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### Fe-promoted cross coupling of homobenzylic methyl ethers with Grignard reagents *via* sp<sup>3</sup> C–O bond cleavage<sup>†</sup>

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The first iron-catalyzed formal cross coupling of homobenzylic methyl ethers with alkyl Grignard reagents is realized. The reaction is proposed to proceed through a sequence of dehydroalkoxylation to form the vinyl-intermediate, followed by Fe-catalyzed selective carbometalation to form a benzylic Grignard reagent.

Iron catalysis is now playing a more and more important role in organic synthesis.<sup>1</sup> Due to their low price, low toxicity and easy availability, iron catalysts show great advantages over other frequently used noble metals. Moreover, iron catalysts exhibit significantly different reactivities in various transformations, which could not be easily performed with other transition metals.

Dialkyl ethers broadly exist in nature and industry and are often used as solvents in organic reactions. Actually, C-O bonds of dialkyl ethers are among the most unreactive chemical bonds due to the poor leaving ability of alkoxides. In most cases, alkyl ethers are very stable towards bases and reductants, while the cleavage of C-O bonds of ethers occurs when the strong Brønsted/Lewis acids are present.<sup>2</sup> In the past few decades, remarkable progress has been reported in the development of transition metal-catalyzed selective cleavage of inert C-O bonds, which showed great importance due to its potential utility in organic synthesis.<sup>3</sup> In contrast to sp<sup>2</sup> C-O bonds, the cleavage of sp<sup>3</sup> C-O bonds, especially in the ether substrates, is less reported.<sup>4</sup> Only a few examples have been demonstrated to apply unactivated alkyl ethers as coupling partners.<sup>5</sup> For example, Kakiuchi and Kochi reported a beautiful example of Ru-catalyzed coupling of alkyl ethers bearing 2- or 4-pyridyl groups with arylboroxines.<sup>5d</sup> In their study, the N-atom

is indispensable for the transformation. However, cross coupling of unsymmetrical normal homobenzylic ethers has never been achieved. Herein we reported the first Fe-catalyzed cross coupling of homobenzylic methyl ethers with Grignard reagents through sp<sup>3</sup> C–O bond cleavage.

Our evaluation was initiated from the reaction of 1-(2methoxyethyl)naphthalene 1a with <sup>n</sup>hexylMgCl (Table S1, see ESI<sup>+</sup>). Various catalysts that have potential abilities to cleave C-O bonds were tested. To our delight, the desired cross-coupling product 3aa was obtained in 30% of GC yield in the presence of  $NiCl_2(PCy_3)_2$  as the catalyst and PCy<sub>3</sub> as an additional ligand in o-xylene. Using NiF<sub>2</sub> as the catalyst improved the yield to 51%. Due to the good activity in C-O bond activation, iron catalysts also attracted our attention.<sup>6</sup> Although various iron salts, such as FeBr<sub>2</sub>, Fe(OAc)<sub>2</sub>, FeBr<sub>3</sub>, FeF<sub>3</sub>, and Fe(acac)<sub>3</sub>, gave very low conversions, FeF<sub>2</sub> gave the best result with 55% yield. Other kinds of fluoride salts, such as CoF<sub>2</sub> and CuF<sub>2</sub>, were also tested and showed no reactivity. The yields increased along with the increasing amount of Grignard reagent and reaction time. The desired product 3aa could be obtained in 64% of isolated yield along with the main byproduct 1-(oct-1enyl)naphthalene (3'aa, in 10% GC yield) when 4.0 equivalents of 2a was used in the presence of FeF<sub>2</sub> as the catalyst and the yields could be higher if more 2a was used. Little of the desired product was detected in the absence of additional catalyst, which may arise from the contaminant of iron salts in the Grignard reagent.

