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Communication

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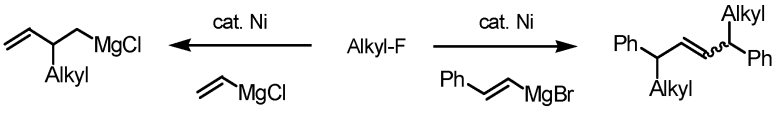

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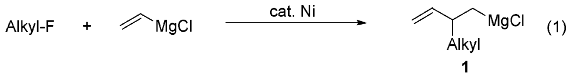
Ni-Catalyzed Alkylative Dimerization of Vinyl Grignard Reagents Using Alkyl Fluorides

Jun Terao, Hiroyasu Watabe, and Nobuaki Kambe*

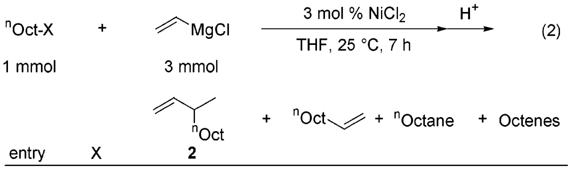
Department of Molecular Chemistry & Science and Technology Center for Atoms, Molecules and Ions Control, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan

Received December 10, 2004; E-mail: kambe@chem.eng.osaka-u.ac.jp

Due to the strong bonding energy of a carbon−fluorine bond, organofluorides have been thought to be one of the most inert classes of organic compounds. As for the aryl fluorides, both catalytic and stoichiometric reactions have already been developed to replace the fluorine atom with other atoms or groups.[1] However, synthetic application of alkyl fluorides still remains undeveloped.[2] We have recently developed a cross-coupling reaction of alkyl fluorides with Grignard reagents with the aid of Ni or Cu catalyst under mild conditions.[3] Here, we disclose that Ni catalyzes the alkylative dimerization reaction of vinyl Grignard reagents using alkyl fluorides under mild conditions, giving rise to 2-alkyl-3-butenyl Grignard reagent (**1**) (eq 1).

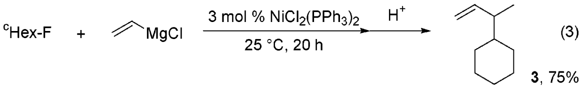


For example, when a reaction of *n*-octyl fluoride (1 mmol) with vinylmagnesium chloride (3 mmol, 1 M in THF) was conducted in the presence of $NiCl_2$ (0.03 mmol) at 25 °C for 7 h, 3-methyl-1-undecene **2** was obtained after protonolysis in 94% yield based on *n*-octyl fluoride as the sole product (eq 2, entry 1). It should be noted that the present reaction proceeds exclusively in the case of alkyl fluorides, whereas the corresponding chlorides, bromides, and iodides undergo reduction, elimination, or cross-coupling with vinyl Grignard reagent either concomitantly (entry 2) or predominantly (entries 3 and 4).

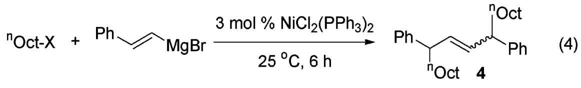


entry	X	**2**	^{n}Oct	^{n}Octane	Octenes
1	F	94%	0%	0%	0%
2	Cl	63%	0%	20%	0%
3	Br	2%	5%	34%	1%
4	I	<1%	9%	44%	2%

When cyclohexyl fluoride was employed, the corresponding product **3** was formed in 75% yield, although a longer reaction time was required, indicating that secondary alkyl groups can be introduced by this reaction (eq 3).

