Synthesis of Polysubstituted Enynes through Iron-Catalyzed Carbomagnesiation of Conjugated Diynes

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Abstract: Symmetrical and unsymmetrical conjugated diynes are chemo-, regio-, and stereoselectively carbomagnesiated with a Grignard reagent at room temperature in the presence of a catalytic amount of $FeCl_2$ without the need for an external ligand. The resulting magnesium intermediate can be further functionalized to give polysubstituted 1,3-enyne derivatives.

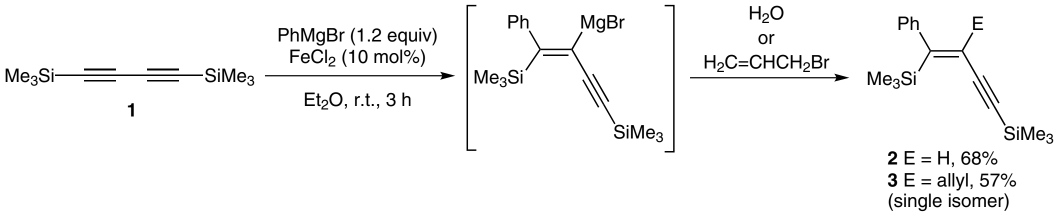
Key words: iron, catalysis, enynes, organometallic reagents, addition reactions

Polysubstituted conjugated enynes are structures of synthetic interest in themselves[1] and for medicinal chemistry[2] and materials science.[3] A conceptually straightforward approach to these compounds[4] includes regio- and stereoselective addition of an organometallic reagent across a diyne, followed by stereospecific electrophilic trapping of the resulting vinylmetal intermediate.[5] There has, however, been a paucity of research activity in this area after pioneering studies on an organozirconium-mediated reaction by Hiyama,[6] and Negishi and Takahashi[7] in the 1990s. We report here an iron-catalyzed[8] carbomagnesiation reaction of a conjugated diyne[9] with a Grignard reagent at ambient temperature, which proceeds chemo-, regio-, and stereoselectively to produce a magnesium intermediate that then reacts with a variety of electrophiles to give polysubstituted enynes.

We previously reported an iron-catalyzed hydromagnesiation of alkynes and diynes,[10] where we speculated that coordination of the substrate to the active iron species is crucial for achieving reactivity and selectivity.[11] With this result in hand, we investigated the carbomagnesiation of a diyne. After considerable experimentation on a prototype reaction between bis(trimethylsilyl)-1,3-diyne (**1**) and Grignard reagents (Scheme 1), we found that **1** reacts with phenylmagnesium bromide (1.2 equiv) in the presence of $FeCl_2$ (10 mol%) at only one of the two triple bonds to produce trisubstituted conjugated diyne **2** in 68% yield upon quenching with water, and a tetrasubstituted diyne **3** in 57% yield upon reaction with allyl bromide. We obtained these products as single regio- and stereoisomers. Although the material balance was not perfect, we neither recovered the starting material nor found byproducts from the diyne by GC, GC–MS, or NMR analysis. The reaction produced a small amount of biphenyl, probably as a result of oxidation of the Grignard reagent by Fe(II) at the beginning of the reaction.

Interestingly, in contrast to the poor performance of other iron salts [$Fe(acac)_2$ (23%), $Fe(acac)_3$ (23%), $FeCl_3$ (25%), FeF_3 (5%), $Fe(OTf)_2$ (12%), $Fe(Oac)_2$ (28%)], $FeCl_2$ was found to be uniquely effective. We also noted that $FeCl_2$ is unique among the others for its poor solubility in diethyl ether, which was the best solvent among other common solvents screened (see the Supporting Information). The presence of monophosphine, diphosphine, diamine, or carbene ligands retarded the reaction, perhaps because they hamper the weak interaction between iron and the diyne substrate, as we speculated in the hydromagnesiation study.[10] Without the iron catalyst, no conversion of the diyne took place. Other first-row transition metals used under the optimized conditions for $FeCl_2$ were inefficient [CuCl (0%), $Mn(OAc)_2$ (0%), $Ni(acac)_2$ (10%), $Co(acac)_2$ (5%)].

