Titanocene-catalyzed alkylative dimerization of vinyl Grignard reagent using alkyl halides†

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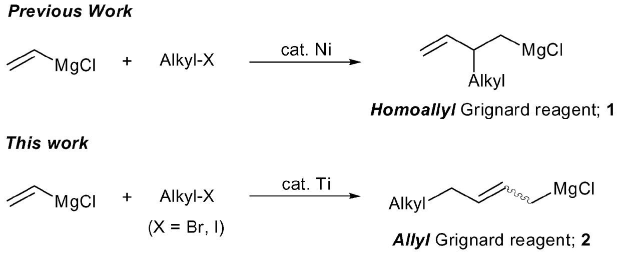
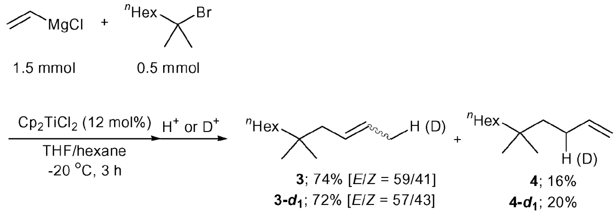
Dimerization of vinyl Grignard reagents and concomitant alkylation with alkyl halides have been achieved by using Cp_2TiCl_2 as a catalyst.

In the past decade, remarkable progress has been made in C–C bond forming reactions using non-activated alkyl halides, which had rarely been employed as carbon sources in conventional transition-metal-catalyzed systems.[1] We have recently developed cross-coupling reactions[2] and regioselective alkylation reactions of C–C unsaturated compounds[3] using alkyl halides and shown that the ate complexes of transition metals formed using Grignard reagents play an important role as active catalytic species. During the course of these studies, we have observed that Ni catalyzes regioselective 2 : 1 coupling of vinyl Grignard reagents with alkyl halides or cyclic ethers to afford alkylated homoallylic Grignard reagents **1** (Scheme 1).[4] Here, we reveal that the alkylative dimerization of vinyl Grignard reagents proceeds regioselectively in the presence of a titanocene catalyst, resulting in allyl Grignard reagents **2**, possessing an alkyl group at the terminal carbon.

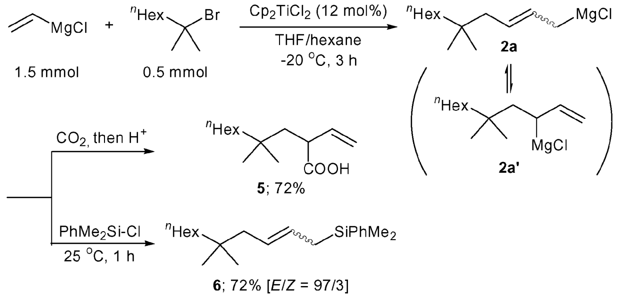
When vinyl magnesium chloride (1.5 mmol, 1.4 M in THF) was reacted with 2-bromo-2-methyloctane (0.5 mmol) in the presence of Cp_2TiCl_2 (0.06 mmol) and hexane (0.22 ml) at –20 °C under nitrogen, a mixture of coupling products **3** and **4** was obtained (Scheme 2). When the reaction mixture was quenched with D_2O, deuterated compounds **3-*d*₁** (*d*-content >98%) and **4-*d*₁** (*d*-content >98%) were formed in 72% and 20% yields, respectively. This result implies that the allyl Grignard reagent **2** was formed in this reaction. The quenching of the resulting mixture with CO_2 or chlorosilane yielded the single regioisomers. For example, CO_2 reacted with the allylic Grignard reagents **2a** *via* a six-membered cyclic transition state to form **5**. On the other hand, the silylation of the terminal carbon of **2a** (or its regioisomer **2a′**) yielded **6**, probably due to the steric hindrance of the silyl group (Scheme 3).



Scheme 1



Scheme 2



Scheme 3

The results obtained using various alkyl halides, along with 3-pentanone as an electrophile, are summarized in Table 1. The use of 2-bromo-2-methyloctane yielded tertiary alcohol **7a** in 87% yield (Table 1, entry 1). Tertiary, secondary, and primary alkyl bromides afforded corresponding products in moderate to good yields (entries 2–5). Under similar conditions, alkyl iodides afforded corresponding alkylated products (entries 6–8); however, no reaction occurred when we used alkyl chlorides and fluorides. The present reaction was sluggish toward substituted vinyl Grignard reagents, such as $MeCH{=}CHMgBr$, $CH_2{=}CMeMgBr$, and $PhCH{=}CHMgBr$.

