table 1 shows that the stereoselectivity of this reaction is relatively low, the method is of particular value in those cases where the desired monobromides are to be dehydrobrominated to provide cyclopropenes and the stereochemistry is not important.[20,21] The method was also successful using 10 mol% of titanium trichloride in dichloromethane as the catalyst, as seen in the reduction of **1b** to a 1:1.1 mixture of *trans*- and *cis*-isomers of monobromide in 88% yield using 1.7 mol equiv. of ethylmagnesium bromide and in the reduction of **1a** and **1c** to the corresponding monobromides using phenylmagnesium bromide and 8 mol%, or ethylmagnesium bromide and 5 mol% of titanium tetrachloride in ether (for details see Experimental part).

The reduction of the tetrabromide **5a** with 2.3 mol equiv. of ethylmagnesium bromide and 10 mol% of titanium isopropoxide in ether for 30 min at 20 °C was also successful, leading to a mixture of three isomeric dibromides **5b** [84% isolated



yield, 28 (*endo*,*endo*):8 (*endo*,*exo*):1 (*exo*,*exo*)] with only 2% of two tribromides. The *endo*,*endo*-isomer has previously been obtained by the addition of monobromocarbene to *endo*-9-bromobicyclo[6.1.0]non-2-ene.[22]

A particularly selective reaction occurred with the 1,1,2-tribromocyclopropanes **1g** or **1h**, leading to a mixture of isomeric 1,2-dibromides in 95% yield with less than 1% of either tribromide or further reduced material in the crude product, and no evidence for reduction of the 2-bromine to give a 1,1-dibromocyclopropane. Indeed, the tetrabromide **1i** was also cleanly converted into the tribromide **2i**, suggesting a considerable increase in the rate of reduction at C-1 caused by a halogen at C-2. Such 1,1,2-tribromo- or 1,1,2,2-tetrabromocyclopropanes are known to be hydrodebrominated by reaction with $LiAlH_4$, Bu_3SnH or $NaBH_4$–EtOH,[23] but with reagents such as diethyl phosphite and either triethylamine or sodium hydride they undergo efficient 1,2-dehalogenation.[24]

It is interesting to compare the ratio of isomers in the present reaction to those in reductions with other reagents. The stereoselectivities for reduction of four dibromides are therefore presented in Table 2.

It is important to note that although selectivities are rarely very high, there are some notable exceptions. Examples are

Table 2 Stereoselectivities of reduction of dibromocyclopropanes to monobromocyclopropanes

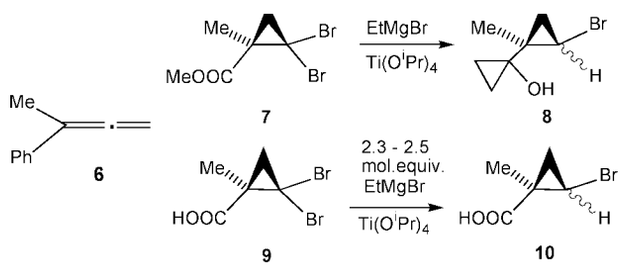
	Starting 1,1-dibromocyclopropanes			
	1a	**1b**	**1d**	2-Alkyl-...
Reagents	*cis*/*trans*- *or endo*/*exo*-ratio between products			
Bu_3SnH [a]	33:67 [d]	65:35 [29]	71:29 [4a]	68:32 (ethyl) [4f]
Zinc–ethanol–potassium hydroxide	50:50 [6]	71:29 [5]	72:28–74:26 [5]	
Zinc–ethanol–HCl [6]	50:50			
Zinc–copper couple, D_2O [7]			89:11 [b]	
Zinc–acetic acid [8]	50:50 [52]		100:0 [c]	
O,*O*′-Diethyl α-lithiomethylphosphonate [9]		21:79	10:90	21:79 (hexyl)
hv, $LiAlH_4$, ether [10,35]			75: 25–78:22 [35]	
Electrochemical DMF–LiCl MeOH–LiCl			53:47–61:39 [11,12] 66:34 [11]	
$NaAl(OCH_2CH_2OCH_3)_2H_2$ [13]		21:79	25:75	
Sodium methyl sulfoxide, DMSO [16]			1:99–10:90	
VCl_3–Zn–$P(OR)(OEt)_2$ [17]	90:10	95:5–90:10	99:1	
Butyllithium, EtOH [25]		0:100		19:81 (hexyl)
$^-PO(OMe)_2$, liq. ammonia [26]		4:96	0:100	5:95 (hexyl)
R_3ZnLi, −85 °C, AcOH, THF [30]		36:64		
$LiAlH_4$ [31]			75:25	
$LiAlH_4$, 1% $AgClO_4$ [32]		91:9	81:19	70:30 (propyl)
$Na_2S_2O_4$, aq. $NaHCO_3$, DMF, i-PrOH, water [33]		75:25	80:20	64:36 (butyl)
$Cr(OAc)_2$, DMSO [34]		83:17	91:9	37:63 (hexyl)
$RhCl_3$, $RhCl(PPh_3)_3$, $[RhCl(cod)_2]$, Na_2PdCl_4, i-PrOH, or $NaBH_4$ [37]	57:43	68:32–80:20		
$HPO(OEt)_2$, Et_3N [38]	29:71	25:75	12:88–20:80	65:35 (hexyl)
EtMgBr, $Ti(O^iPr)_4$ (this work)	33:67	52:48	79:21	63:37 (hexyl)

[a] The intermediate equilibrating *exo*- and *endo*-radicals are trapped highly stereoselectively in the presence of an electron poor alkene from the *exo*-face.[39] [b] >94% deuterated at position 7. [c] Only *endo*-bromide for **1d**, 90:10 for bicyclo[6.1.0]nonane. [d] The ratio in this reaction has been reported to be 67:33.[20b] When the reaction was repeated, the ratio reported above was obtained. The assignment of the stereochemistry of **2a** was therefore confirmed by oxidation to *trans*-2-bromo-1-methylcyclopropanecarboxylic acid and comparison of this with an authentic sample.[86]

reactions with an alkyllithium at low temperature where an intermediate organometallic species is protonated on work-up,[25] and, *e.g.*, reduction with $^-PO(OMe)_2$[26] or VCl_3–Zn–$P(OR)(OEt)_2$[17] which is thought to involve a reversible redox cycle involving low-valent vanadium and the formation of a cyclopropyl radical which is further reduced to the anion. It is also possible that the cyclopropane substituents play a key role in determining the selectivity; the effect of radical structure and interaction with a metal on stereochemistry and reactivity has been discussed in some detail;[27] for the 7-bromobicyclo-[4.1.0]heptan-7-yl radical, 78–80% of the *exo*-radical (*i.e.*, *endo*-bromine) is present at equilibrium.[28] The selectivity in the present method matches closely that in, *e.g.*, reduction with tri-*n*-butyltin hydride.

It should be noted that while the titanium catalysed reaction is very efficient using Grignard reagents, it is not successful using an alkyllithium. Thus reaction of **1a** in ether with 1 mol equiv. of *n*-butyllithium in hexane in the presence of 5 mol% of titanium isopropoxide at 20 °C for 1 h gave 1% of fully reduced cyclopropane, 69% of allene **6**, 19% of monobromides and 11% of starting material. A very similar mixture of products (1, 77, 21, 2% respectively) was obtained when the reaction was carried out at −90 °C for 1 h. The allene **6** is a typical product of the reaction of 1,1-dibromocyclopropanes with an alkyllithium, apparently through rearrangement of a cyclopropylidene or a related carbenoid.[40] However, titanium tetrabutoxide has been reported to promote the reduction of dibromocyclopropanes by diisobutylaluminium hydride in refluxing dioxane, leading to a mixture of monobromides and fully reduced cyclopropanes; unfortunately no isomer ratios are available from this work.[36]

The reaction of **7** with ethylmagnesium bromide and 10 mol% titanium isopropoxide led to a concurrent Kulinkovich reaction at the ester group and reduction of the dibromides to a monobromide (**8**). The corresponding reaction of the acid **9** was less selective and a mixture of *cis*- and *trans*-monobromoacids **10** in ratio 1.5:1 was isolated in good yield together with **8** (*ca.* 11%). When this reaction was repeated but 1 mol equiv. of EtMgBr was added before the titanium isopropoxide, followed by 1.5 mol equiv. of the Grignard reagent, the two monobromoacids were isolated in the ratio 1.2:1, together with **8** (13%) and a trace of **9**.



The present method may also be applied to dichlorides; these results have been described briefly earlier,[19] and will be described in full elsewhere.[41]

The nature of the Grignard reagent

(a) Is catalysis necessary?

It is important to note that the reaction of methylmagnesium bromide with **1d** in refluxing tetrahydrofuran in the absence of a catalyst is known to lead to monobromides, in a reaction thought to involve a radical mechanism with abstraction of the hydrogen from the carbon α- to oxygen in the solvent tetrahydrofuran.[42] However, the reported yields for this reaction are lower than those for the present method. When 2 mol equiv. of methylmagnesium bromide was added to **1d** in ether–THF–toluene in the presence of 10 mol% of titanium isopropoxide, a rapid reaction equivalent to that reported above with EtMgBr–$Ti(O^iPr)_4$ was not observed and a considerable amount of **1d** remained even after 18 h. There was a very similar stereoselectivity with both the titanium isopropoxide promoted reaction with ethylmagnesium bromide and the apparently non-promoted reaction with methylmagnesium bromide.[42] Reaction of **1a** with 1.3 mol equiv. of MeMgBr in ether solution did occur relatively rapidly at room temperature, *ca*. 50–60% reduction to **2a** and **3a** occurring in 1 h; in this case, the addition of 10 mol% $Ti(O^iPr)_4$ increased the rate only slightly, *ca*. 80% reduction occurring in 1 h. To compare the two Grignard reagents, reactions were carried out under standard conditions in which the reagents (1.3 mol equiv.) were added over 10 min to a stirred solution of **1a** in ether at 20 °C in a water bath and the products were examined over an extended period by GLC (Fig. 1). The addition was carried out in this way as the reaction with EtMgBr and $Ti(O^iPr)_4$ was strongly exothermic. It is clear that the slowest reaction occurs with EtMgBr in the absence of the catalyst, and that in the presence of 2 mol% $Ti(O^iPr)_4$ essentially complete reaction to **2a/3a** had occurred on completion of the addition; in this case further reduction to **4a** then occurred more slowly. The uncatalysed reaction with MeMgBr was considerably faster than that with EtMgBr, but addition of 2 or 10 mol% $Ti(O^iPr)_4$ in this case caused only a marginal increase in rate; in all these reactions with MeMgBr, the only products observed were **2a** and **3a**. It is interesting to note that in the uncatalysed reaction with EtMgBr, an approximately equal quantity of allene **6** was obtained in addition to **2a/3a** up to 1 h, but that the reaction continued and after 1 day *ca*. 40% conversion of **1a** had occurred but the ratio of **6** to **2a/3a** was now 4 : 1.