The scope of the carbomagnesiation reaction is summarized in Table 1. The reaction proceeded exclusively on only one triple bond for both symmetrical and unsymmetrical diynes. In all cases, the carbometalation reaction proceeded regioselectively to place the metal atom next to the unreacted triple bond.[7] The reaction proceeded in a *syn*



Scheme 1 Iron-catalyzed carbomagnesiation of 1,3-diynes followed by reaction of the magnesium intermediate with electrophiles

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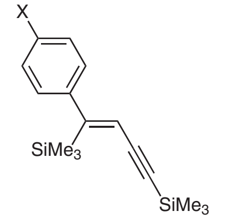
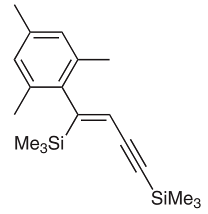
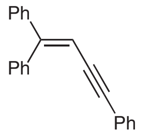
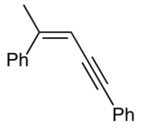
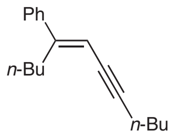
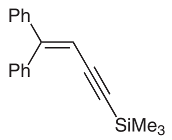
fashion for disilyldiyne (entries 1–5) and dialkyldiyne (entry 8) derivatives, for which a mixture of stereoisomers was reported in the zirconium-catalyzed reactions.[6,7] In contrast, diaryldiynes showed a tendency toward isomerization, and a roughly 1:1 mixture of isomers was obtained (see the Supporting Information). This problem requires further investigation and will be the subject of future studies. An unsymmetrical diyne (entry 9) reacted with chemo-, regio-, and stereoselectivity, and the product was obtained as a single isomer.

Electron-rich (Table 1, entries 3 and 4) and electron-deficient (entry 2) Grignard reagents reacted smoothly. The reaction was not sensitive to steric bulk, thus a mesityl group could also be introduced (entry 5). Methylmagnesium bromide (entry 7) reacted with moderate yield, and a trace amount of regioisomer was observed. When an alkyl Grignard reagent possessing a β-hydrogen was used, hydromagnesiation of the diyne mainly proceeded, as previously observed.[10]

The vinylmagnesium intermediate can be trapped by an electrophile (Scheme 2). For example, when iodobenzene and a palladium catalyst were added after the carbomagnesiation was over, a tetraphenylated enyne was obtained as a single product (Scheme 2, eq. 1). A nickel-catalyzed

Table 1 Iron-Catalyzed Carbomagnesiation of Conjugated Diynes with RMgBr followed by Protonolysis[a]