A plausible reaction pathway is shown in Scheme 4. First, titanocene dichloride reacts with two equivalents of vinyl magnesium chloride to afford divinyl titanocene **8**, which undergoes reductive coupling to afford a titanocene–butadiene complex **9**.[5,6] Then, **9** reacts with vinyl magnesium chloride to afford a titanate complex **10**.[7] Subsequent one-electron transfer from **10** to alkyl halides yields alkyl radicals along with a titanocene(III) complex **11**.[8] Finally the addition of the alkyl radicals to a coordinated butadiene ligand of **11**, or to free

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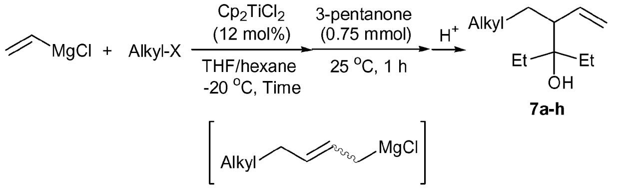
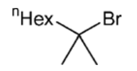
† Electronic supplementary information (ESI) available: Typical experimental procedures and analytical data of products. See DOI: 10.1039/b813596g

Table 1 Titanocene-catalyzed coupling reaction of vinyl Grignard reagent with alkyl halides and quenching with 3-pentanone[a]

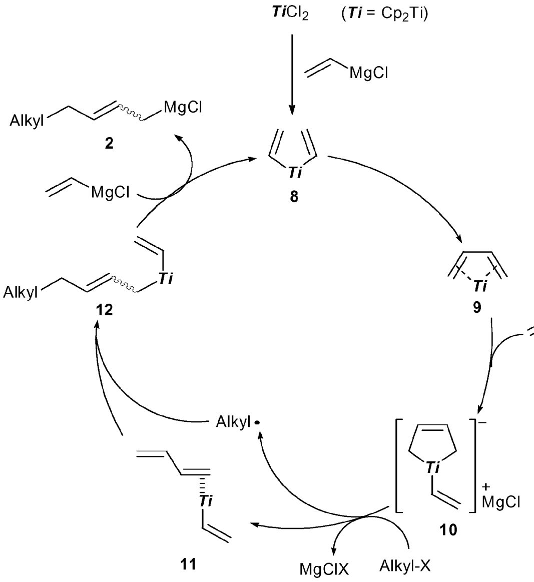


7a-h

2a-h

Entry	Alkyl-X	Time/h	Product	Yield (%)[b]
1		3	**7a**	87
2	$^t C_4H_9$-Br	1	**7b**	77
3	$^s C_4H_9$-Br	3	**7c**	64
4	2-Norbornyl-Br	3	**7d**	63
5[c]	$^n C_4H_9$-Br	4	**7e**	50
6	1-Adamantyl-I	1	**7f**	56
7[c]	$^n C_8H_{17}$-I	1	**7g**	48
8	$^c C_6H_{11}$-I	3	**7h**	69

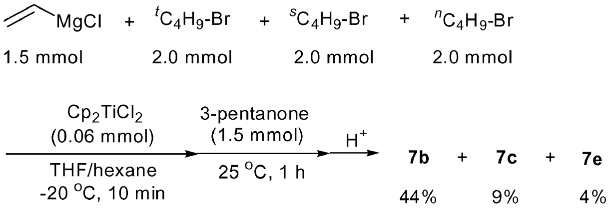
[a] Cp_2TiCl_2 (0.06 mmol), hexane (0.22 ml), alkyl halide (0.5 mmol) vinyl Grignard reagent (1.5 mmol), −20 °C, then 3-pentanone (0.75 mmol) 25 °C, 1 h. [b] Isolated yield. [c] Vinyl Grignard reagent (1.7 mmol) and Cp_2TiCl_2 (0.075 mmol) were used.



Scheme 4

butadiene followed by recombination with Cp_2Ti(vinyl), leads to the formation of an η^1-allyltitanocene complex **12**,[9] which undergoes transmetallation with vinyl magnesium chloride to yield allyl Grignard reagent **2** and regenerate **8**.[10]

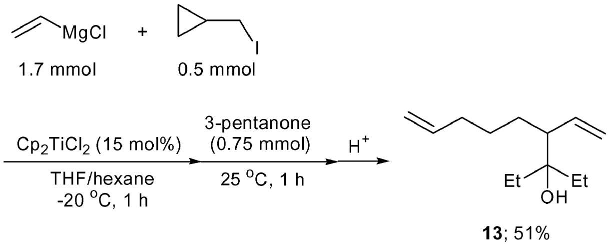
We performed two control experiments to confirm the radical mechanism of the alkylation step. We first carried out a competitive reaction by using equimolar amounts of *n*-butyl, *sec*-butyl, and *tert*-butyl bromides to obtain the relative reactivities of alkyl halides (Scheme 5). The quenching of the reaction with 3-pentanone afforded alcohols **7b**, **7c** and **7e** in 44%, 9% and 4% yields, respectively. The evidence that alkyl bromides with more branched chains reacted faster than those with less branched chains may suggest that alkyl groups are introduced to the coupling products as alkyl radical intermediates.