When compound **1a** was treated with 10 mol% titanium isopropoxide and 0.2 mol equiv. of EtMgBr followed by 1.1 mol equiv. of MeMgBr, the rate of reaction leading to the corresponding monobromides was markedly faster than in the reaction with MeMgBr alone, suggesting the formation of a species on reaction of the isopropoxide with EtMgBr which promotes the further reaction with MeMgBr.

It is important to note that a number of metal derivatives are known to promote the reactions of Grignard reagents with aliphatic and aromatic halides. Thus, *e.g.*, the reaction of arylmagnesium halides in tetrahydrofuran with cobalt(II) chloride in the presence of a haloalkane leads to the formation of products apparently derived from the aryl radical and the alkyl radical,[43] although the product of cross coupling (ethylbenzene) is only produced in 5% yield, suggesting that the real mechanism may be more complex (see Supplementary Information, Scheme A).[44] Moreover, methylmagnesium bromide reacts with bromobenzene in anisole in the presence of cobalt chloride to give a mixture of isomeric methoxybiphenyls together with a smaller amount of biphenyl.[45] The intermediacy of radicals in these reactions has been confirmed by their trapping with anthracene.[46] It is also known that cobalt halides,[48] cuprous bromide,[49] and a number of other metal species[50] promote the reaction of RMgX with R^1X to give RR^1. Reduced products equivalent to those obtained in the present work were not reported in these systems. Since the publication of the preliminary results of the present work it has also been reported that

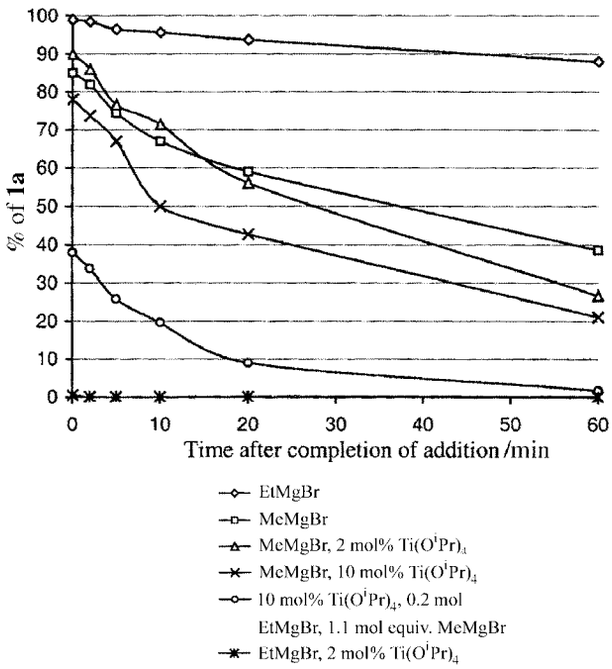


Fig. 1 Relative rates of reduction of **1a** at 20 °C.

Grignard reagents do reduce 1,1-dichlorocyclopropanes in the presence of either cobalt(II) chloride or $Fe(dbm)_3$.[47]

In order to try to determine the mechanism of the reaction in the presence of titanium isopropoxide, and to explain the apparent differences between methylmagnesium bromide and ethylmagnesium bromide, a series of control experiments has been carried out. It was first necessary to determine whether a range of alkylmagnesium bromides would react with a dibromocyclopropane in the absence of the titanium-based catalyst. The results of this study, for which compound **1a** was chosen as a standard cyclopropane, are shown in Table 3.

In this and following Tables all figures represent product ratios as determined by GLC using uncorrected peak areas; relative responses for **1a**, **2a**, **3a** and **6** were determined and are given in the Experimental section. Figures in brackets for individual compounds represent product ratios determined on the basis of integration of the ^1H NMR spectra. All figures must therefore be regarded as accurate only within the normal limits of these techniques. The following conclusions may be drawn from Table 3:

(i) The reaction of each of the Grignard reagents with **1a** did occur to some extent even in the absence of catalyst.

(ii) With 1.3 mol equiv. of EtMgBr, about 5% reduction occurred in 1 h; another product (7%) was the allene **6**.[51] Even after 24 h about 57% starting material still remained, and a mixture of monobromides and allene in *ca.* 1 : 4 ratio was seen. The allene is a typical product of the reaction of 1,1-dibromocyclopropanes with MeLi, a reaction thought to involve the intermediacy of a 1-lithio-1-bromocyclopropane.[40] By analogy it may perhaps arise in the present reaction by formation of a 1-bromocyclopropyl anion (or a related organometallic) either from the dibromide or through a subsequent reaction of either or both monobromides.

(iii) Reduction with methylmagnesium bromide occurred considerably faster than with the other Grignard reagents examined except *tert*-butylmagnesium bromide and no allene **6** was formed.

(iv) Only in two cases was any doubly reduced cyclopropane (**4a**) observed.

(v) With 2 mol equiv. of *tert*-butylmagnesium bromide, compound **1a** gave up to 73% of the monobromides **2a** and **3a** after a total of 22 h (entry 18), but in this case no allene was observed. It is interesting to note, however, that *tert*-

Table 3 Reduction of **1a** with Grignard reagents in ether with no catalyst.[a] (Data for intermediate reaction times are given in the Supplementary Information, Table 3)

N	Grignard	Total Grignard/ mol equiv.	Time of stirring/h	**1a**	**2a** and **3a**	**4a**	**6**
14	MeMgBr	1.30	24	13 [15]	85 [85 (2.4 : 1)]	2 [0]	0
15	EtMgBr[b]	1.30	24	43 [57]	10 [9 (1.6 : 1)]	0	47 [34]
16	*sec*-BuMgBr	1.00	2	36	36	1	28
		2.00	1	13 [21]	38 [53 (1.5 : 1)]	1	49 [26]
17	3-PentylMgBr	1.00	18	41 [43]	21 [18 (1.6 : 1)]	0	38 [39]
18	*t*-BuMgBr	1.00	14	62	38	0	0
		2.00	8	23 [27]	77 [73 (1.7 : 1)]	0	0
19	*t*-BuMgBr	4.00	72	[4]	[96 (1.7 : 1)]	[0]	[<1]
20	PhMgBr	1.00	24	73 [74]	27 [26 (2.3 : 1)]	0	6 [−]
21	$PhCH_2MgBr$	1.00	16	81 [78]	19 [22 (1.8 : 1)]	0	0
22	$PhCH_2CH_2MgBr$	1.00	51	84	10	0	6
		2.00	24	73 [65]	14 [23 (2.8 : 1)]	0	13 [13]

[a] In this and following Tables: 1) each block of results corresponds to a single experiment; *e.g.* in 16, 1 mol equiv. of *sec*-BuMgBr was added initially followed by a second mol equiv. after 2 h and the products analysed after an additional 1 h; 2) in each case the initial 10 min corresponded to the time for addition of the reagents; 3) all figures are either relative GLC peak areas or those in [ ] represent the ^{1}H NMR analysis of the crude reaction product at the end of each reaction based on integration. [b] The ratio between **2a/3a** and **6** and the rate of reduction seem to depend somewhat on the age of the EtMgBr in the uncatalysed reaction.

butylmagnesium bromide proves to be an effective and selective reagent for the monohydrodebromination of functionalised *gem*-dibromocyclopropanes, such as 1,1-dibromo-2-cyano-2-methylcyclopropane, under the same conditions. These data will be published elsewhere.[52]

(b) The effect of the Grignard reagent on the catalysed reaction

The corresponding reactions were then carried out in the presence of varying amounts of titanium isopropoxide as shown in Table 4. There are clearly a number of sharp differences between these reactions and those described in Table 3:

(i) The reaction with 2-butylmagnesium bromide was highly selective and led to essentially complete reduction of the dibromide to monobromide with 1.04 mol equiv. of reagent in 30 min in the presence of 5 mol% of the catalyst. Ethylmagnesium bromide was almost as selective but 1.3 mol equiv. was required for complete monoreduction in a reaction which was complete in 10 min in the presence of 2 mol% of catalyst; in the same way 1.25 mol equiv. of phenethylmagnesium bromide was required for essentially complete monoreduction with 2 mol% catalyst. 3-Pentylmagnesium bromide also required 1.3 mol equiv. for complete reaction with 10 mol% of catalyst. In this case the reaction with only 2 mol% of catalyst was rather non-selective. In each case the reaction with added Grignard appeared to be complete in *ca.* 10 min, no major change in ratio occurring after a further 20 min. It is important to note that in the absence of titanium isopropoxide, reductions with all four of these Grignard reagents were rather inefficient and that all four have a β-hydrogen available for elimination to produce, *e.g.*, a titanacyclopropane as in Scheme 1.

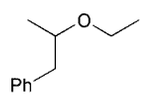
(ii) Reduction of 7,7-dibromobicyclo[4.1.0]heptane with 2 mol equiv. of methylmagnesium bromide in ether–THF–toluene in the presence of 10 mol% titanium isopropoxide for 18 h led to an approximately 3.5 : 1 ratio of *endo*- and *exo*-monobromides and starting material (see Experimental part).‡ This appears to confirm that the reaction with MeMgBr is not markedly promoted by the presence of the titanium isopropoxide.

‡ In this case it was not possible to distinguish the fully reduced bicycloheptane from the solvents by GLC.

(iii) Reduction with benzylmagnesium bromide was slower and less selective than with the four reagents described in (i), only 41% monoreduction occurring with 1 mol equiv. of the reagent after 16 h, even in the presence of 10 mol% of catalyst (Table 4, entry 34). A more detailed comparison of the results with this reagent is given in Table 5. With 5 mol equiv. of Grignard and 22 mol% of catalyst, the reduction had only occurred to the extent of about 60% after 13 h, and even after 36 h some starting dibromide remained and only *ca.* 12% double reduction to **4a** had occurred.

A direct comparison of the uncatalysed reaction (Table 5, 39; see also Table 3, 21) and reaction in the presence of 10 mol% of titanium isopropoxide (entry 38) shows only a *ca.* doubling in the proportion of monoreduction in the latter case. It may also be significant that in this reaction, which appears to be largely unaffected by the catalyst, only small amounts (*ca.* 2%) of benzyl bromide were observed in the products by GLC; in the case of phenethylmagnesium bromide, the reactions of which were catalysed by the titanium reagent, about 19% of phenethyl bromide was observed in the absence of titanium isopropoxide.

In addition, an increased quantity of the ether **11** was observed in the catalysed reactions, together with some increase in the level of 1,2-diphenylethane (**12**), a compound which was also present if the initial Grignard reagent was quenched with water (Table 5) in agreement with the literature.[75] Compound **11** is formed in reactions of benzylmagnesium bromide in ether in the presence of either xenon difluoride or titanium tetrachloride;[53,54] the former reaction is also reported to lead to a small amount of the dimer **12**.[53] Compound **12** is also the product of the decarboxylation of phenylacetic acid using Co(III).[55] Compound **11** appears to arise by a coupling of a benzyl radical with an α-ethoxyethyl radical, although alternative mechanisms may be possible. Compound **12** may also in principle arise through a radical coupling. Perhaps it is more likely that the molecules interact with the titanium centre leading to reactive species that combine to form **11** and **12**.