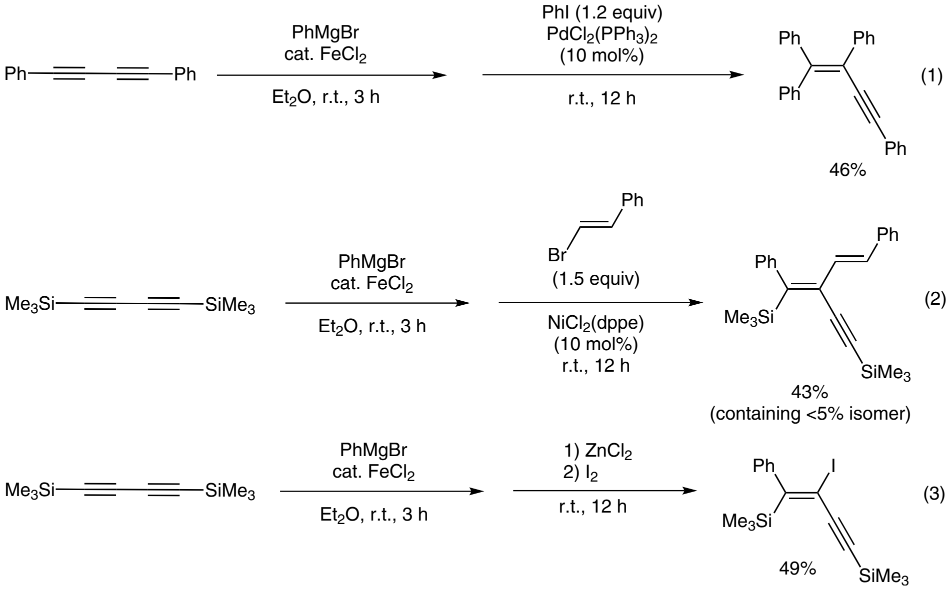
Entry	Diyne	R in RMgBr	Product	Yield (%)[b]
1	$Me_3Si-C\equiv C-C\equiv C-SiMe_3$	4-XC_6H_4		68 (X = H)
2				69 (X = F)
3				83 (X = OMe)
4				69 (X = Me)
5	$Me_3Si-C\equiv C-C\equiv C-SiMe_3$	Mes		65
6	$Ph-C\equiv C-C\equiv C-Ph$	Ph		62
7	$Ph-C\equiv C-C\equiv C-Ph$	Me		43[c]
8	$n\text{-Bu}-C\equiv C-C\equiv C-n\text{-Bu}$	Ph		55[d]
9	$Ph-C\equiv C-C\equiv C-SiMe_3$	Ph		64

[a] Reaction conditions: conjugated diyne (0.3–0.4 mmol), $FeCl_2$ (10 mol%) and Grignard reagent (1.2 equiv) in Et_2O, r.t., 3 h. See the Supporting Information for details.

[b] Isolated yield.

[c] An isomer was produced in 5% yield.

[d] An isomer was produced in 8% yield.



Scheme 2

cross-coupling with bromostyrene gave a stereodefined dieneyne derivative (Scheme 2, eq. 2). We could also transform the magnesium intermediate into an iodoenyne (Scheme 2, eq. 3), which can be utilized as an electrophile for coupling with a nucleophile.

In conclusion, we have developed conditions to effect iron-catalyzed carbomagnesiation of a conjugated diyne with an aryl Grignard reagent in diethyl ether at ambient temperature.[14] As observed for several iron-catalyzed reactions that we have reported recently,[10,12] the reaction conditions do not require an external ligand, probably because the substrate itself acts as a ligand to the iron catalyst. Such simplicity of procedure, and the chemo-, regio-, and stereoselectivity of the reaction, together with the merits of iron catalysis[13] make this reaction an attractive alternative to the zirconium-catalyzed reactions.[6,7] Control of selectivity for a broader range of substrates will be the subject of future studies.

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(14) **Typical Procedure (Scheme 1):** In an oven-dried Schlenk tube, $FeCl_2$ (5.0 mg, 0.040 mmol) was added to a solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne (**1**; 78 mg, 0.40 mmol) in Et_2O (1.6 mL). After 15 min, a solution of phenylmagnesium bromide in Et_2O (0.35 mL, 1.46 mol/L, 0.48 mmol) was added to the reaction mixture at r.t., and the resulting mixture was stirred at r.t. for an additional 3 h, then H_2O (3.0 mL) was added. The organic phase was extracted with EtOAc (3 × 5 mL), then the mixture was passed over a pad of Florisil. The volatiles were removed in vacuo to obtain an oily brown residue. The crude mixture was purified by column chromatography (hexane 100%) to afford the desired compound (74 mg, 68%) as a colorless oil. GC analysis and ^1H NMR analysis of the crude product indicated that only one isomer was obtained.
(*Z*)-1-Phenyl-1,4-bis(trimethylsilyl)but-1-en-3-yne (2): ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.21 (m, 3 H), 7.05–7.03 (m, 2 H), 6.14 (s, 1 H), 0.25–0.22 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.8, 145.1, 128.0, 126.7, 126.4, 122.0, 104.9, 100.5, –0.3, –0.4. GC MS (EI): *m/z* (%) = 272 (27), 257 (52), 199 (17), 155 (16), 73 (100).