Selective Double Carbomagnesiation of Internal Alkynes Catalyzed by Iron-N-Heterocyclic Carbene Complexes: A Convenient Method to Highly Substituted 1,3-Dienyl Magnesium Reagents

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Ⓢ *Supporting Information*

ABSTRACT: Controlled multicarbometalation of alkynes has been envisaged as an efficient synthetic method for dienyl and polyenyl metal reagents, but an effective catalyst enabling the transformation has remained elusive. Herein, we report that an iron(II)-N-heterocyclic carbene (NHC) complex $(IEt_2Me_2)_2FeCl_2$ (IEt_2Me_2 = 1,3-diethyl-4,5-dimethylimidazol-2-ylidene) can serve as a precatalyst for the double carbometalation of internal unsymmetrical alkynes with alkyl Grignard reagents, producing highly substituted 1,3-dienyl magnesium reagents with high regio- and stereoselectivity. Mechanistic studies suggest the involvement of low-coordinate organoiron(II)-NHC species as the in-cycle intermediates. The strong σ-donating nature of IEt_2Me_2 and its appropriate steric property are thought the key factors endowing the iron-NHC catalyst fine performance.

Transition-metal-catalyzed carbometalation is a useful method for generating organometallic compounds that are valuable nucleophiles in organic synthesis.[1] Currently, the most successfully developed carbometalation reaction is the monocarbometalation of alkyne, being used for the stereo- and regioselective synthesis of vinyl lithium, magnesium, aluminum, and zinc reagents (Figure 1a). Ideally, the vinyl metal reagent formed from a mono-carbometalation reaction might undergo further carbometalation reactions with alkynes to produce di-, tri-, and even polyenyl metal reagents. While a controlled di- or multicarbometalation method to selectively produce dienyl- or polyenyl metal reagents has not been reported yet, its feasibility can be inferred from the formations of 1,3-diene byproducts in transition-metal-catalyzed carbometalation and hydrosilylation of alkynes.[2,3] Moreover, the uncontrolled polymerization of terminal alkynes catalyzed by $Ti(OBu^n)_4/AlEt_3$ (1:4) and $Fe(acac)_3/AlEt_3$ (1:3) is thought to be a carbometalation reaction of alkynes (Figure 1b).[4] Thus, controlling the degree of alkyne insertion is a key issue. In this regard, we report herein the achievement of selective double-carbometalation reaction of unsymmetrical internal alkynes with alkyl Grignard reagents using an iron(II)-N-heterocyclic carbene (NHC) complex as catalyst (Figure 1c). The iron-catalyzed reaction furnishes 1,3-dienyl magnesium reagents with high regio- and stereoselectivity, which are useful synthons for the preparation of highly substituted 1,3-diene derivatives.

Noting the capability of $Fe(acac)_3/AlEt_3$ in promoting the polymerization of terminal alkynes[4a,b] and the fine performance of $Fe(acac)_3/IPr$ (IPr = 1,3-di(2′,6′-diisopropylphenyl)imidazol-2-ylidene) in catalyzing the arylmagnesiation of unactivated internal alkynes,[5] we targeted iron-NHC catalysts for controlled multicarbometalation of alkynes.[6] After screening a series of iron-NHC complexes for the reaction of phenyl(methyl)acetylene with MeMgBr, the N-ethyl carbene complex $(IEt_2Me_2)_2FeCl_2$ proved an effective catalyst for the double-carbometalation reaction. The reaction of phenyl(methyl)acetylene with 0.70 equiv of MeMgBr and 5 mol % of the iron catalyst in THF at room temperature for 15 min, followed by hydrolysis, gives the diene, (E)-2,4-dimethyl-1,3-diphenyl-1,3-pentadiene (**1a**), and the monoene, 2-methyl-1-phenylpropene (**2a**), in 88% and 2% GC yields, respectively (entry 1 in Table 1), and the isomers of **1a** being trace. The identity of **1a** was confirmed by NMR and mass spectroscopy characterization[7] as well as by single-crystal X-ray diffraction studies on its derivatives (*vide infra*). The E-configuration of **1a** implies the *syn*-addition nature of the double-carbometalation reaction, at least for the second carbometalation step.