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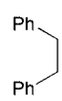

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Table 4 Reduction of **1a** with different Grignards and $Ti(O^iPr)_4$ in ether.[a] (Data for intermediate reaction times are given in the Supplementary Information, Table 4)

N	Grignard	Grignard/ mol equiv.	$Ti(O^iPr)_4$/ mol%	Time of stirring	**1a**	**2a** and **3a**	**4a**	**6**
23	MeMgBr	1.30	10	24 h	5 [6]	93 [94 (2.3 : 1)]	2 [0]	0 [0]
24	EtMgBr	1.30	2	10 min	2 [0]	98 [94[b] (2.0 : 1)]	0 [0]	0 [0]
25	EtMgBr[c]	3.00	10	1.5 h	0 [0]	0 [0]	97 [93[b]]	0 [0]
26	2-BuMgBr	0.80	5	30 min	21	79	0	0
		1.04		30 min	<1 [0]	100 [97[b] (2.0 : 1)]	0 [0]	0 [0]
27	2-BuMgBr	2.40	10	10 h	0	13	87	0
		2.64		30 min	0 [0]	<1 [0]	>99 [95[b]]	0 [0]
28	3-PentylMgBr	1.3	2	3 h	39 [33]	45 [49 (1.5 : 1)]	0 [0]	16 [18]
29	3-PentylMgBr	1.00	10	30 min	20	80	0	0
		1.25		30 min	4	96	0	0
		1.30		10 min	3 [0]	97 [100 (2.0 : 1)]	0 [0]	0 [0]
30	3-PentylMgBr	2.00	10	1 h	0	75	25	0
		3.00		17 h	0	22	78	0
		4.00		42 h	0 [0]	4 [0]	96 [100]	0 [0]
31	*t*-BuMgBr	1.00	10	4 h	56	44	0	0
		2.00		14 h	4 [3]	96 [97 (1.9 : 1)]	0 [0]	0 [0]
32	PhMgBr	1.00	2	30 min	26	73	1	0
		1.50		20 min	5 [0]	93 [100 (2.6 : 1)]	3 [0]	0 [0]
33	PhMgBr	2.00	10	1 h	0	72	28	0
		3.00		1 h	0	35	65	0
		4.00		14 h	0 [0]	0 [0]	100 [100]	0 [0]
34	$PhCH_2MgBr$	1.00	10	16 h	59 [58]	41 [42 (1.8 : 1)]	0 [0]	0 [0]
35	$PhCH_2CH_2MgBr$	1.00	2	30 min	20	80	0	0
		1.25		30 min	3	93	4	0
		1.30		10 min	3 [0]	92 [100 (1.8 : 1)]	5 [0]	0 [0]
36	$PhCH_2CH_2MgBr$	1.00	10	10 min	18	77	5	0
		2.00		1 h	0	83	17	0
		3.00		4 h	0	49	51	0
		4.00		11 h	0	17	83	0
		5.00		24 h	0 [0]	3 [0]	97 [100]	0 [0]

[a] These reaction mixtures were quenched with D_2O. There was no deuterated monobromide in the products by GC/MS or ^1H NMR spectroscopy. [b] Isolated yield. [c] With less than 3 mol equiv. of EtMgBr, the reaction did not go to completion.

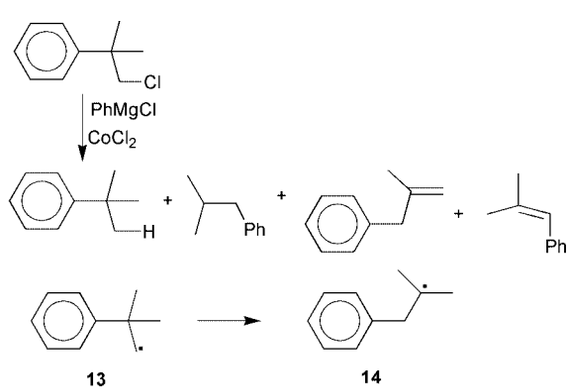
Table 5 Reduction of **1a** with benzylmagnesium bromide

N	Grignard/ mol equiv.[a]	$Ti(O^iPr)_4$/ mol%	Time of stirring/h	PhMe	**12**	**11**	**1a**	**2a** and **3a**	**4a**
37	5.00	22	36	149[b] [133]	71 [57]	84 [64]	1 [0]	83 [88 (1.8 : 1)]	16 [12]
38	1.00	10	16	33 [27]	41 [15]	33 [20]	59 [58]	41 [42 (1.8 : 1)]	0 [0]
39	1.00	0	16	42 [28]	23 [15]	23 [12]	75 [78]	25 [22 (1.8 : 1)]	0 [0]

[a] Decomposing the Grignard reagent itself with D_2O gave d-toluene, 85%; benzyl alcohol, 6.5%; bibenzyl, 9%; no **11** was observed. [b] Figures represent GLC responses relative to total cyclopropane-derived product at 100%.

(iv) Although reduction with phenylmagnesium bromide was still relatively fast (see Table 4, entry 32), each aliquot of added Grignard reagent appeared to require around 30 min for complete reaction and the reaction was much less selective than with the reagents described in (i) above. Reduction of **1a** to give **4a** was also relatively slow. It is known that phenylmagnesium chloride does not react with neophyl chloride (1-chloro-2-methyl-2-phenylpropane), but that in the presence of cobalt(II) chloride a mixture of products is obtained.[56]

These are thought to arise by the formation and rearrangement of the radical **13** to **14**.§



The reaction of neophyl chloride with ethylmagnesium bromide in the presence of titanium isopropoxide (2 mol%) led to a similar mixture of products (*tert*-butylbenzene 32%,

§ It is well known that cyclopropylmethyl radicals ring-open extremely rapidly to butenyl radicals (see *e.g.*, J. C. Walton, in *Carbocyclic Three-membered Ring Compounds*, Houben Weyl, **E17C**, 2438). Reaction of cyclopropylmethyl bromide with ethylmagnesium bromide in the presence of titanium tetraisopropoxide, however, led to a very complex product mixture.

Table 6 Reduction of **1a** (entries 40–43) and **2a** + **3a** (entry 44) with phenethylmagnesium bromide in ether.[a] (Data for intermediate reaction times are given in the Supplementary Information, Table 6)

N	Grignard/ mol equiv.	$Ti(O^iPr)_4$/ mol%	Time of stirring	**1a**	**2a** and **3a**	**4a**	**6**	Ethyl-benzene	Styrene	**17**	**18**	β-Phenyl-ethyl bromide
40	1.00	0	51 h	84	10	0	6	32	4	4	7	12
	2.00		24 h	73 [65]	14 [23 (2.8 : 1)]	0 [0]	13 [13]	152 [166]	7 [7]	6	16	21 [19]
41[b]	0.80	2	5 min	35 [29]	65 [72 (2.0 : 1)]	0 [0]	0 [0]	29 [64]	5 [2]	32	5	0 [0]
42[c]	1.00	2	30 min	20	80	0	0	37	5	29	7	0
	1.25		30 min	3	93	4	0	70	7	32	10	0
	1.30		10 min	3 [0]	92 [100 (1.8 : 1)]	5 [0]	0 [0]	61 [100]	6 [6]	31	8	0 [0]
43	1.00	10	10 min	18	77	5	0	38	6	17	3	0
	2.00		1 h	0	83	17	0	91	9	17	11	0
	3.00		4 h	0	49	51	0	220	17	21	20	0
	4.00		11 h	0	17	83	0	358	23	27	32	0
	5.00		24 h	0 [0]	3 [0]	97 [100]	0 [0]	479 [500]	32 [34]	28	46 [50]	0 [0]
44[d]	2.00	10	1 h	0	55	45	0	229	15	3	12	0
	3.00		18 h	0 [0]	3 [0]	97 [100]	0 [0]	273 [293]	25 [29]	6	16 [25]	0 [0]

[a] Quenching the Grignard reagent with D_2O gave >88% of ethylbenzene, <1.6% of styrene and <10% of **18** by GLC; 91% ethylbenzene, 1% of styrene, 6% of **18** and 2% of phenethyl alcohol was deuterated by GC/MS data. [b] The layers were separated after addition of 0.8 mol equiv. of Grignard reagent. The bottom layer contained ether and phenethyl alcohol by ^1H NMR in D_2O. The upper layer was quenched with D_2O. The D_2O layer contained only ether. The organic layer contained the products shown in entry 41, by ^1H NMR. [c] One half of the ether was distilled from the reaction mixture at atmospheric pressure (there was no ethyl vinyl ether in the distillate by GLC) and then this ether was treated with bromine. There were no new products by GLC or ^1H NMR. The rest of the reaction mixture was treated with D_2O. The bottom layer contained D_2O and ether by ^1H NMR. Non-deuterated **2a** and **3a** were isolated from the upper layer. [d] Quenched after 18 h with D_2O. $PhCH_2CH_2D : PhCH_2CH_3 = 1.7 : 1$ by GC/MS.

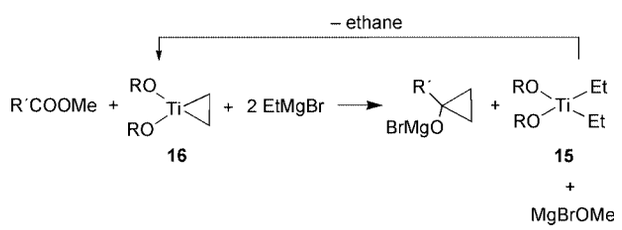
isobutylbenzene 9%, 2-methyl-3-phenylpropene 4%) at reflux in ether for 48 h. In the absence of titanium isopropoxide, neophyl chloride remained unreacted. This may suggest that the titanium promoted reaction also involves radical intermediates.

(v) *tert*-Butylmagnesium bromide appeared to behave in a rather similar manner to phenylmagnesium bromide although the monoreduction which occurred with 2 mol equiv. of the Grignard reagent in the presence of 10 mol% titanium isopropoxide was very selective, no **4a** being observed.

(vi) Reaction of the dibromide **1a** with 2.6–5.0 mol equiv. of the Grignard reagents discussed in (i) or of phenylmagnesium bromide, in each case in the presence of the catalyst, led to almost complete double reduction to **4a**; in no case was any allene **6** observed. No other cyclopropane-derived products were detected in this reaction.

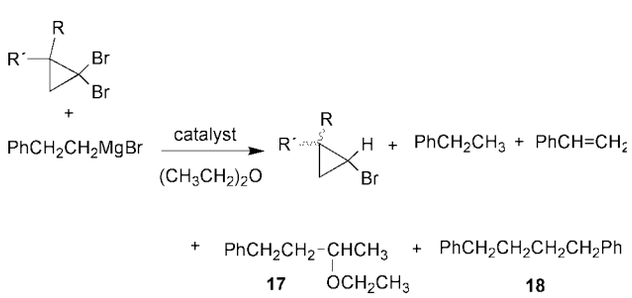
The fate of the Grignard alkyl group

The Kulinkovich reaction of esters with *e.g.*, EtMgBr in the presence of titanium isopropoxide has been explained in terms of a catalytic cycle involving the loss of ethane from a diethyltitanium species.