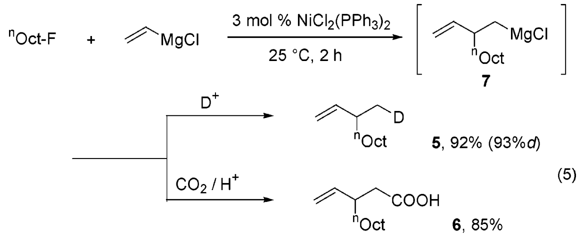


No reaction took place with either MeCH=CHMgBr or CH_2=CMeMgBr under conditions identical to those of eq 2, and alkyl fluorides were recovered. Interestingly, PhCH=CHMgBr gave double alkylative vinyl coupling product **4** in 69% yield as the sole product (*E*/*Z* = 62/38) (eq 4). In comparison to alkyl fluorides, reactions using alkyl chloride (40%) and bromide (18%) were less efficient.

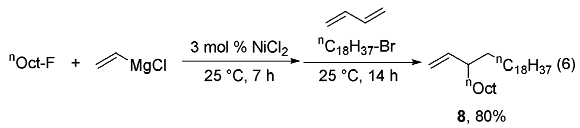


69% (X=F), 40% (X=Cl), 18% (X=Br)

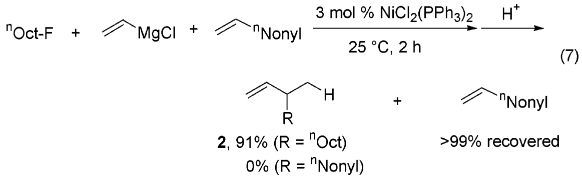
When a reaction of *n*-octyl fluoride with vinyl Grignard reagent was quenched with D_2O, deuterated compound **5** (*d*-content > 93%) was formed in 92% yield (eq 5). When CO_2 was introduced after the reaction, carboxylic acid **6** was obtained in 85% yield (eq 5). These results imply that the butenyl Grignard reagent **7** is formed in the present reaction.



As a synthetic application of the thus-formed **7**, we undertook further alkylation by Ni-catalyzed cross-coupling reaction with alkyl halides.[4] Into a solution of **7** prepared in situ under conditions similar to those of eq 2 were added stearyl bromide (3.0 mmol) and 1,3-butadiene (1 mmol). After stirring at 25 °C for 14 h, the desired coupling product **8** was obtained in 80% yield, where two different alkyl groups are introduced regioselectively to the butenyl skeleton derived from the vinyl Grignard reagent (eq 6).

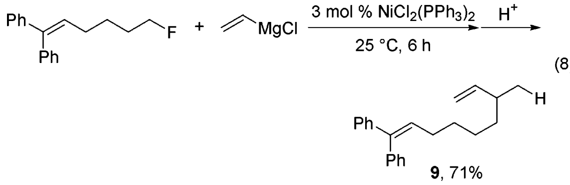


To elucidate the reaction pathway, we first tested the intermediary of alkenes, which may be formed by cross-coupling of alkyl fluorides with vinyl Grignard reagents, since it is known that Ni catalyzes carbomagnetization of alkenes.[5] A reaction of *n*-octyl fluoride with vinyl Grignard reagent was carried out in the presence of 1-undecene (1 mmol) at 25 °C for 2 h under conditions identical to those of eq 2. Quenching the reaction mixture with 1 N HCl afforded **2** in 91% yield, and unreacted 1-undecene was recovered (eq 7). This result clearly indicates that 1-alkenes are not involved as intermediates.



10.1021/ja042565r CCC: $30.25

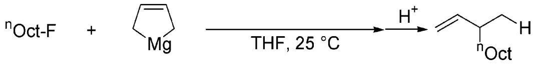
When the reaction depicted in eq 8 was run employing 6-fluoro-1,1-diphenyl-1-hexene as an alkyl fluoride, diene **9** was obtained as the sole coupling product in 71% yield, without formation of any cyclopentane derivatives, which may arise from ring-closing of the 6,6-diphenyl-5-hexenyl radical if generated.[6] This result would rule out a radical mechanism.



