Fe–Cu cooperative catalysis in the isomerization of alkyl Grignard reagents†

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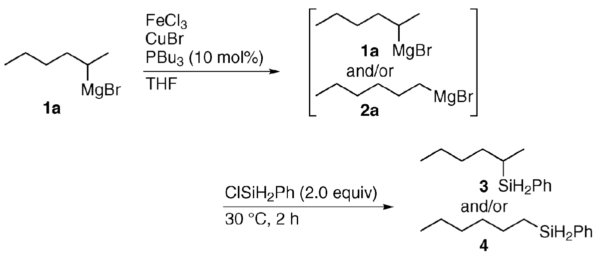
Alkyl Grignard reagents were found to be isomerized to more stable ones in high isomerization ratios (>99%) under cooperative catalysis by iron and copper, which promote isomerization of alkyl groups and transmetalation between Fe–Mg, respectively.

Alkyl Grignard reagents, obtainable simply by mixing alkyl halides with magnesium metal, are one of the most convenient alkylmetals in organic synthesis. Ti(IV) and Ni(II) complexes are known to catalyze isomerization of secondary alkyl Grignard reagents to primary ones through a β-hydride elimination–hydrometalation sequence but the conversion is generally low.[1–4] On the other hand, we have developed arylmagnesiation of alkynes catalyzed by iron and copper complexes, featuring a rare example of cooperative catalysis of two different metals, where iron and copper deal with addition to alkynes and transmetalation between Fe–Mg, respectively.[5,6] Here we report that Fe–Cu cooperative catalysis works effectively in the isomerization of alkyl Grignard reagents to more stable ones, where isomerization of the alkyl groups and transmetalation between Fe–Mg are promoted by Fe and Cu, respectively.[7]

The efficiency of the catalyst system was evaluated for the isomerization of 2-hexylmagnesium bromide (**1a**) to 1-hexyl derivative **2a**, which is more favored both electronically and sterically. Thus, **1a** was treated with a catalyst consisting of $FeCl_3$ (2.5 mol%) and/or CuBr (5 mol%) along with PBu_3 (10 mol%), and the isomerization ratio was determined after transformation to 2-hexyl(phenyl)silane (**3**) and 1-hexylsilane **4** upon treatment with chloro(phenyl)silane (2 equiv.) at 30 °C for 2 h (Table 1). With both the iron and copper catalysts, isomerization was completed within 10 min at −25 °C to give **4** in 83% yield and with >99% selectivity (entry 1).[8] The isomerization was slow at a lower temperature (entries 2 and 3), whereas the isomerization ratio decreased as the reaction temperature was raised, probably because the catalyst is unstable at higher temperatures (entries 4 and 5). In contrast, with the iron catalyst alone, the isomerization proceeded only to a small extent (⩽3%) even over a prolonged reaction period or at a lower temperature (entries 6–8). CuBr did not catalyze the isomerization at all in the absence of $FeCl_3$ (entry 9). Thus obtained **2a** reacted with benzaldehyde and CO_2 to give alcohol **5** and carboxylic acid **6a** (Scheme 1). Under the cooperative catalysis, other 2-alkyl Grignard reagents **1b** and **1c** also underwent complete isomerization (Scheme 1).

Several results are available to discuss the reaction mechanism. The Fe–Cu-catalyzed isomerization of 1,1,1-trideuterio-2-hexylmagnesium reagent **1a-*d*$_3$** followed by the reaction with CO_2 gave 2,2,3-trideuterioheptanoic acid (**6a-*d*$_3$**) (Scheme 2). The result that a deuterium atom migrated from the α-position to β is consistent with the β-hydride elimination–hydrometalation mechanism, as proposed in the titanium-catalyzed isomerization.[2] Stoichiometric reactions of $FeCl_3$ or CuBr with 2-octylmagnesium chloride (**1b**) gave us a clue toward solving which catalyst is responsible for the isomerization of the alkyl group. Thus, treatment of $FeCl_3$–PBu_3 with **1b** (6 equiv.) at −25 °C for 10 min followed by quenching with D_2O gave 1-deuteriooctane (**7**) in 77% yield (based on Fe), whereas the same treatment of CuBr–PBu_3 gave only 2-deuteriooctane (Scheme 3).[9] The production of **7** in the reaction of $FeCl_3$ is