This cycle amounts to the reduction of one molecule of the Grignard reagent to ethane and the oxidation of the second one to give the cyclopropanol. At first sight, some of the differences in reactions with dibromocyclopropanes might be explained in terms of whether or not the Grignard reagent contained a β-hydrogen, which could eliminate to form a titanacyclopropane such as **16**. For example, reactions with methyl- or benzylmagnesium bromides do not appear to be markedly promoted by titanium isopropoxide. To establish whether the present reduction occurs through intermediates of the above type, it was necessary to know the fate of the alkyl group of the Grignard reagent—in principle the complete monoreduction of 1 mol equiv. of **1a** by 1 mol equiv. of a Grignard reagent would be possible by a sequence involving the above mechanism, and with the liberation of 0.5 mol equiv. of the alkane, provided that each molecule of the derived titanacyclopropane **16** was able to convert two molecules of dibromocyclopropane into monobromide. However, even in this case, the origin of the hydrogen in the monobromide is not clear and the second 0.5 mol equiv. of the alkyl group of the Grignard might be expected to be oxidised. To examine these possibilities, the fate of the phenethyl groups in the reaction of phenethylmagnesium bromide with **1a** in the presence of titanium isopropoxide was examined. The major products containing this group were ethylbenzene, styrene and a product incorporating the solvent, ether, compound **17**. This compound has been observed earlier in the reactions of phenethylmagnesium bromide in benzene with 2,4-dichloro-1-(1-ethoxyethyl)benzene in the presence of titanium tetrachloride (1 mol equiv.).[54] In addition compound **18** was observed, but the proportion of this in reactions was generally close to that obtained on quenching the Grignard reagent itself with water.

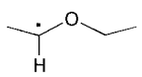
The results (Table 6) may be summarised as follows:



(i) When the dibromide **1a** was treated with the Grignard reagent with no catalyst present, only *ca.* 10% reduction to the monobromide occurred in 51 h; quenching with water led to ethylbenzene together with small amounts of 1,4-diphenylbutane (**18**) and styrene. It is worth noting that this uncatalysed reaction still appeared to be proceeding after 22–51 h. The

reaction was also rather non-selective, leading to almost as much allene **6** as monobromides **2a** or **3a**. A relatively large amount of phenethyl bromide was also observed.

(ii) In the presence of 2 mol% of catalyst, 1 mol equiv. of Grignard reagent led to a *ca.* 4:1 ratio of monobromides to dibromide and 1.25 mol equiv of Grignard was required for essentially complete monoreduction as discussed earlier; this reaction was fast, being complete in less than 10 min. Under these conditions, no allene **6** was observed and instead the minor cyclopropane-derived product was **4a**. The major product derived from the Grignard phenethyl group was ethylbenzene; however, about 25% was contained in the product incorporating the solvent, **17**. This again appears to be derived from a formal coupling of a phenethyl radical and the radical **19** although the real mechanism by which it is produced may be much more complex. No phenethyl bromide was observed in the reaction in the presence of titanium isopropoxide.



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Quenching of the reaction with D_2O did not lead to deuterium incorporation (by MS) into **2a** or **3a** or into the ethylbenzene, indicating that the hydrogen required in the reduction of the Grignard reagent to ethylbenzene is also introduced before work-up.

The Grignard reagent itself was also treated with titanium isopropoxide in the absence of the dibromocyclopropane. The results, given in Table 7 in the Supplementary Information, show that:

(i) Quenching the Grignard reagent itself in ether with water, led to small amounts of styrene (<1.6%), 1,2-diphenylbutane (<10%) and phenylethanol (2%) as well as ethylbenzene; on quenching with D_2O after 84 h, the ethylbenzene showed over 91% deuteration by ^1H and ^{13}C NMR. No compound **17** was observed.

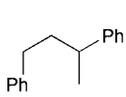
(ii) When 10 mol% of titanium isopropoxide was added, quenching with D_2O after 84 h, approximately the same mixture was isolated, although the levels of styrene had reached *ca*. 6%. However, the deuteration level of the ethylbenzene was considerably reduced (to 50–60%).

(iii) With 20 mol% of titanium isopropoxide, quenching with D_2O after 84 h gave ethylbenzene which contained only 13% deuterium.

It is interesting to note that MS evidence was obtained for small quantities of the dimer **20** isomeric with **18**.[57] The above results suggest that titanium isopropoxide promotes the decomposition of the Grignard reagent even in the absence of dibromide, and that radical intermediates are involved.

Products derived from the solvent, ether

To examine in more detail the products of insertion into ether, the reaction of 2,2-dimethyl-1,1-dibromocyclopropane with 1.2 mol equiv. of ethylmagnesium bromide and 5 mol% of titanium isopropoxide was carried out on a 0.3 mol scale. The estimated total yields were: 2-butyl ethyl ether (**21**) (66 mmol), 2-butyl isopropyl ether (**23**)[78] (28 mmol), 2,3-diethoxybutane (**22**) (36 mmol) and possible ether oligomers (3.59 g, equivalent to *ca.* 49 mmol of monomeric ether), and that of 1,1-dimethyl-1-bromocyclopropane was 240 mmol from ^1H NMR data. Thus the total number of equivalents of identified ether-derived products, discounting oligomers, was over 69% of the monobromide yield.



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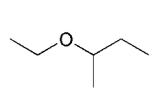

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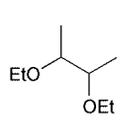

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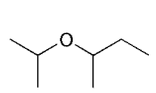

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Product **21** appears to arise through the alkylation of the solvent by the Grignard reagent and was difficult to isolate in small-scale reactions because of its volatility. Compound **23** apparently arises by exchange of one of the ethyl groups of the solvent for an isopropyl residue in the titanium isopropoxide, together with alkylation and in agreement was not observed in the reaction using titanium tetrachloride. The dimer **22** was obtained as a mixture of stereoisomers. It has been reported in the UV photolysis of diethyl ether as a minor product postulated as arising by the dimerisation of two radicals (**19**),[58] and in the photolysis of *cis*-bicyclo[6.1.0]nonan-2-one in ether solution.[59] It is a major component in the photoinduced reduction of dibromocyclopropanes by lithium aluminium hydride in ether, a reaction postulated as involving the initial homolytic cleavage of a carbon–bromine bond;[35] application of this reaction to 7,7-dibromobicyclo[4.1.0]heptane leads to an almost identical *exo*/*endo* ratio to that observed with EtMgBr and titanium isopropoxide (Table 2). Compound **22** has also been reported as a minor product (3%) in the reaction of a monobromocyclopropane with magnesium in ether.[60] A similar reaction, apparently the coupling of two radicals, has been reported in the reduction of 7,7-dichlorobicyclo[4.1.0]heptane with magnesium anthracene in tetrahydrofuran which leads primarily to the product of apparent coupling of bicyclo[4.1.0]-heptan-7-yl and anthracenyl radicals. Interestingly, the corresponding 7,7-dibromo-compound leads instead to monobromides as well as products typical of cyclopropylidene intermediates.[61]

When 2,2-dimethyl-1,1-dibromocyclopropane was treated with 1.2 mol equiv. of EtMgBr in the presence of titanium tetrachloride, complete reduction to **2c** and **3c** occurred and the ether-derived products were **21** and **22** (30 and 14% relative to monobromides). As expected, no **23** was detected in this case.

A comparison of the various products derived from the reaction of **1a** with the series of reagents, PhMgBr, $PhCH_2MgBr$, $PhCH_2CH_2MgBr$, is presented in the Supplementary Information (Table 10).

Deuterium labelling and solvent studies

The above results clearly indicate that the reactions of dibromocyclopropanes with a number of Grignard reagents in ether solution are faster and more selective in the presence of titanium isopropoxide, but that the nature of this effect is dependent on the exact Grignard reagent used. It was clear that in this process one bromine on the cyclopropane was replaced by hydrogen; the origin of this hydrogen, however, was not certain. Five general possibilities for the hydrogen source needed to be considered: the Grignard reagent, the solvent, the catalyst, the work-up and the C–H bonds of the starting cyclopropane itself and of derived products. The final possibility seems unlikely in the present cases at least because the cyclopropane products shown above are recovered in such high yields and because no products which could be ascribed to further reactions after hydrogen removal have been observed. The fourth possibility could readily be excluded since in no case did work-up of the reaction with D_2O lead to the incorporation of deuterium into the cyclopropane (Table 4, footnote *a*). In many cases, the catalyst was only present at 2 mol%, and therefore it would seem highly unlikely that this could provide more than a small fraction of the necessary hydrogen; moreover, the reaction was also successful using titanium tri- or tetrachloride rather than titanium isopropoxide as catalyst (see above) and, in these last cases at least, it is clear that the hydrogen cannot be derived from the catalyst.

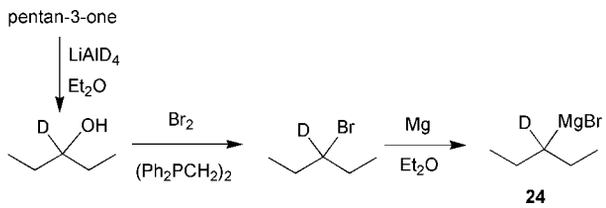
In order to examine the source of the hydrogen in the reduction of dibromides to monobromides a deuterated Grignard reagent (**24**) was prepared and used to reduce **1a**.

Reaction of **1a** with 0.65 mol equiv. of **24** in the presence of 5 mol% of $Ti(O^iPr)_4$ led after 10 min to a 33:67 mixture

Table 9 Reduction of **1a** with phenethylmagnesium bromide in THF (N 54) and d_8-THF (N 55).[a] (Data for intermediate reaction times are given in the Supplementary Information, Table 9)

N	$PhCH_2CH_2MgBr$/ mol equiv.	$TiCl_4$/ mol%	Time of stirring/h	**1a**	**2a** and **3a**	**4a**	Ethyl-benzene	Styrene	**18**
54	1.00	5	1	40	60	0	68	16	2
	1.6		1	0 [0]	97 [100, 1.5:1]	3	129 [120]	16 [15]	4
55	1.2	5	1	57 [64]	43 [36, 1.5:1[b]]	0	111 [90][c]	9 [12]	2

[a] Decomposing the Grignards with H_2O gave 95% ethylbenzene, 1% styrene, and 2% **11** by GLC. [b] Major monobromide contains 30, minor 47% deuterium in position 1 by GC/MS and ^{1}H NMR. [c] No deuterium incorporated into the ethylbenzene.



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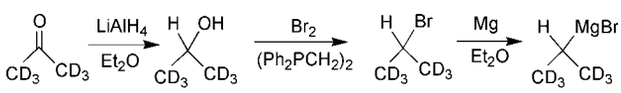
of monobromides and starting material; this ratio was little changed after 30 min (36:64). Addition of a further 0.65 mol equiv. of the Grignard reagent **24** led to a ratio of **2a**:**3a**:**1a** of 35:20:45. Small amounts of 3,4-dideuterio-3,4-diethylhexane were observed by GC/MS, possibly arising from the preparation of the Grignard reagent; three unidentified minor products with short retention times were also observed. The key observation was that no deuterium was incorporated into **2a** or **3a** by ^{1}H NMR or GC/MS.