The use of NHCs with appropriate steric bulkiness is essential to ensure the selective double-carbometalation reaction. Under similar reaction conditions, the reaction using $(IMe_2Me_2)_2FeCl_2$ that bears the less bulky NHC ligand IMe_2Me_2 (IMe_2Me_2 = 1,3,4,5-tetramethylimidazol-2-ylidene, Chart 1) gives **1a** in lower yield (entry 2), wherein alkyne polymerization as indicated by thickening of the mixture during the reaction course was noticed.
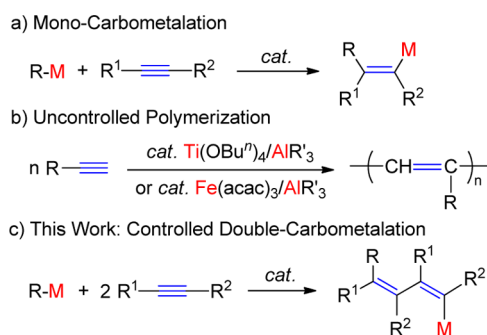

a) Mono-Carbometalation

b) Uncontrolled Polymerization

c) This Work: Controlled Double-Carbometalation

Figure 1. Transformations of alkynes under carbometalation conditions.

Table 1. Carbometalation of Phenyl(methyl)acetylene Followed by Hydrolysis[a,b]

|			GC yield (%)	
entry	catalyst	conv. (%)	1a	2
1	(IEt$_2$Me$_2$)$_2$FeCl$_2$	99	88	2
2	(IMe$_2$Me$_2$)$_2$FeCl$_2$	87	57	4
3	(IPr$_2$Me$_2$)$_2$FeCl$_2$	99	81	12
4[c]	(IMes)$_2$FeCl$_2$	91	20	4
5[c]	FeCl$_2$ + 2 IPr	80	7	2
6[c]	FeCl$_2$ + 2 PPh$_3$	44	4	2
7[c]	FeCl$_2$	40	1	3
8[c]	Fe(acac)$_3$	46	2	3
9	none	0	0	0

[a]Reactions were carried out in THF (1.0 mL) at rt under a nitrogen atmosphere using 1.0 mmol of phenyl(methyl)acetylene and 0.70 mmol of MeMgBr with 5 mol % catalyst loading. [b]Conversions and GC yields were based on the alkyne with n-dodecane as the internal standard. [c]Polyalkynes were formed.

Chart 1. NHC Ligands Used in the Study
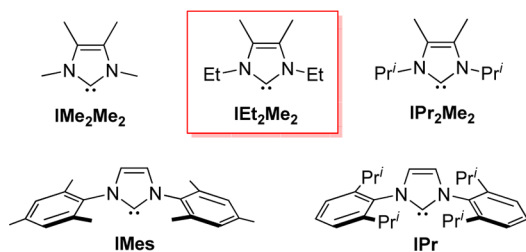
The use of the bulkier NHC-iron catalyst (IPr$_2$Me$_2$)$_2$FeCl$_2$ (IPr$_2$Me$_2$ = 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene, Chart 1) leads to the decrease of the double-/monocarbometalation selectivity (entry 3). The reactions employing the more steric demanding NHC ligands, IMes (IMes =1,3-dimesitylimidazol-2-ylidene) and IPr, mainly afford polyalkynes (entries 4 and 5).[7] Similarly, the trials with FeCl$_2$/PPh$_3$, FeCl$_2$, and Fe(acac)$_3$ as catalysts have alkyne polymerization being dominating (entries 6−8). A control experiment without the addition of any iron catalyst indicates the inertness of phenyl(methyl)acetylene toward MeMgBr (entry 9).

The evidence supporting the formation of the 1,3-dienyl magnesium reagent was gained from the quenching experiment with D$_2$O, which yielded the deuterated product **1a-D** in 82% yield with 98% deuterium incorporation at the olefinic carbon position (Scheme 1). The in situ formed 1,3-dienyl magnesium species can also be trapped by I$_2$, paraformaldehyde, and allyl bromide to form the 1,3-dienyl iodide **3a**, the homoallylic alcohol **4**, and the cross-coupling product **6**, respectively, in good yields (Scheme 1), reflecting the synthetic utility of the double-carbometalation reaction. The esterization of **4** gives **5**. A single-crystal X-ray diffraction study confirmed its stereochemistry as an E-isomer (Figure S1), supporting the syn-addition nature of the carbometalation reaction.