Table 1 Isomerization of 2-hexylmagnesium bromide[a]



Entry	Amount (mol%)		T/°C	Time	Yield (%)[b]	**3** : **4**[b]
	$FeCl_3$	CuBr				
1	2.5	5	−25	10 min	83 (81)[c]	1 : >99
2	2.5	5	−40	10 min	95	94 : 6
3	2.5	5	−40	24 h	77	1 : >99
4	2.5	5	−10	10 min	88	15 : 85
5	2.5	5	30	10 min	89	95 : 5
6	2.5	0	−25	10 min	84	97 : 3
7	2.5	0	−25	24 h	74	97 : 3
8	2.5	0	−40	24 h	83	98 : 2
9	0	5	−25	10 min	>99	>99 : 1

[a] The reaction was carried out in THF (2.0 mL) under a nitrogen atmosphere using 2-hexylmagnesium bromide (**1a**: 0.30 mmol) and PBu_3 (30 μmol) in the presence of $FeCl_3$ (7.4 μmol) and/or CuBr (15 μmol), which was followed by treatment with $ClSiH_2Ph$ (0.60 mmol) at 30 °C for 2 h. [b] Determined by GC. [c] Isolated yield based on **1a** is given in the parentheses.

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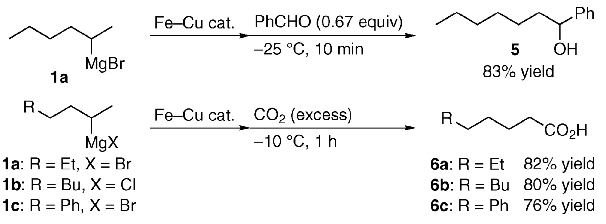
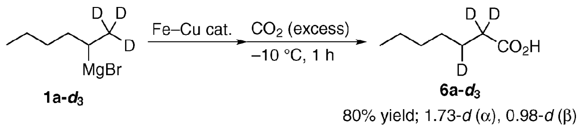
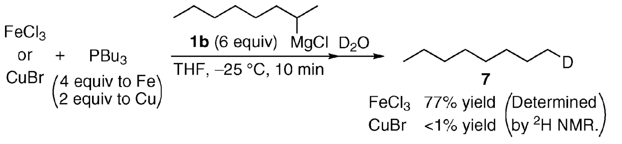


Scheme 1



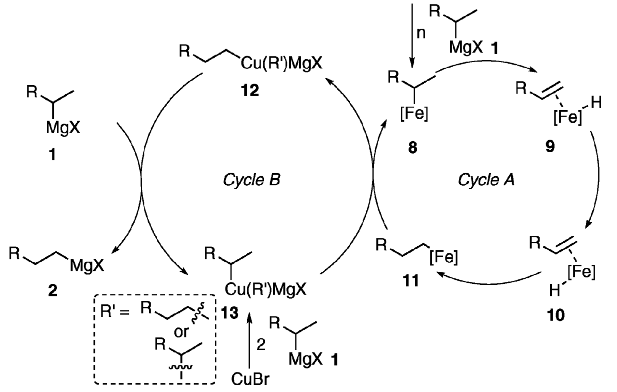
Scheme 2



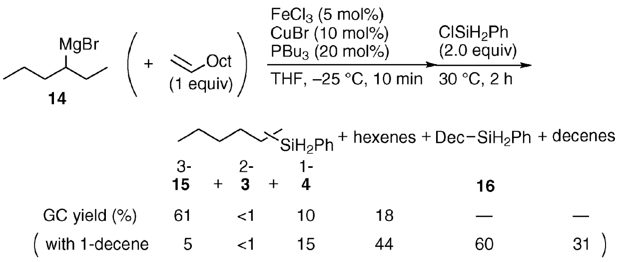
Scheme 3

ascribed to a 1-octyliron species generated through isomerization of the octyl group on iron. From these results, in addition to the essential role of copper as a co-catalyst, we assumed that a cooperative catalysis similar to that in the arylmagnesiation of alkynes[5] is operative as shown in Scheme 4. Here, $FeCl_3$, after being converted into 2-alkyliron complex **8** upon reaction with **1**, promotes isomerization of alkyl groups through a β-hydride elimination–hydrometalation sequence to give **11** (cycle A),[10] which goes into cycle B on transmetalation with cuprate **13** to give 1-alkylcuprate **12** and to regenerate **8**. Further transmetalation of **12** with **1** gives 1-alkyl Grignard reagent **2** and regenerates cuprate **13**.