In addition the deuterated Grignard reagent **25** was prepared by similar methods and used to reduce **1a**. Reaction of 1.15 mol equiv. of this Grignard reagent with the dibromide in ether, catalysed by 1.1 mol% of $TiCl_4$·2THF gave after 30 min a mixture of *trans*-:*cis*-monobromides:starting material in the ratio 1.6:1.0:0.4. No deuterium incorporation was observed in either **2a** or **3a** by ^{1}H NMR.



25

These two results appear to rule out the transfer of either the α- or β-hydrogens of the Grignard reagent to the dibromide, at least in these particular reductions. Given the strong dependence of the reduction on the nature of the Grignard reagent it would perhaps be dangerous to rule out such transfers in other cases.

To determine the effect of the solvent on the reaction, ethylmagnesium bromide was prepared in anisole and in $CD_3OC_6H_5$ solution; although the reduction of **1a** was successful, no deuterium was incorporated into the products **2a/3a** (for details and Table 8, see supplementary data provided). Phenethylmagnesium bromide was therefore prepared in d_8-THF and the reaction with **1a** catalysed by $TiCl_4$ was compared to that in the non-deuterated solvent (see Table 9).

The reaction in tetrahydrofuran itself occurred cleanly with 1.6 mol equiv. of the Grignard reagent. No products equivalent to **21** or **22** were observed. Both monobromides were deuterated when the reaction was carried out in deuterated solvent, although the levels of deuteration were only moderate and, interestingly, were not equal. The reaction was not taken to completion because of restrictions in the scale due to the use of labelled solvent. The low level of deuteration may either reflect the difficulty of this experiment on the small scale that was required, or may be explained if there are alternative reactions which can provide a source of hydrogen and the primary kinetic isotope effect with d_8-tetrahydrofuran causes the reaction kinetics to favour these alternatives. The lack of any deuteration (by MS) in the ethylbenzene was, however, surprising.

Table 11 Reduction of **1a** with ethylmagnesium bromide with 1 mol equiv. of $TiCl_4$ in THF (by ^{1}H NMR)

N	EtMgBr/ mol equiv.	Time of stirring/min	**1a**	**2a**	**3a**	**4a**
63	1.00	20	100	0		0
64	2.00	20	85	15 (1.6:1)		0
65	3.00	20	35	65 (1.6:1)		0
66	6.00	120	0	31 (1:4)		69

Similar levels of deuteration have been reported in the reaction of 1-bromo-1-methyl-2,2-diphenylcyclopropane with magnesium in d_8-tetrahydrofuran and in that case when the reaction was carried out in d_{10}-ether, the level of deuteration was rather low (7%).[74] Although the detailed mechanism of this reaction has been the subject of considerable argument, a radical mechanism is generally proposed.[74]

The effect of increased catalyst concentration

When 1 mol equiv. of titanium tetrachloride was added to dibromocyclopropane **1a**, reduction to **2a/3a** began only during addition of the second equivalent of Grignard reagent (Table 11). With a second mol equiv. of Grignard reagent only about 15% reduction was observed; even with a third equivalent of Grignard reagent 35% of the dibromide **1a** remained unreacted. This is consistent with the formation of a Ti(II) species by reduction of the titanium tetrachloride with 2 mol equiv. of Grignard reagent[37] occurring before an active species is formed which can reduce the dibromocyclopropane.

The results of a competition experiment between **1a** and ethyl butyrate (*i.e.*, the standard Kulinkovich reaction) are presented in the Supplementary Information provided (Table 12).

General mechanistic considerations

The results discussed above may be summarised as follows.

1. Selective monohydrodebromination of *gem*-dibromocyclopropanes can be performed in high yield by means of ethylmagnesium bromide (1.0–1.4 mol equiv.) in ether in the presence of 2–10 mol% of titanium isopropoxide (Table 1). Where possible, a mixture of *exo*- and *endo*-monobromocyclopropanes is obtained with an isomer ratio similar to that in related hydrodebrominations often thought to involve radical intermediates.

2. In the presence of 3–5 mol equiv. of Grignard reagent and *ca.* 10 mol% of titanium isopropoxide, the dibromocyclopropanes were converted efficiently into the corresponding dihydrocyclopropanes.

3. Hydrodebromination of 1,1,2-tribromo- and 1,1,2,2-tetrabromocyclopropanes in the presence of the titanium derivative mentioned above takes place with high chemoselectivity: in all cases CBr_2 fragments in the molecules are reduced before the CHBr ones. Moreover, 1,2-dehalogenation,

Table 13 Comparison of uncatalysed and catalysed reductions of **1a** with different Grignards

Grignard	N	Uncatalysed **2a** + **3a**, 1.0 mol equiv. of Grignard	N	Catalysed **2a** + **3a**	Grignard/ mol equiv.	$Ti(O^iPr)_4$/ mol%	Effect
MeMgBr	14	33%, 20 min[a]	23	50%, 20 min	1.3	10	Low
EtMgBr	15	2% + 2% of others, 20 min[a]	24	98%, 20 min	1.3	2	Large
2-BuMgBr	16	37% + 18% of others, 40 min	26	100%, 20 min	1.04	5	Large
3-PentylMgBr	17	10% + 6% of others, 20 min	28	30%+ 5% of others, 20 min	1.3	2	Low
				97%, 20 min	1.3	10	Large
t-BuMgBr	18	12%, 1 h	31	27%, 1 h	1.0	10	Low
PhMgBr	20	5%, 20 min	32	92% + 7% of others, 20 min	1.5	2	Large
$PhCH_2MgBr$	21	19%, 16 h	34	41%, 16 h	1.0	10	Low
$PhCH_2CH_2MgBr$	22	2%, 20 min	—	95% + 5% of others, 10 min	1.3	2	Large

[a] 1.3 mol equiv. of Grignard reagent was used.

which is typical for polyhalocyclopropanes in reactions with lithium alkyls, diethyl phosphite–triethylamine and some other reagents, does not take place in these transformations.

4. In these catalysed reactions the only products detected arising from dibromocyclopropane were either monobromide or dihydrocyclopropane depending on the conditions. It is to be noted that such hydrodebromination of bromocyclopropanes with Grignard reagents does also occur without catalyst. However, the rate and chemoselectivity were generally considerably lower than in the presence of catalyst; *e.g.*, in many uncatalysed reactions up to 39% by ^1H NMR of allene **6** was formed (Table 3, entry 17).

5. $TiCl_4$, $TiCl_4$·2THF, and $TiCl_3$ proved to be similar to $Ti(O^iPr)_4$ in selectivity and effectiveness as catalysts.

6. Hydrodebromination of bromocyclopropanes in the presence of the catalysts mentioned above can be effective with Grignard reagents either having α- or β-hydrogen atoms or those without them. Among those reagents that led to the most effective reduction of **1a** in the presence of the titanium catalyst were ethyl-, 2-phenylethyl-, 2-butyl-, 3-pentyl-, phenyl-, 3-deuterio-3-pentylmagnesium bromide *etc.* which have a β-hydrogen (Table 13). On the other hand, the catalytic effect of titanium isopropoxide in reactions of *tert*-butyl- and benzylmagnesium bromide with no β-hydrogen was rather low; however, strong catalysis did occur with phenylmagnesium bromide (Table 13). It was found that ethylmagnesium bromide and phenethylmagnesium bromide are also effective reagents in the presence of titanium isopropoxide in THF as a solvent. It is to be noted that anisole proved to be a less effective solvent than ether or THF.

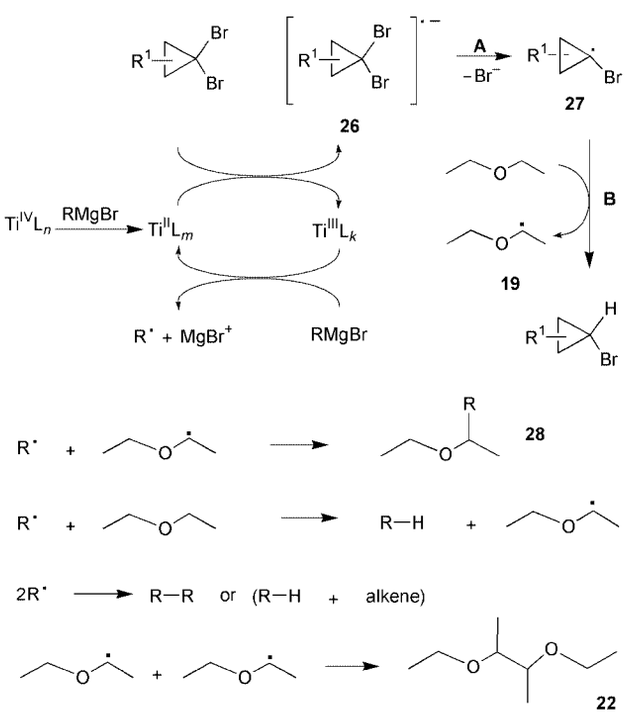
7. To reveal the origin of hydrogen in the hydrodebromination, the following experiments were performed: a) quenching of the reaction mixtures with D_2O; b) using deuterated Grignard reagents: $(CD_3)_2CHMgBr$, $Et_2CDMgBr$; c) using anisole-CD_3 as a solvent. No deuterium was incorporated in the hydrodebrominated compounds under any of these conditions. However, reduction of **1a** with 2-phenylethylmagnesium bromide in d_8-THF in the presence of titanium tetrachloride did lead to partially deuterated cyclopropanes.

8. Full analysis of the products in the reductive debromination showed the presence of the products of alkylation, arylation or dimerisation of ether. Furthermore, Grignard reagents were found to form appropriate dimers of Wurtz-type. In several reactions the latter were formed in relatively high yields.

9. The second reduction, *i.e.* of dibromide **1a** to hydrocarbon **4a** in one reaction or of the monobromides **2a**/**3a** to **4a**, was again very efficient (Table 6). No cyclopropane containing products other than **3a** were observed. In particular, there was no evidence for products derived by coupling of radical precursors of the products with the solvent. Related products were observed in the reaction of 1-bromocyclopropane with magnesium in ether, though not in the reaction of hexyl bromide with magnesium; this has been the basis of a considerable discussion of the mechanism of the formation of Grignard reagents.[72] It is interesting to note that the opposite result is observed in the present reaction, *i.e.* that products RCHMe–OEt are observed from the reaction of RMgX with the dibromocyclopropane in ether in the presence of the catalyst (X = alkyl, phenyl, benzyl) but no products including the cyclopropane group and the solvent have been isolated.

The above results can be used to analyse the key steps of the reaction mechanism. As follows from Table 11, hydrodebromination of *gem*-dibromocyclopropanes in the presence of an equimolar amount of titanium tetrachloride begins on addition of the second equivalent of Grignard reagent. At the same time, catalytic hydrodebromination of bromocyclopropanes taking place with 2–10 mol% of titanium(IV) compounds requires 1.0–1.3 mol equiv. of RMgBr. These data clearly show that hydrodebromination of one C–Br fragment of the bromocyclopropanes requires only 1 mol equiv. of Grignard reagent.