With the optimized reaction conditions in hand, we examined the scope of Grignard reagents (Table 1). Primary alkyl Grignard reagents with different chain lengths reacted well to give the desired products in moderate to good yields. Notably, the counter anion of Grignard reagents is crucial for this reaction. For example, *n*hexylMgCl reacted well, while *n*hexylMgBr completely failed. It is important to note that both methyl and phenyl Grignard reagents were completely unreactive, which indicated that the presence of  $\beta$ -H was intrinsically important to this transformation. To our delight, secondary Grignard reagents were even better than primary ones to proceed this chemistry. However, tertiary Grignard reagents completely failed under these conditions, which is similar to previous observation.<sup>6b</sup>

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 Table 1
 Substrate scope of Grignard reagents<sup>a</sup>

1a	✓ OMe + RMgCl		3'
Entry	RMgX	Product	Yield <sup><math>b</math></sup> (%)
1	<sup>n</sup> HexylMgCl	3aa	75 (10)
2	<sup>n</sup> OctylMgCl	3ab	75 (9)
3	<sup>n</sup> BuMgCl	3ac	63 (12)
4	EtMgCl	3ad	33 (13)
5	<sup>n</sup> HexylMgBr	3aa	$<5^{c}$
6	MeMgCl	3ae	$< 5^{c}$
7	PhMgCl	3af	$< 5^{c}$
8	<sup>t</sup> BuMgCl	3ag	$< 5^{c}$
9	<sup>c</sup> HexylMgCl	3ah	85 (7)
10	<sup>c</sup> PentylMgCl	3ai	84 (7)
11	<sup>i</sup> PrMgCl	3aj	82 (8)
12	<sup>i</sup> BuMgCl	3ak	71 (10)

<sup>*a*</sup> Reaction conditions: 0.2 mmol of **1a**, 1.2 mmol of Grignard reagent, 0.02 mmol of FeF<sub>2</sub>, 0.08 mmol of PCy<sub>3</sub>, 2 mL of *o*-xylene. <sup>*b*</sup> Isolated yields. Numbers in parentheses are GC yields of **3**'. <sup>*c*</sup> Determined by GC using decane as an internal standard.

Table 2 Substrate scope of arylethyl methyl ethers



<sup>*a*</sup> Reaction conditions: 0.2 mmol of **1**, 1.2 mmol of **2h**, 0.02 mmol of  $FeF_2$ , 0.08 mmol of  $PCy_3$ , 2 mL of *o*-xylene. Numbers in parentheses are GC yields of 3'. <sup>*b*</sup> Reduction products were detected in 5% GC yield. <sup>*c*</sup> 2-Methoxy-6-vinylnaphthalene was detected in 7% GC yield. <sup>*d*</sup> <sup>1</sup>H NMR yield (0.2 mmol of benzyl methyl ether was used as an internal standard). <sup>*e*</sup> 4-Vinylbiphenyl was detected in 14% GC yield.

Various methyl ethers bearing different aryl groups at the β-position were further examined (Table 2). Fused ring substrates 1a-1d reacted well and afforded the corresponding products in moderate to good yields. The desired product 3ad was also obtained in 47% yield with retention of aryl C-OMe under identical reaction conditions. The lower yield arose from the partial reduction of aryl C-OMe by the cleavage of the sp<sup>2</sup> C-O bond. To our interest, the coupling product of aryl C-OMe was not observed. Besides the fused ring substrates, the phenyl substrates 1e-1k could also accomplish this transformation with good activities. Notably, the steric effect on the aryl ring did not have a significant influence on the reactivity (1e and 1f). Alkyl- and aryl-substituted phenyl substrates (1g and 1h) reacted smoothly to afford the desired products. N-containing groups, such as N-pyrrolyl (1j) and N-pyrrolidinyl (1k), were also tolerated well. Similar to 1d, the aryl C-OMe bond in 1i was also partly reduced, yet the desired product could be obtained in

63% yield. Unfortunately, the secondary alkyl ether **1** did not undergo this transformation, which may be induced by the steric hindrance.

Substrates with leaving groups other than methoxyl were also examined (eqn (1)). The reaction of ethyl ether **1m** with **2a** proceeded to give **3aa** in 40% GC yield, while *tert*-butyl ether **1n** and phenyl ether **1o** were much less reactive and most of the starting materials were recovered. Substrates with other leaving groups, such as pivalate **1p**, carbamate **1q** and alcohol **1r**, did not afford the desired coupling product and the alcohol **1r** was obtained in all these three cases.