Scheme 5

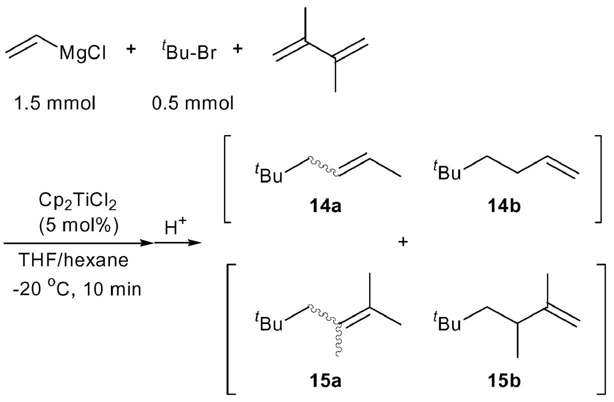
Next, we employed cyclopropylmethyl iodide as an alkylating reagent. As expected, an acyclic product, **13**, was obtained *via* the ring opening of the cyclopropylmethyl radical to 3-butenyl radical (Scheme 6).[11]

From a mechanistic viewpoint, it is interesting to examine whether the alkyl radical attacks butadiene coordinated to the Ti complex or that in the free state. In order to determine this behavior of the alkyl radical, we reacted the vinyl Grignard reagent with *tert*-butyl bromide in the presence of 2,3-dimethylbutadiene at different concentrations, and the ratio of **15** to **14** was plotted against the amount of 2,3-dimethylbutadiene added (Scheme 7). Fig. 1 shows that the addition of 2,3-dimethylbutadiene causes a decrease in the ratio of **15** to **14**; however, this ratio does not obey the first-order kinetics equation on the concentration of 2,3-dimethylbutadiene, *i.e.*, three times the concentration of the 2,3-dimethylbutadiene leads to a 1.7 times increase in the ratio. This result may imply that the alkyl radical attacks the coordinated form of 2,3-dimethylbutadiene and not free 2,3-dimethylbutadiene,



13; 51%

Scheme 6



Scheme 7

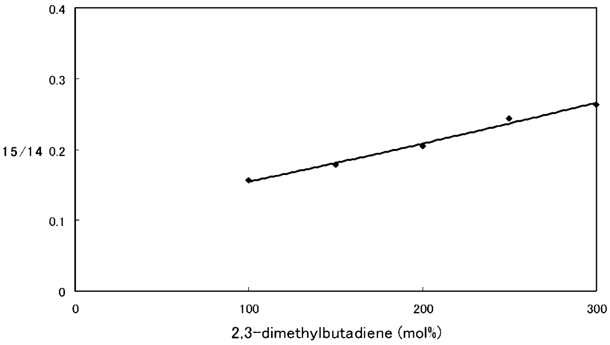
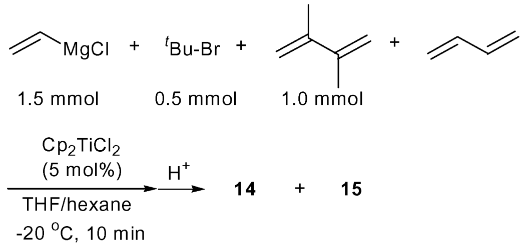


Fig. 1



Scheme 8

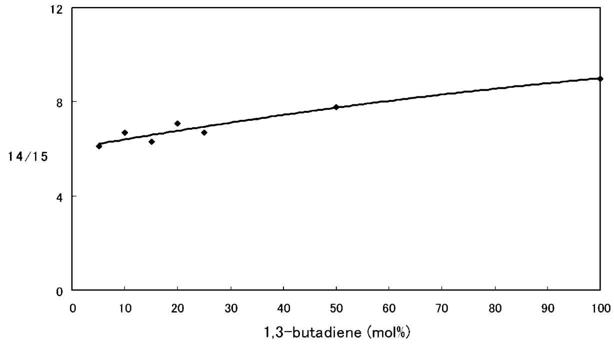


Fig. 2

where the former 2,3-dimethylbutadiene is formed by ligand exchange in the titanocene complex **11**. Next, we carried out similar competitive reactions in the presence of a constant concentration of 2,3-dimethylbutadiene and varying amounts of 1,3-butadiene (Scheme 8). Fig. 2 shows the ratio of **14** to **15** plotted against the amount of 1,3-butadiene used, revealing that the concentration of 1,3-butadiene did not significantly affect the ratio of the two products (the addition of 20 times the amount of butadiene increased the ratio of **14** to **15** ratio by only 1.5 times). This result clearly suggests that the alkyl radical does not attack free 1,3-butadiene, which, however, may inhibit ligand exchange in the titanocene complex **11**.

In conclusion, we have shown that titanocene catalyzes the alkylative dimerization of a vinyl Grignard reagent with alkyl halides to afford allyl Grignard reagents possessing a carbon chain at a terminal carbon. The Ti catalyst would play an important role in the generation of alkyl radicals from alkyl halides by electron transfer from Ti(III) ate complexes. It is also proposed that alkyl radicals would preferentially attack coordinated butadiene rather than free butadiene.

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