It is well known that the reaction of TiX_4 with Grignard reagents leads to either TiX_3 or TiX_2 species, *i.e.* to a reduction of the titanium.[62] One possible explanation of the hydrodebromination is that these Ti(III) or Ti(II) species then transfer one electron to the C–Br bond to give radical anions (**26**) which lose halide to give radicals (**27**) (Scheme 2). These



Scheme 2

then abstract a hydrogen from the carbon α- to oxygen in the ether solvent (step B). Radical recombination reactions between the alkyl radicals and ether-derived radicals then could lead to the observed products. The derived titanium species return to the low-valent form by reaction with the next molecule of Grignard reagent. This is consistent with the results of the deuteration studies but does lead to questions as to why reactions are more efficiently catalysed with some Grignard reagents than with others. It is also worth noting that the reaction of related di- or mono-bromocyclopropanes with magnesium in ether, a reaction thought to involve intermediate radicals related to **27**, gives small amounts of products apparently formed by trapping of these with **19**;[4g] in the present system, no such products were observed.

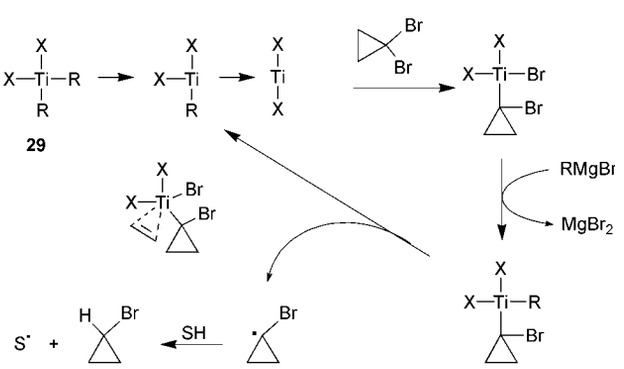
It is difficult to be precise about the processes involved in the transfer of electrons from the reactive titanium species to the dibromide. However, it is known that alkyltitanium(IV) halides lose alkyl radicals.[62]

$$CH_3TiBr_3 \xrightarrow{-CH_3^{\cdot}} TiBr_3$$

$$(CH_3CH_2)_2TiCl_2 \xrightarrow{-2\,Et^{\cdot}} TiCl_2$$

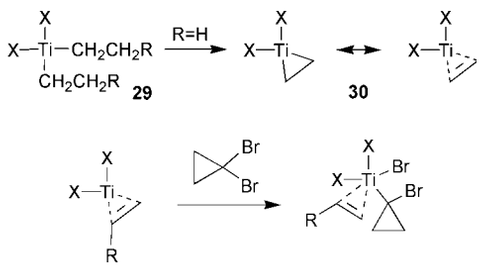
$$TiCl_4 + 2\,n\text{-BuLi} \xrightarrow{THF} n\text{-}Bu_2TiCl_2 \longrightarrow TiCl_2{\cdot}2THF$$

If the current process is simply an electron transfer from a low-valent titanium species to the bromine of the bromocyclopropane, it is difficult to see how the differences in catalytic effect with each particular Grignard reagent may be explained. In particular the fact that little catalytic effect is observed with methyl and *tert*-butyl Grignards but a large one is seen with ethylmagnesium bromide makes it difficult to identify an explanation based on oxidation potentials. An alternative explanation is that reaction involves the formation of intermediates incorporating a titanium–cyclopropane bond. Thus an alternative catalytic cycle could involve oxidative addition of a TiX_2 species to the carbon–bromine bond of the cyclopropane (Scheme 3).¶



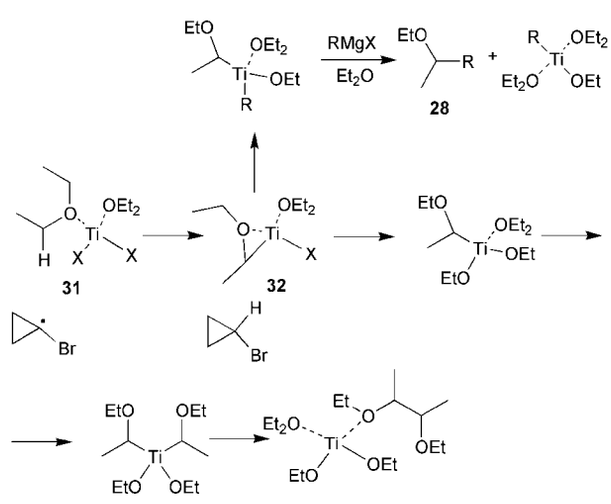
Scheme 3

Although the difference between the Grignards may relate to detailed structural factors such as electron density, size or state of oligomerisation or indeed to their oxidation potential, this process could again, in principle, occur with any Grignard reagent. Given the many publications which propose a titanacyclopropane as an intermediate in the Kulinkovich reaction, an alternative possibility is that, in some cases at least, the presence of a β-hydrogen in the Grignard reagent is important in generation of a catalytically active intermediate. An alternative scheme incorporating such an intermediate is presented below, *e.g.* for a reaction involving EtMgBr, elimination of ethane from **29** leads to a titanacyclopropane.



This clearly offers an alternative route into the catalytic cycle in which the alkene may remain bonded to titanium throughout the cycle, perhaps in place of a solvent molecule coordinated to titanium and hence may affect the catalytic activity.

It is interesting to note that no products of coupling of the cyclopropane to the alkyl group of the Grignard reagent are observed in any of the reactions reported. The cyclopropyl intermediate seems to remove a hydrogen selectively from the solvent, ether or THF. Moreover, the quantities of the ether (**22**) that are produced in the reactions are in some cases quite large. It is interesting to speculate whether this may be explained by activation of an ether molecule by co-ordination to titanium. A possible representation of such a process is given in Scheme 4, in which a cyclopropyl radical abstracts a hydrogen from **31** to produce the titanaepoxide equivalent **32** of the commonly quoted titanacyclopropane intermediate **16** in the Kulinkovich reaction. Opening of this by a Grignard reagent may then explain the relatively efficient formation of products (**28**), while in principle repetition of the process could lead to **33**, which on rearrangement could liberate **22**. The use of such a process to lead to compounds **28** could perhaps explain why no deuterium is incorporated into the Grignard derived products when the reaction is carried out in d_8-THF—the 'alkyl radical' being trapped in this alternative process rather than by hydrogen abstraction from ether solvent.

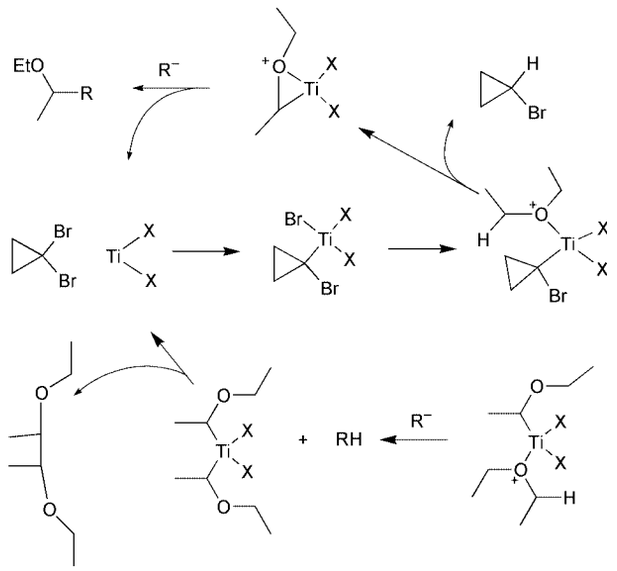


Scheme 4

Although most of the results described in this paper are consistent with a radical mechanism, it should be noted that two-electron processes may also be used to explain the observed products (Scheme 5).

One key element in proposing a mechanism for the hydrodehalogenation discussed in this paper is the stereochemical consequence of the reaction, *i.e.* inversion or retention at the carbon bearing the bromine in the reduction of monobromocyclopropanes. The determination of this stereochemistry will

¶ It should be noted that all the reactions in this paper were carried out in ether solvents and therefore that any or all of these titanium intermediates may incorporate additional ether ligands around the titanium.



Scheme 5

be discussed elsewhere. Whatever the result of these studies, it seems clear that the combination of a suitable Grignard reagent and a catalytic quantity of TiX_4 represents one of the most efficient and effective methods for converting a dibromocyclopropane into the corresponding monobromide.

Experimental

Reagents were obtained from commercial suppliers and were used without further purification unless stated. Dichloromethane was distilled over calcium hydride, diethyl ether and tetrahydrofuran were distilled over sodium wire and benzophenone, petrol was the fraction collected at 40–60 °C. Reactions requiring anhydrous conditions were performed using oven dried glassware (250 °C) under a positive atmosphere of argon. Organic solutions were dried over anhydrous magnesium sulfate, and, unless stated, were evaporated at 14 mmHg. Yields quoted are for the purified compounds unless stated. All new compounds were homogeneous by TLC or by GLC. GLC was conducted using a Perkin-Elmer Model F17 F.I.D. on a capillary column (30 m × 0.32 mm id Phase, DB5 split ratio of 50:1) using nitrogen as carrier gas. The relative responses of **1a**, **2a** + **3a** and **4a** were found to be 1:1.12 ± 0.06:1.42 ± 0.1. TLC was performed using Aldrich silica gel 60 plates (F254). Compounds were visualised either by examination under an ultraviolet source or by exposure to iodine vapour. Column chromatography was conducted with Matrex silica 60 gel under medium pressure. Infrared spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer as liquid films unless otherwise stated. Low-resolution mass spectra were obtained using a Finnigan Mat 1020 spectrometer. Mass measurements refer to ^{79}Br isotope unless stated and were obtained from the Swansea Mass Spectrometry Service. NMR spectra were recorded in $CDCl_3$ unless otherwise stated on a Bruker AC250 instrument at 250 MHz for protons and 62.9 MHz for carbon and in the latter case were broad-band decoupled. In most cases DEPT spectra were also run and the signs of signals (+ for CH, CH_3; − for CH_2) are indicated on the data for the broad-band decoupled spectrum. Those signals with no sign in such a spectrum are quaternary.

The total base strengths of Grignard reagents were determined as follows: Grignard reagent (1.00 ml) was added to water (10 ml) under argon. A 0.10 M solution of hydrochloric acid (20 ml) was then added and this was titrated with a 0.10 M solution of sodium hydroxide using methyl orange as an indicator.

Preparation and standardisation of Grignard reagents and additional spectroscopic data for some known compounds are presented in the Supplementary Information.

Reduction of dibromocyclopropanes with EtMgBr and titanium isopropoxide in ether

Standard procedure. 1.0 M Ethylmagnesium bromide in ether (12.5–14 ml, 12.5–14.0 mmol, 1.25–1.40 mol equiv.) was added over 10 min to a stirred solution of the dibromocyclopropane (10.0 mmol) and titanium isopropoxide (57–570 mg, 0.2–2.0 mmol, 2–20 mol%) in ether (20 ml) under nitrogen.‖ Stirring was continued for 10 min at 20 °C when water (5 ml) was added carefully, followed by 10% sulfuric acid (20 ml). The aqueous layer was extracted with ether (20 ml) and the combined organic layers were washed with water (25 ml), dried and evaporated at either 760 or 14 mmHg. The product was treated with petroleum (5 ml), filtered through silica (5 g), washing the silica with petroleum (50 ml), and evaporated to give the monobromocyclopropane(s). The product was generally pure enough to use directly; if necessary it was purified by distillation or column chromatography.