Substrate scope study revealed that the (IEt$_2$Me$_2$)$_2$FeCl$_2$-catalyzed double-carbometalation reaction can be extended to a series of aryl(alkyl)acetylenes, enabling the stereoselective synthesis of versatile highly substituted 1,3-dienes.[8] As shown

**Scheme 1. Transformations of the Resultant 1,3-Dienyl Magnesium Reagent**
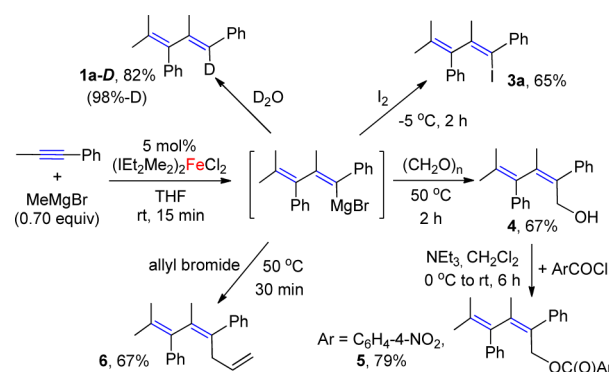
in Table 2, the reactions of MeMgBr with aryl(methyl)acetylenes having electron-donating or -withdrawing groups on the para-

Table 2. Synthesis of Highly Substituted 1,3-Diene Derivatives from Iron-Catalyzed Double Carbometalation of Internal Alkynes[a,b]
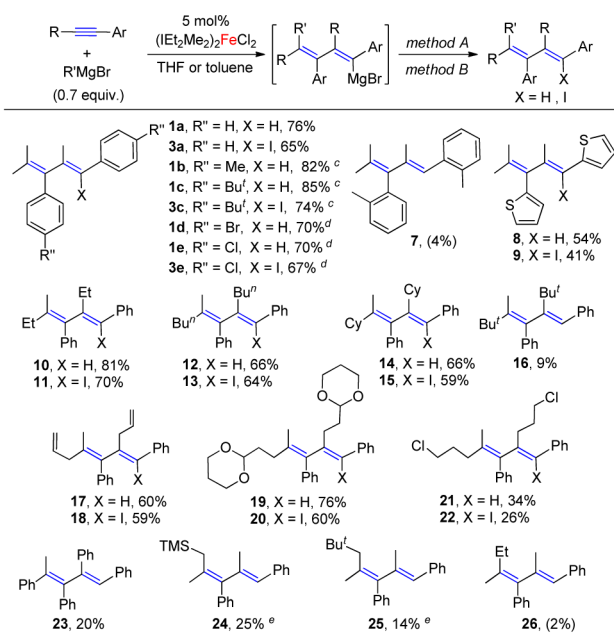
[a]Reaction was carried out in THF (1.0 mL) at rt for 15 min under a nitrogen atmosphere using 1.0 mmol of an alkyne, 0.70 mmol of RMgBr, and 0.050 mmol of (IEt$_2$Me$_2$)$_2$FeCl$_2$, and then quenched with H$_2$O at room temperature (method A) or with 0.75 mmol of I$_2$ at −5 °C (method B). [b]Isolated yields based on the alkyne, and the yields in the brackets are the GC yields. [c]Carbometalation step was conducted in THF at 0 °C for 1 h. [d]Carbometalation step was conducted in toluene at 0 °C for 1 h. [e]Carbometalation step was conducted in THF at 50 °C for 8h.

position of phenyl ring can all afford the 1,3-dienes (**1a−1e**) and 1,3-dienyl iodides (**3a**, **3c**, and **3e**) in good isolated yields (65−85%), along with trace amount of the monocarbometalation products and the isomers of the dienes. The high yields of the dienes with p-chloro- and p-bromo-phenyl substitutes (**1d**, **1e**, and **3e**) reflect the compatibility of the iron-catalyzed reaction to aryl halides, being in contrast to the reported iron-catalyzed dehalogenation reactions of aryl halides with organometallic reagents.[9] Due to the steric demanding nature of (o-tolyl)

(methyl)acetylene, its reaction produces the double-carbometalation product **7** in low yield. In addition to the phenyl-substituted acetylenes, the heteroarene-substituted acetylene (2-thienyl) (methyl)acetylene is also effective for the iron-catalyzed double-carbometalation reaction, affording the 1,3-dithienyl-1,3-dienes, **8** and **9**, in 54% and 41% isolated yields, respectively. Phenyl(alkyl)acetylenes with long and/or substituted alkyl chain are also suitable to the double-carbometalation reaction. The attainment of the dienes **10−22**, among which the structure of **15** is established by X-ray crystallographic study (Figure 2),
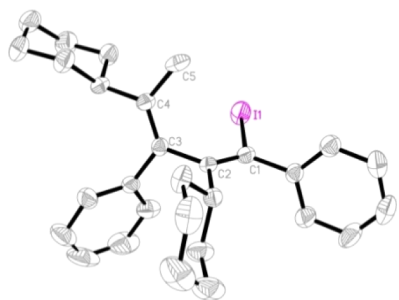