During the optimization of the reaction, the styrene derivatives were observed as the major by-product along with different amounts of the Grignard reagent. We hypothesized that the desired cross coupling reaction might go through the sequence of dehydro-alkoxylation and carbometalation, in which the styrene derivative was generated as a key intermediate. To prove our supposition, 1-vinylnaphthalene **4a** was submitted to the typical conditions. Actually, the addition between **4a** and **2a** was performed, however, in a relatively low yield (eqn (2), see ESI<sup>†</sup>). Notably, this kind of addition reaction could not proceed smoothly in the absence of FeF<sub>2</sub>, which indicated the importance of the iron catalyst.<sup>7</sup>

If the carbometalation took place, a new benzyl Grignard reagent should be generated and could be quenched by other electrophiles. When the reaction was quenched with CD<sub>3</sub>OD, the corresponding alkylated product **3aa** was obtained in 63% isolated yield with 66% deuterium at the benzylic position within 12 h (eqn (3), see ESI<sup>†</sup>), which verified our hypothesis to some extent. However, the relatively low ratio of deuterium incorporation indicated that other possibilities, such as direct cross coupling of C–OMe with the Grignard reagent, were also possible in this reaction.

Furthermore, to demonstrate the utility of this new methodology, carbon-based electrophiles and silyl chlorides were used to trap the generated secondary benzylic Grignard reagent (Table 3). For example, the carbomagnesiation of **1a** for 12 h, followed by trapping with MeI, Me<sub>3</sub>SiCl or Et<sub>3</sub>SiCl, gave the corresponding products respectively.

Previous research indicated that activated olefins, such as cyclopropenes,<sup>8</sup> vinyl cyclopropanes,<sup>9</sup> activated allenes<sup>10</sup> and conjugated



<sup>*a*</sup> Reaction conditions: 0.5 mmol of **1a**, 3.0 mmol of **2h**, 0.075 mmol of FeF<sub>2</sub>, 0.2 mmol of PCy<sub>3</sub>, 3 mL of *o*-xylene. <sup>*b*</sup> MeI (3.0 mmol). <sup>*c*</sup> Me<sub>3</sub>SiCl (3.0 mmol). <sup>*d*</sup> Et<sub>3</sub>SiCl (3.0 mmol).



dienes,<sup>11</sup> can be carbometallated with Grignard reagents in the presence of Fe catalysts. While for styrene derivatives, only hydromagnesiation was observed in the presence of Ni or Fe catalysts.<sup>12</sup> To the best of our knowledge, this is the first example of iron-catalyzed carbomagnesiation of styrene derivatives with high regio-selectivity.<sup>13</sup> Moreover, this reaction showed good chemo-selectivity in carbomagnesiation other than hydromagnesiation.

Based on these results, a possible mechanism was proposed (Scheme 1): dialkyl ether 1 underwent dehydroalkoxylation under the reaction conditions to give the corresponding olefin 4. FeF<sub>2</sub> was converted to alkyl-Fe species 5 in the presence of alkyl Grignard reagent 2 and PCy<sub>3</sub>. Subsequently, the carbometallation between alkyl-Fe species 5 and the olefin 4 afforded benzylic iron species 6, followed by transmetallation with alkyl Grignard reagent 2 to produce alkyl-Fe species 5 and benzylic Grignard reagent 7, which was terminated with EtOH to give the product 3. The byproduct 3' would be generated from the  $\beta$ -H elimination of the benzylic metal species 6 or 7. However, the pathway of the direct cross coupling could not be ruled out due to the relatively moderate efficiency of direct addition from styrene derivatives and deuterium incorporation.

In conclusion, the first Fe-catalyzed formal cross coupling of homobenzylic methyl ethers with alkyl Grignard reagents was realized through cleavage of homobenzylic sp<sup>3</sup> C–O bonds. The reaction presumably proceeded through the sequence of dehydroalkoxylation to form the vinyl-intermediate, followed by carbometalation to form benzylic Grignard reagents and quenching with proton. The first example of iron-catalyzed carbomagnesiation of styrenes was also demonstrated other than hydromagnesiation. Further studies to reduce the amount of Grignard reagents, increase the catalytic efficiency, clearly understand the detailed mechanism as well as use other electrophilic reagents to efficiently react with the generated benzylic Grignard reagents are in progress.

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