The experimental details for known cyclopropanes are presented in the Supplementary Information.

3,10-Dibromo-*r*-1,*t*-2-tricyclo[7.1.0.0^{2,4}]decane (5b). 3,3,10,10-Tetrabromo-*r*-1,*t*-2-tricyclo[7.1.0.0^{2,4}]decane (**5a**)[67] (226 mg, 0.5 mmol) was reduced as above using titanium isopropoxide (28 mg, 0.1 mmol, 20 mol%) and 1.0 M ethylmagnesium bromide (1.15 ml, 1.15 mmol, 2.3 mol equiv.), adding over 15 min and stirring for 40 min to yield the *3,10-dibromo-r-1,t-2-tricyclo[7.1.0.0^{2,4}]decane* (**5b**)[22] (123 mg, 0.42 mmol, 84%) as a mixture of three isomers (*endo*,*endo*; *endo*,*exo* and *exo*,*exo*) in a ratio 28:8:1 which showed δ_H: 0.70–1.50 (8H, m), 1.57–2.50 (4H, m), 2.54 ($2H_{exo,exo}$, dd, *J* 3.3, 3.3 Hz), 2.59 ($1H_{exo,endo}$, dd, *J* 3.7, 3.7 Hz), 3.49 ($1H_{exo,endo}$, t, *J* 7.5 Hz), 3.50 ($2H_{endo,endo}$, t, *J* 7.1 Hz); δ_C (*endo*,*endo*): 16.3+, 22.3+, 27.0−, 28.6−, 33.2+; δ_C (*endo*,*exo*): 17.4+, 22.0+, 23.9+, 26.2−, 27.1+, 27.8−, 28.4, 28.8−, 29.9+, 32.3+; ν_{max}: 2920 s, 2852 s, 1446 s, 1251 s, 602 m cm^{-1}.

1-(2-Bromo-1-methylcyclopropyl)cyclopropanol (8). 1.0 M Ethylmagnesium bromide (40 ml, 40.0 mmol, 4.0 mol equiv.) was added to a solution of methyl 2,2-dibromo-1-methylcyclopropanecarboxylate (**7**) (2.72 g, 10.0 mmol) and titanium isopropoxide (1.14 g, 4.0 mmol, 40 mol%) in ether (80 ml) for 2 h. The mixture was quenched after 1 h by dropwise addition of 15% solution of sulfuric acid (40 ml) and the water layer was extracted with ether (10 ml). The combined ether layers were dried and evaporated to give a crude product which was passed through a column of silica (ether–petrol, 2:3) to give pure *1-(2-bromo-1-methylcyclopropyl)cyclopropanol* (**8**) (Calculated for $C_7H_{12}BrO$: 191.0072. Found M^+: 191.0069) (1.24 g, 6.5 mmol, 65%) which showed δ_H: 0.32 (1H, ddd, *J* 10.4, 6.2, 4.5 Hz), 0.46 (1H, ddd, *J* 10.4, 6.1, 4.6 Hz), 0.61 (1H, ddd, *J* 10.6, 6.2, 4.6 Hz), 0.64 (1H, dd, *J* 6.4, 4.7 Hz), 0.75 (1H, ddd, *J* 10.6, 6.1, 4.5 Hz), 0.95 (1H, dd, *J* 8.1, 6.4 Hz), 1.41 (3H, s), 2.10 (1H, s), 2.99 (1H, dd, *J* 8.1, 4.7 Hz); δ_C: 11.7−, 12.2−, 19.0+, 20.9−, 25.3, 27.1+, 59.1; MS (CI, NH_3): 210 (2), 208 (2), 193 (3), 191 (3), 163 (4), 161 (4), 135 (3), 133 (3), 112 (9), 111 (100); ν_{max}: 3356 s, 3087 m, 3006 m, 2966 m, 2932 m, 1459 m, 1444 m, 1378 m, 1227 s, 1163 s, 1085 m, 1037 m, 1012 s, 955 m, 930 s, 903 m cm^{-1}.

‖ When reactions were carried out in ether with 1–3 mol equiv. of Grignard reagent under the standard conditions described a second layer began to form below the ether as the reaction proceeded. The nature of the second layer was not fully determined but studies are discussed later (see Table 6, entry 41). The second layer was not observed when the reactions were carried out in a more diluted ether solution or a further excess of Grignard reagent was added.

2-Bromo-1-methylcyclopropanecarboxylic acid (10). (*a*) 1.0 M Ethylmagnesium bromide in ether (2.3 ml, 2.3 mmol, 2.3 mol equiv.) was added over 10 min to a stirred solution of 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**9**) (244 mg, 1.0 mmol) and titanium isopropoxide (28 mg, 0.1 mmol, 10 mol%) in ether (3 ml) under nitrogen. Stirring was continued for 10 min at 20 °C when water (1 ml) was added carefully, followed by 10% sulfuric acid (5 ml). The aqueous layer was extracted with ether (3 × 5 ml) and the combined organic layers were washed with aq. NaOH (10 ml of 2%, 5.0 mmol). The organic layer was dried and evaporated to yield nothing. The water layer was treated with 10% aq. sulfuric acid (5 ml, 5.5 mmol) and extracted with ether (3 × 10 ml). The combined organic layers were dried and evaporated at 14 mmHg to give a mixture of *trans*- and *cis*-2-bromo-1-methylcyclopropanecarboxylic acids[70] (160 mg) (all spectra as below) and starting material (1.50 : 1.00 : 0.34 molar ratio; 133 mg, 0.81 mmol, 81% yield of monobromoacids and 27 mg, 0.11 mmol, 11% of starting material).

(*b*) 1.0 M Ethylmagnesium bromide in ether (2.5 ml, 2.5 mmol, 1.0 mol equiv.) was added to a stirred solution of 2,2-dibromo-1-methylcyclopropanecarboxylic acid (610 mg, 2.5 mmol) in ether (7 ml) under nitrogen then titanium isopropoxide (70 mg, 0.25 mmol, 10 mol%) and 1.0 M ethylmagnesium bromide (3.75 ml, 1.5 mol equiv.) during 10 min was added. Stirring was continued for 10 min at 20 °C when water (2 ml) was added carefully; work up as above gave crude product (80 mg). Chromatography on silica (5 g, ether–petrol, 2 : 3) gave pure 1-(2-bromo-1-methylcyclopropyl)cyclopropanol (**8**) (62 mg, 0.33 mmol, 13%) identical to that above. 10% Sulfuric acid (15 ml, 16.5 mmol) was added to the water layer and this was extracted with ether (3 × 25 ml). The combined organic layers were dried and evaporated at 14 mmHg to give a mixture of *trans*- and *cis-2-bromo-1-methylcyclopropanecarboxylic acids*, which showed ^{1}H NMR and IR data identical to the literature,[80,81] and starting material (331 mg, 1.20 : 1.00 : 0.02 molar ratio; 327 mg, 1.98 mmol, 79% yield of monobromo acids and 4 mg, 0.02 mmol, 1% of starting material).

Mechanistic investigations

General method of analysis of reactions of 1a with Grignard reagents. The reactions were monitored by removing samples (0.1 ml) for GLC at 10 min, 30 min, 1 h and at appropriate intervals thereafter, after every addition of Grignard reagent.

Details of individual experiments are given in the Supplementary Information.

Reactions of neophyl chloride with ethylmagnesium bromide in ether. (*a*) 2.35 M Ethylmagnesium bromide (10 ml, 24.0 mmol, 1.2 mol equiv.) was added to neophyl chloride (3.37 g, 20.0 mmol) and titanium isopropoxide (114 mg, 0.4 mmol, 2 mol%) in ether (50 ml) over 10 min. The mixture was refluxed for 48 h and then quenched by dropwise addition of water (10 ml) followed by 15% aq. sulfuric acid (3 ml) and extracted with ether (10 ml). The combined ether layers were dried and evaporated to give crude product (3.03 g) which showed (^{1}H NMR): neophyl chloride 55%, *tert*-butylbenzene (δ_H: 1.39 s (9H), 7.20 m (5H)—identical to an authentic sample) 32%, isobutylbenzene (identical to an authentic sample) 9%, 2-methyl-3-phenylpropene (δ_H identical to that in literature[76]) 4%.

(*b*) 2.35 M Ethylmagnesium bromide (10 ml, 24.0 mmol, 1.2 mol equiv.) was added to neophyl chloride (3.37 g, 20 mmol) in ether (50 ml) over 10 min. The mixture was refluxed for 48 h; work up as above gave a crude product (3.34 g) which was identical to the starting material by GLC and ^{1}H NMR.

Reaction of cyclopropylmethyl bromide with ethylmagnesium bromide in ether. 1.04 M Ethylmagnesium bromide (25 ml, 26.0 mmol, 1.3 mol equiv.) was added to a solution of cyclopropylmethyl bromide (2.70 g, 20.0 mmol) and titanium isopropoxide (114 mg, 0.4 mmol, 2 mol%) in ether (10 ml) for 10 min. The mixture was quenched after 1 h by dropwise addition of water (10 ml) followed by 15% aq. sulfuric acid (3 ml) and the water layer was extracted with ether (10 ml). The combined ether layers were dried and evaporated to give a crude product that gave after distillation fractions: (a) bp 52–70 °C at 50 mmHg (0.48 g), (b) residue (0.47 g). Fraction (a) contained at least seven different compounds, including starting monobromide (by ^{1}H and ^{13}C NMR), two ether dimers (**22**) (see below) and isobutyl ethyl ether (by GC/MS) and two or three unsaturated compounds (by ^{1}H and ^{13}C NMR), the mixture showed δ_H: 0.40 (2H, m), 0.60–1.10 (4.5H, m), 1.1–1.8 (8H, m), 1.9–2.15 (2H, m), 3.34 (2H, d, *J* 7.6 Hz), 3.3–3.7 (2H, m), 4.9–5.1 (1.2H, m), 5.4 (0.2H, m), 5.75–5.90 (0.6H, m); δ_C: 2.7−, 5.7−, 7.9−, 13.5+, 13.8+, 14.4+, 15.0+, 15.2+, 15.6+, 16.0+, 19.2+, 19.7+, 22.7−, 25.3+, 28.4−, 29.2−, 29.9−, 32.0−, 33.6−, 34.7−, 35.7−, 35.8−, 39.9−, 50.7−, 58.3−, 63.5−, 63.6−, 64.4−, 64.6−, 64.8−, 65.8−, 67.7−, 74.4+, 76.4+, 77.4+, 78.1+, 114.3−, 114.4−, 128.3+, 138.7+, 138.9+. Fraction (b) contained at least six different compounds by GC/MS (δ_H: 0.8–2.4 (18H, m), 3.3–3.7 (2H, m), 4.85–5.10 (2H, m), 5.35–5.50 (1H, m), 5.70–5.90 (1H, m); δ_C: 7.92–43.46 (37 peaks), 63.6−, 75.1+, 114.1−, 114.4−, 130.3+, 138.8+, 139.2+. GC/MS (major component): 166 (0.5), 137 (0.5), 125 (2), 109 (2), 95 (8), 82 (7), 81 (8), 73 (100), 67 (7), 56 (9)).