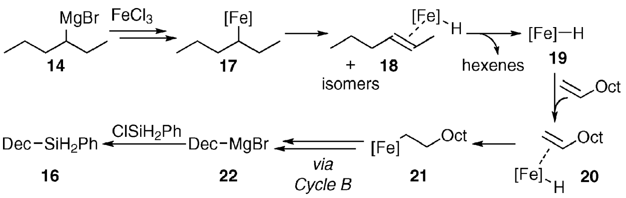
In contrast to 2-hexylmagnesium bromide (**1a**), 3-hexyl derivative **14** did not undergo the efficient isomerization to **2a**, even in the presence of twice the amount (Fe: 5 mol%) of the Fe–Cu catalyst, giving 3-hexyl(phenyl)silane (**15**) and 1-hexylsilane **4** in 61% and 10% yields, respectively, upon treatment with $ClSiH_2Ph$ (Scheme 5). Coproduction of a considerable amount (18% yield) of hexenes, mainly consisting of internal ones, implies that the sterically demanding internal alkenes dissociate from complexes **18**, generated from **17** as shown in Scheme 6, to give free iron–hydride complex **19**, which decomposes with loss of the catalytic activities.[11] The reaction of **14** in the presence of 1-decene (1 equiv.) gave 60% yield of 1-decylsilane **16**, where most of the MgBr moiety was transferred from the C_6 component to C_{10}.[3,12] As shown in Scheme 6, the added terminal alkene probably prevents free iron–hydride complex **19** from decomposition by forming complex **20**, which is converted into **21** through hydroironation and then to **22** *via* cycle B.[13]



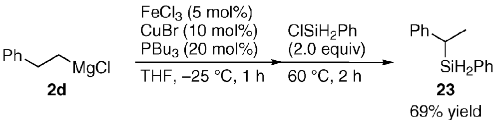
Scheme 4



Scheme 5



Scheme 6



Scheme 7

The Fe–Cu system also catalyzed isomerization of β-phenethylmagnesium chloride (**2d**) to the α-phenethyl derivative, presumably because the anion stabilizing ability of the phenyl group surpasses the steric repulsion between the phenyl and MgCl groups.[14] Thus, treatment of **2d** with the Fe–Cu catalyst (5 mol% of Fe) at −25 °C for 1 h followed by the reaction with $ClSiH_2Ph$ gave **23** in an isomeric purity over 99% (Scheme 7).

In conclusion, we have disclosed that an effective cooperative catalysis is observed in the isomerization of alkyl Grignard reagents to more stable ones with a system consisting of iron and copper, which promote isomerization of alkyl groups and transmetalation between iron and magnesium, respectively.

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Notes and references

[1] Isomerization triggered by a double bond or a strained cycle, as in allylic and cyclopropylmethyl Grignard reagents, is known. For a review, see: E. A. Hill, *J. Organomet. Chem.*, 1975, **91**, 123–271.