Figure 2. Molecular structures of **15** showing 30% probability ellipsoids and a partial atom scheme. Selected distances (Å) and angles (deg): C1−I1 2.137(4), C1−C2 1.330(6), C2−C3 1.514(6), C3−C4 1.331(6), C1−C2−C3−C4 76.9(6).

unambiguously confirms the *syn*-addition character of the carbometalation reaction. The low yield of the *tert*-butyl-substituted diene **16**, again, indicates that the iron-catalyzed reaction is sensitive to steric nature of alkynes. The obtainment of the chloroalkyl-substituted dienes **21** and **22** suggests that the iron-catalyzed carbometalation reaction is competitive to cross-coupling reactions.[10] Probably due to steric effects, the methylmagnesiation of diphenyl acetylene and the alkylmagnesiation reactions with Me_3SiCH_2MgBr and Bu^tCH_2MgBr give the dienes **23−25** in low yields. The ongoing study revealed the $(IEt_2Me_2)_2FeCl_2$-catalyzed double-carbometalation reactions of phenyl(methyl)acetylene with EtMgBr and PhMgBr merely afford trace amounts of the dienes, which might be related to the instability of IEt_2Me_2-supported iron ethyl and phenyl species.[11]
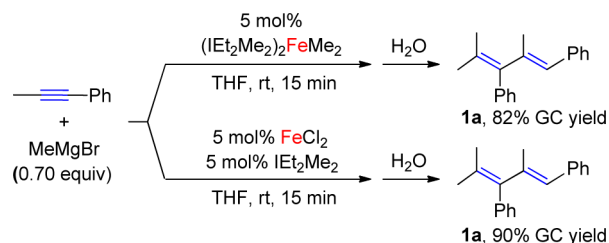
The achievement of the iron-catalyzed double-carbometalation reaction posed the questions on the identity of the in-cycle organoiron intermediates and the factors rendering the high double-carbometalation selectivity. For the former question, low-coordinate iron(II)-NHC methyl and alkenyl species seem the reasonable intermediates. Our previous study showed that $(IEt_2Me_2)_2FeCl_2$ can react with MeMgBr (2 equiv) to form the high-spin iron(II) methyl complex $(IEt_2Me_2)_2FeMe_2$.[11] The iron(II) methyl complex (0.20 mmol) then proved reactive toward phenyl(methyl)acetylene, producing the double-carbometalation product in 0.05 mmol (13% yield relative to the amount of methyl anion in $(IEt_2Me_2)_2FeMe_2$) in 12 h (Scheme 2). Notably, the addition of 1 equiv of $MgBr_2\cdot Et_2O$ to the mixture can significantly accelate the rate, and upon which the reaction in 15 min can furnish the double-carbometalation product in 70% yield (0.28 mmol, the yield is relative to the amount of methyl anion in $(IEt_2Me_2)_2FeMe_2$) and the monocarbometalaion product in 24% yield (0.09 mmol) (Scheme 2). The enhanced rate and increased yield of the double-carbometalation product hint the higher reactivity of the three-coordinate iron(II) methyl species, which can be formed by NHC abstraction from $(IEt_2Me_2)_2FeMe_2$ by $MgBr_2$, toward alkyne insertion. A

Scheme 2. Reactions of $(IEt_2Me_2)_2FeMe_2$ with Phenyl(methyl)acetylene
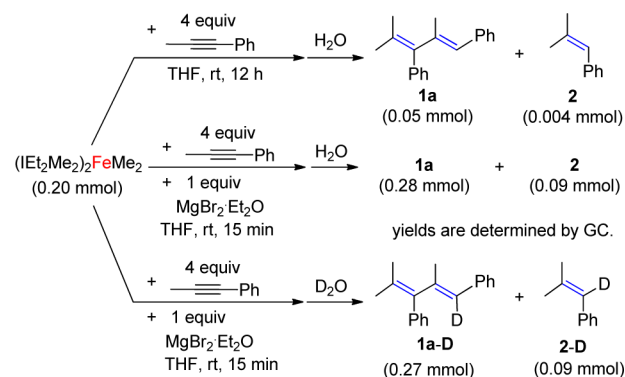
quenching experiment using D_2O indicated the formations of the deuterated products **1a-D** and **2-D** (Scheme 2). These observations suggest that the three-coordinate iron(II) methyl species $(IEt_2Me_2)FeXMe$ (**A**, X = Me or vinyl) could be the genuine speices performing a carbometalation reaction with alkyne and that the three-coordinate iron(II) vinyl species $(IEt_2Me_2)FeX(CPh = CMe_2)$ (**B**, X = Me or vinyl) and $(IEt_2Me_2)FeX(CPh = CMeCPh = CMe_2)$ (**C**, X = Me or vinyl) are the intermediate and product, respectively, in these stoicheometric reactions. The capability of open-shell organoiron(II) species to undergo alkyne insertion reaction is also supported by previously reported hydrometalation of alkynes by Holland's β-diketiminato iron(II) hydride[12] and the carbometalation of alkynes by our iron(II) phenyl species $(IPr_2Me_2)_2FePh_2$.[13] In addition to these stoicheometric reactions, both $(IEt_2Me_2)_2FeMe_2$ and the 1:1 mixture of $FeCl_2/IEt_2Me_2$ proved efficient catalysts for the double-carbometalation reaction (Scheme 3).