Large scale reduction of 1,1-dibromo-2,2-dimethylcyclopropane

(*a*) 1.0 M Ethylmagnesium bromide (328 ml, 0.36 mol, 1.2 mol equiv.) was added to 1,1-dibromo-2,2-dimethylcyclopropane (68.38 g, 0.3 mol) and titanium isopropoxide (4.26 g, 15 mmol, 5 mol%) in ether (300 ml) over 45 min. The mixture was quenched after 20 min by dropwise addition of water (120 ml) followed by 15% aq. sulfuric acid (40 ml) and water layer was extracted with ether (2 × 50 ml). The combined ether layers were dried and evaporated to give crude product which gave after distillation seven fractions: (a) <40 °C at 200 mmHg (9.02 g), (b) <55 °C at 200 mmHg (6.68 g), (c) <50 °C at 100 mmHg (8.18 g), (d) 30–40 °C at 50 mmHg (26.03 g), (e) <60 °C at 50 mmHg (4.97 g), (f) <60 °C at 20 mmHg (1.96 g), (g) residue (3.59 g). Fractions (a), (b), (c) were combined, dissolved in 25 ml of pentane and separated on silica (60 g) (eluting with pentane) to give 1,1-dimethyl-2-bromocyclopropane (**2c**) and 2-butyl ethyl ether (860 mg, bp 81.5–84 °C).[78,82,84] Fraction (d) was dissolved in 50 ml of pentane and separated on silica (100 g) eluting with pentane to give **2c** which was combined with that from fractions (a), (b), (c) to give **2c** (21.13 g, bp 46 °C/130 mmHg) and 2-butyl 2-propyl ether (226 mg).[78] Fraction (e) was separated on silica (eluting with 2 : 1 pentane–ether) to give 2,3-diethoxybutane[58–60] (198 mg) as a mixture of diastereoisomers. The residue showed δ_H: 0.7–0.9 (1H, m), 0.9–1.2 (3H, m), 1.2–1.8 (1H, m), 3.1–3.7 (1H, m); δ_C: 15–16+, 20–24+, 40–43−, 63–65−, 68–72+; ν_{max}: 3461 m, 2970 s, 2930 s, 2874 s, 1722 m, 1665 m, 1641 m, 1243 m, 1108 br, s cm^{-1}; MS (EI 70 eV): 287 (0.1), 95 (4), 87 (16), 73 (100), 69 (12), 57 (8), 55 (10); MS (CI, NH_3): 241 (0.1), 152 (1), 137 (1.6), 135 (4.7), 133 (4.4), 119 (4.5), 117 (4.5), 97 (6), 87 (11), 86 (7), 85 (44), 84 (10), 83 (100), 80 (7), 78 (18), 66 (12), 64 (22).

(b) With 5 mol% of titanium isopropoxide. 1.15 M Ethylmagnesium bromide (5.2 ml, 6.0 mmol, 1.2 mol equiv.) was added to 1,1-dibromo-2,2-dimethylcyclopropane (1.14 g, 5.0 mmol) and titanium isopropoxide (71 mg, 0.25 mmol, 5 mol%) in ether (5 ml) over 10 min. The mixture was quenched after 20 min by dropwise addition of water (2 ml) followed by 15% sulfuric acid (1 ml). Samples for GLC were taken 10 min after Grignard addition and after the addition of the acid.

(c) With 5 mol% of titanium tetrachloride. 1.15 M Ethylmagnesium bromide (5.2 ml, 6.0 mmol, 1.2 mol equiv.) was

added to 1,1-dibromo-2,2-dimethylcyclopropane (1.14 g, 5.0 mmol) and titanium tetrachloride (47 mg, 0.25 mmol, 5 mol%) in dry ether (5 ml) over 10 min. The mixture was quenched after 20 min by dropwise addition of water (2 ml) followed by 15% sulfuric acid (1 ml) and a solution of EDTA (2.1 g, 6.5 mmol) in water (15 ml). Samples for GLC were taken as in (b) and after addition of EDTA.

Reaction of 1a with 3-deuterio-3-pentylmagnesium bromide (24) in presence of $Ti(O^iPr)_4$. 2,2-Dibromo-1-methyl-1-phenylcyclopropane (435 mg, 1.5 mmol) was reduced by the standard procedure using titanium isopropoxide (21 mg, 0.075 mmol, 5 mol%) and a 0.54 M solution of 3-deuterio-3-pentylmagnesium bromide (1.8 ml, then, after 30 min, 1.8 ml more, 1.3 mol equiv.) for 1 h to yield **3a** (20 mol%) and **2a** (35 mol%), as a mixture with starting material. The ^{1}H NMR, ^{13}C NMR and GC/MS spectra of the products were identical to those of the non-deuterated monobromides, described above.

Reaction of 1a with 1,1,1,3,3,3-hexadeuterio-2-propylmagnesium bromide (25) in the presence of $TiCl_4$·2THF. Compound **1a** (2.61 g, 9.0 mmol) was reduced by the standard procedure using $TiCl_4$·2THF (38 mg, 1 mmol, 1.1 mol%) and a 0.75 M solution of 3-deuterio-3-pentylmagnesium bromide (14 ml, 10.5 mmol, 1.17 mol equiv.) to yield **2a** and **3a**, as a mixture with starting material in the ratio 1.6 : 1.0 : 0.4. No deuterium incorporation was observed in either **2a** or **3a** by ^{1}H NMR.

Reaction of 1a with phenethylmagnesium bromide in THF. 1.01 M Grignard reagent (0.99 ml, 1.0 mmol, 1.0 mol equiv.) in THF was added to **1a** (290 mg, 1.0 mmol) and titanium tetrachloride (9 mg, 0.05 mmol, 5 mol%) in THF (1 ml) over 10 min. After 1 h, further Grignard reagent (0.6 ml, 0.6 mmol, 0.6 mol equiv.) was added. The mixture was quenched after 1 h by dropwise addition of D_2O (0.5 ml); work up as above gave an oil (390 mg), which showed **2a**/**3a** (36%), 1,4-diphenylbutane (2%), ethylbenzene (48%) and styrene (6%) by GLC and **2a**/**3a** (1.5 : 1), ethylbenzene (120) and styrene (15) by ^{1}H NMR (see footnote *a*, 3) Table 3 for an explanation of the NMR analysis method).

Reaction of 1a with phenethylmagnesium bromide in d_8-THF. 1.0 M Grignard reagent (1.2 ml, 1.2 mmol, 1.2 mol equiv.) in d_8-THF was added to **1a** (290 mg, 1.0 mmol) and titanium tetrachloride (9 mg, 0.05 mmol, 5 mol%) in d_8-THF (1 ml) over 10 min. After 1 h, further Grignard reagent (0.6 ml, 0.6 mmol, 0.6 mol equiv.) was added. Quenching after 1 h with water (0.5 ml) and work up as above gave a crude product which showed (^{1}H NMR) **2a**/**3a** (36%, 1.5 : 1), **4a** (64%), ethylbenzene (90%) and styrene (12%). Monobromide **2a** contained 30%, **3a** 47% deuterium in position 1 by GC/MS and ^{1}H NMR; (*m*/*z*, %) for **2a**: 133 (5), 132 (52), 131 (100, $M^+ - Br$), 129 (12), 128 (7), 117 (7), 116 (23), 115 (14), 92 (9), 91 (47); (*m*/*z*, %) for **3a**: 133 (9), 132 (97), 131 (100, $M^+ - Br$), 129 (13), 128 (7), 117 (9), 116 (27), 115 (16), 92 (14), 91 (45). No deuterium was incorporated into the ethylbenzene.

Reduction of 1a and ethyl butyrate. 1.04 M Ethylmagnesium bromide (0.48 ml, 0.5 mmol, 0.5 mol equiv.) was added to **1a** (290 mg, 1.0 mmol), ethyl butyrate (116 mg, 1.0 mmol) and titanium isopropoxide (7 mg, 0.02 mmol) in ether (2 ml) over 5 min. After 10 min, further Grignard reagent (0.48 ml, 0.5 mmol, 0.5 mol equiv.) was added over 5 min. After 10, 30 and 50 min, further Grignard reagent (0.96 ml, 1.0 mmol, 1.0 mol equiv.) was added over 10 min. Quenching after 10 h with H_2O (2 ml) and work up as above gave a mixture which contained by GLC **1a** (0.1%), **2a** + **3a** (90%, 1 : 2 by ^{1}H NMR), **4a** (9.9%), ethyl butyrate (0.5%), 3-ethylhexan-3-ol (58.3%), and one more peak (41.2%). By GC/MS, the penultimate peak was a mixture (1 : 1) of 3-ethylhexan-3-ol and 1-propylcyclopropan-1-ol.

Reduction of phenethyl bromide. 1.04 M Ethylmagnesium bromide (1.06 ml, 1.1 mmol, 1.1 mol equiv.) was added to phenethyl bromide (185 mg, 1.0 mmol) and titanium isopropoxide (7 mg, 0.02 mmol, 2 mol%) in ether (1 ml) over 10 min. Quenching after 10 min by dropwise addition of H_2O (1 ml) and work up as above gave a mixture which by GLC contained 1.3% of ethylbenzene and 98.7% of starting material.

(*E*)-2-Bromo-1-methylcyclopropanecarboxylic acid. To a stirred mixture of (*E*)-2-bromo-1-methyl-1-phenylcyclopropane (211 mg, 1.0 mmol) and $NaIO_4$ (3.85 g, 18 mmol) in acetonitrile (2.5 ml), carbon tetrachloride (2.5 ml) and distilled water (3.65 ml) at room temperature was added $RuCl_3 \cdot xH_2O$ (6 mg, 0.022 mmol, 2 mol%). The mixture was stirred vigorously for 24 h. Dichloromethane (6 ml) was then added to the mixture. The liquid layer was removed. The residue was washed with 20 ml of distilled water and dichloromethane 5 × 5 ml. HCl (3 ml) was added to the combined liquid layers and the organic layer was separated. The water layer was extracted with dichloromethane (3 × 5 ml). The combined organic layers were washed with water (3 × 10 ml) and evaporated. The residue was dissolved in a saturated solution of sodium bicarbonate (30 ml), extracted with dichloromethane (3 × 5 ml) and HCl was added until the pH was 1.0. The water layer was extracted with dichloromethane (3 × 5 ml), and the combined organic layers were dried and evaporated to give (*E*)-2-bromo-1-methylcyclopropanecarboxylic acid as a colourless oil (105 mg, 0.59 mmol, 59%) which was identical to an authentic sample by ^{1}H and ^{13}C NMR.[85]

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