2. For titanium-catalyzed isomerization to give *n*-alkyl Grignard reagents, see: (*a*) H. L. Finkbeiner and G. D. Cooper, *J. Org. Chem.*, 1961, **26**, 4779–4780; (*b*) G. D. Cooper and H. L. Finkbeiner, *J. Org. Chem.*, 1962, **27**, 1493–1497; (*c*) B. Fell, F. Asinger and R. A. Sulzbach, *Chem. Ber.*, 1970, **103**, 3830–3841. For nickel-catalyzed isomerization to give *n*-alkyl and α-arylalkyl Grignard reagents in the presence of an alkene, see: (*d*) L. Farády and L. Markó, *J. Organomet. Chem.*, 1971, **28**, 159–165..
3. *n*-Alkyl and α-arylalkyl Grignard reagents are obtained by metal-catalyzed exchange between terminal alkenes and alkyl Grignard reagents. For Ti catalysts, see: (*a*) H. L. Finkbeiner and G. D. Cooper, *J. Org. Chem.*, 1962, **27**, 3395–3400; (*b*) E. C. Ashby and R. D. Ainslie, *J. Organomet. Chem.*, 1983, **250**, 1–12, see also ref. 2*a* and *b*. For Ni catalysts, see: (*c*) L. Farády, L. Bencze and L. Markó, *J. Organomet. Chem.*, 1967, **10**, 505–510, see also ref. 2*d*..
4. Isomerization of the alkyl group derived from alkyl Grignard reagents during the transition metal-catalyzed cross-coupling reaction with aryl halides is known. For an early example, see: K. Tamao, Y. Kiso, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.*, 1972, **94**, 9268–9269.
5. E. Shirakawa, T. Yamagami, T. Kimura, S. Yamaguchi and T. Hayashi, *J. Am. Chem. Soc.*, 2005, **127**, 17164–17165.
6. For a recent review on cooperative catalysis, see: J. M. Lee, Y. Na, H. Han and S. Chang, *Chem. Soc. Rev.*, 2004, **33**, 302–312. See also references cited in ref. 5.
7. $FeCl_3$ is reported to catalyze the exchange between 1-propylmagnesium bromide and styrene to give α-phenethylmagnesium bromide, albeit in a low yield (15%), see ref. 3*a*.
8. Some amount of Grignard reagents must be consumed for reduction of the iron(III) complex and formation of dialkylcuprates. Kochi and Neumann reported that iron(III) complexes are reduced to iron(I) complexes by an excess amount of alkyl Grignard reagents: (*a*) S. M. Neumann and J. K. Kochi, *J. Org. Chem.*, 1975, **40**, 599–606. On the other hand, in the iron-catalyzed cross-coupling of alkyl Grignard reagents with aryl electrophiles, complexes of -2 valent iron were shown to be active species by Fürstner and co-workers: (*b*) A. Fürstner and A. Leitner, *Angew. Chem., Int. Ed.*, 2002, **41**, 609–612; (*c*) A. Fürstner, A. Leitner, M. Méndez and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856–13863.
9. The reaction mixture quenched by D_2O was diluted with $CHCl_3$ and subjected to ^2H NMR analysis. The yield was determined using $Cl_2CDCDCl_2$ as an internal standard.
10. Isomerization from *tert*-butylmetal to a more stable isobutylmetal with iron is known: (*a*) J. Vela, J. M. Smith, R. J. Lachicotte and P. L. Holland, *Chem. Commun.*, 2002, 2886–2887; (*b*) J. Vela, S. Vaddadi, T. R. Cundari, J. M. Smith, E. A. Gregory, R. J. Lachicotte, C. J. Flaschenriem and P. L. Holland, *Organometallics*, 2004, **23**, 5226–5239.
11. Hexenes are produced in 6% yield also in the Fe–Cu-catalyzed reaction of **1a** in entry 1 of Table 1, probably during reduction of the iron(III) complex to a catalytically active low valent complex.
12. The transfer ratio of the MgBr moiety from the C_6 component to C_{10} was much less using 1-hexylmagnesium bromide (**2a**) instead of **14**. Thus, the reaction of **2a** in the presence of 1-decene under the same conditions as in Scheme 5 gave **4** (70% yield), hexenes (11% yield), **16** (7% yield) and decenes (92% yield).
13. The addition of 1-decene after 30 min premixing of all the other components did not affect the yields of **15**, **4** and hexenes (59%, 7% and 23%, respectively), where most of 1-decene remained unreacted (1-decene: 83%; **16**: 3%).
14. Isomerization of β-phenethyltantalum to the α-phenethyl derivative is known: H. Guo, F. Kong, K. Kanno, J. He, K. Nakajima and T. Takahashi, *Organometallics*, 2006, **25**, 2045–2048. For formation of α-arylethyl Grignard reagents by metal-catalyzed exchange between vinylarenes and alkyl Grignard reagents, see ref. 2*a*, *d* and 3*a*.