Scheme 3. $(IEt_2Me_2)_2FeCl_2$- and $FeCl_2/IEt_2Me_2$-Catalyzed Double-Carbometalation Reactions

Accordingly, a catalytic cycle involving three-coordinate organoiron(II)-NHC species shown in Scheme 4 is proposed for the iron-catalyzed double-carbometalation reaction. Under the catalytic reaction condition, the interaction of the precatalyst $(IEt_2Me_2)_2FeCl_2$ with MeMgBr produces the three-coordinate iron(II) methyl species **A**, which then performs carbometalation with an alkyne molecule to give the iron(II) alkenyl species **B**. Intermediate **B** reacts with another alkyne molecule to give the iron(II) dienyl species **C** that undergoes transmetalation with MeMgBr to yield the dienyl magnesium reagent and regenerate **A**. During the course, the high stereo- and regio-selectivity of the carbometalation reaction should originate from the *cis*-addition nature of the migratory insertion and steric nature of the aryl(alkyl)acetylens. Bergman has used the latter factor to account the regioselective insertion reaction of nickel(II) methyl species $(acac)Ni(PPh_3)Ph$ with phenyl(alkyl)acetylenes.[14] In

Scheme 4. Proposed Catalytic Cycle for the Iron-Catalyzed Carbometalation Reaction
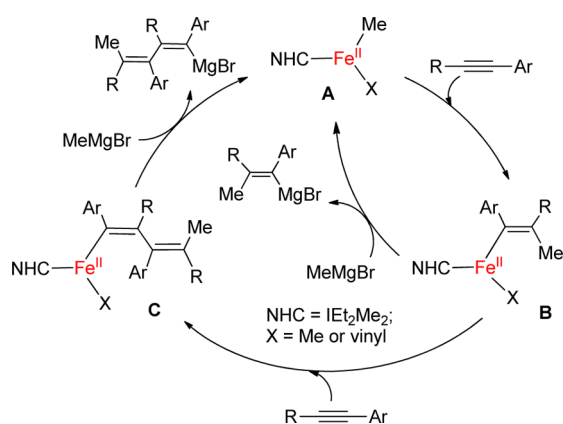
terms of the high double-carbometalation selectivity, the strong σ-donating nature of the NHC ligand in combination with its appropriate steric property of IEt$_2$Me$_2$ should be the key contributing factors.[15] Benefiting from these features, the ligand displacement of IEt$_2$Me$_2$ by carboanions or an alkyne molecule might be hard to occur on the organoiron intermediates **A**–**C**, thereby depressing the side reaction of uncontrolled multi-carbometalation to form oligomers or polymers.[4] On the other hand, the appropriate steric property of IEt$_2$Me$_2$ could allow the iron alkenyl species **B** to react with a molecule of alkyne, leading to double carbometalation, but render the further reaction of the iron dienyl species **C** with alkyne difficult due to steric repulsion between the NHC ligand and the highly substituted 1,3-dienyl group. The molecular structures of **5** and **15** clearly indicate the highly substituted dienes have nonplanar 1,3-diene cores and are sterically demanding.

In summary, we found that iron(II)-NHC complexes can serve as catalysts for the double-carbometalation reactions of unsymmetrical internal alkynes with alkyl Grignard reagents. The high regio- and stereoselectivity of the iron-catalyzed reaction enables the selective synthesis of highly substituted 1,3-dienyl magnesium reagents. The achievement of the double-carbometalation reaction demonstrates the feasibility of controlling the degree of multicarbometalation of alkynes upon judicious selection of catalysts. Inspired by this, we are now pursuing an iron-catalyzed controlled triple-carbometalation reaction for the production of 1,3,5-trienyl metal reagents.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12522.

Experimental details and data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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