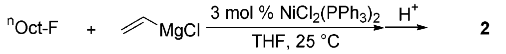
(8)

9, 71%

It is known that alkyl iodides, bromides, or chlorides react with (2-butene-1,4-diyl)magnesium **10** at a γ-vinylic carbon to give 2-alkyl-3-butenyl Grignard reagents **1**.[7] So we carried out the direct reaction of *n*-octyl fluoride with 1.5 equiv of **10** in the presence and absence of a catalytic amount of NiCl$_2$(PPh$_3$)$_2$. The time course of the formation of **2** was plotted in Figure 1 together with the result of the catalytic reaction depicted in eq 10. At any stage of the reaction, **2** was formed more efficiently in the catalytic system than in the direct reactions. These results would suggest that a more reactive intermediate in comparison to **10** might be formed in the present catalytic system.



10 **2** (9)



(10)

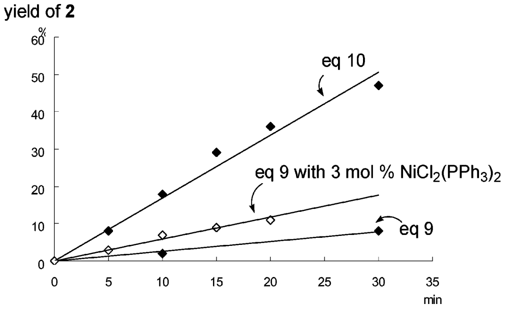
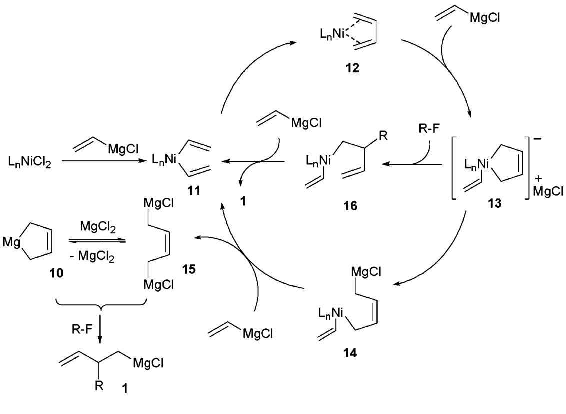


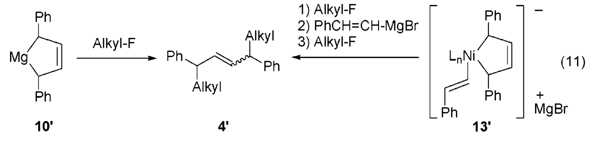
Figure 1. Time course of the formation of **2** in eqs 9 and 10.

Although the detailed mechanism of this coupling reaction has not been clarified yet, plausible reaction pathways are shown in Scheme 1. Nickel dichlorides react with 2 equiv of vinyl Grignard reagents to generate divinylnickel complex **11**, which readily forms nickel−butadiene complex **12** via reductive coupling.[8] Then, **12** reacts again with the vinyl Grignard reagent to give **14** via nickelate complex **13**.[9] Subsequent transmetalation of **14** with vinyl Grignard reagent regenerates **11** along with allylic Grignard reagent **10** or **15**, which reacts with alkyl fluorides, giving rise to **1**. Alternatively, direct reaction of **13** with alkyl fluorides leading to **16** followed by transmetalation with vinyl Grignard reagent also affords **1**. In this system, cationic magnesium would activate the C−F bond by the eminent Mg−F interaction.[3a]

Scheme 1. Plausible Reaction Pathways



When PhCH═CHMgBr is used, the reaction follows a similar pathway via metallacyclopentene intermediates **10′** and/or **13′**, which react with 2 equiv of alkyl halides at both benzylic positions (eq 11).



(11)

In conclusion, a novel dimerization coupling reaction of vinyl Grignard reagents with alkyl fluorides has been developed with the aid of Ni catalysts. The present study provides the first example of a catalytic reaction that demonstrates the superiority of alkyl fluorides as alkylating reagents over the corresponding bromides and iodides as well as chlorides,[2,3a] which may undergo oxidative addition toward Ni(0) such as **12** or electron transfer from **13** leading to the formation of reduction or cross-coupling products. On the other hand, alkyl fluorides are inert for such reactions, and this is key to accomplishing this clean reaction.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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