Iron-catalyzed carbolithiation of alkynes having no heteroatoms†

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Alkyl- and aryllithium compounds were found to add to alkynes having no heteroatoms in the presence of an iron or iron–copper catalyst to give various trisubstituted vinyllithium compounds.

Carbometalation of alkynes is a highly effective method to prepare multisubstituted alkenes because the metal moiety of the resulting alkenylmetals can be further transformed to various organic groups.[1,2] Organolithium compounds are one of the most easily available organometals but their high basicity has severely restricted their use in the alkylmetalation of alkynes.[3,4] Namely, the deprotonation of not only acetylenic protons but also propargylic protons generally predominates over the addition.[5,6] Alkyllithiation of alkynes having propargyl protons is possible when the addition is accelerated through intramolecular reaction[7] or by a heteroatom directing group such as an alkoxy or amino group on alkynes,[8] but simple alkyl groups on alkynes are prone to suffer deprotonation. Significant improvement was achieved by Hosomi and co-workers with the introduction of iron catalysts, where even a methyl group on alkynes is compatible with alkyllithiation, though the disclosed alkynes are limited to those having an ether or amine moiety at the opposite site to the alkyl group.[9,10] Here we report an improved iron catalyst system, which is applicable to alkyllithiation of alkynes having no heteroatoms. We also found that a Fe–Cu cooperative catalyst is effective for aryllithiation of alkynes.[10a]

Suitable reaction conditions for alkyllithiation of alkynes were surveyed in the reaction of butyllithium (**1a**) with 1-phenylpropyne (**2a**) using 5 mol% of an iron catalyst (Table 1). The reaction conditions optimized by Hosomi and co-workers[9] for butyllithiation of heteroatom-containing alkynes were found not to be effective for the addition to **2a**. Thus, treatment of **1a** (3.0 equiv.) with **2a** (1.0 equiv.) in the presence of Fe(acac)$_3$ (5 mol%) in toluene at −20 °C for 2 h gave only 5% yield of (*E*)- and (*Z*)-2-methyl-1-phenyl-1-hexene (**5a** and **6a**) in 98 : 2 ratio after methanolysis (entry 1). Another set of conditions (FeCl$_3$ in Et$_2$O), which was the second best in the Hosomi's paper, worked much better here to give **5a** and **6a** in 61% yield with 82% conversion of **2a**, though the stereoselectivity was low (66 : 34) (entry 2). Addition of 20 mol% of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to this combination increased the yield to 85% with full conversion of **2a** (entry 3). Under these conditions, only 15 min was required for satisfactory conversion (entry 4). The yield was slightly increased on further addition of PPh$_3$ (10 mol%) and reduction of the amount of **1a** to 1.5 equiv. (entries 5 and 6). Although each entry thus far resulted in a low **5a**/**6a** value, **5a** predominated (**5a** : **6a** = 98 : 2) at 1 min reaction time with 12% conversion of **2a** (entry 7), showing that the initial product is *syn* adduct **3a**, which isomerizes to **4a** under the reaction conditions. It was found that the reaction with an excess amount of **2a** over **1a** improved the stereoselectivity, though the yield based on **1a** is not high (entry 8). Considering that a certain amount of butyllithium (**1a**) is consumed for the reduction of FeCl$_3$ to a catalytically active low valent species, the reduction with zinc metal was conducted before the addition of **1a**. Thus, pretreatment with zinc (20 mol%) increased the yield to 85% (entry 9). Use of reduced amounts of **2a** lowered the stereoselectivities (entries 10 and 11), whereas the yield was decreased with an increased amount of **2a** (entry 12). Treatment of **1a** (3.0 equiv.) with **2a** in the presence of TMEDA and PPh$_3$ but in the absence of an iron catalyst gave phenylallene (38%) and 3-phenylpropyne (10%), generated through deprotonation of propargyl protons, but no butyllithiation products (entry 13).

Table 2 illustrates the scope of the iron-catalyzed alkyllithiation in use of two sets of conditions, methods A and B. When the products do not have *E*/*Z* isomers (R^1 = R^2), operationally more simple method A was chosen, where 1.5 equiv. of alkyllithium **1** to alkyne **2** is used (*cf.* entry 6 of Table 1). In the case where R^1 and R^2 are different, we used method B, which employs 1.5 equiv. of **2** to **1** in combination with zinc as a reductant, to minimize the *E*/*Z* isomerization (*cf.* entry 9 of Table 1). Aryl(butyl)acetylenes having an electron-withdrawing or -donating group on the benzene ring accepted the addition of butyllithium (**1a**) generally in high yields (entries 1–6). Butyllithiation of 1-phenyl-1-hexyne using method B proceeded in a high yield (entry 7). Alkynes having an alkyl group other than butyl reacted stereoselectively with butyllithium under method B conditions (entries 8–10). The reaction of other alkyllithium compounds gave addition products in high stereoselectivities (entries 11 and 12).

Attempts to apply the catalyst system of the alkyllithiation to aryllithiation failed[11] but the Fe–Cu cooperative catalysis that is effective for arylmagnesiation of alkynes[10a] also worked here. Thus, the reaction of phenyllithium (**7a**: 2.0 equiv.) with 1-phenylpropyne (**2a**: 1.0 equiv.) in the presence of Fe(acac)$_3$ (5 mol%), CuBr (10 mol%) and PBu$_3$ (40 mol%) in Et$_2$O at 30 °C for 3 h gave 62% yield of (*E*)-1,2-diphenylpropene (**8a**) and its stereo- and regioisomers (**9a** and **10a**) in 93 : 5 : 2 ratio (Scheme 1). The aryllithiation proceeded in high

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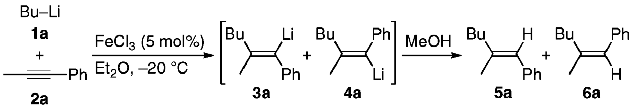
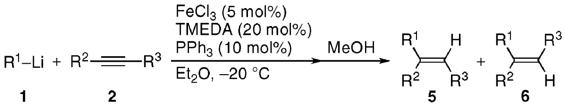
Table 1 Iron-catalyzed butyllithiation of 1-phenylpropyne followed by methanolysis[a]



Entry	Amount **1a**/**2a** (equiv.)	Additives (mol%)	t/min	Consumed **2a** (equiv.)[b,c]	Yield[c,d] (%)	Ratio **5a** : **6a**[c]
1[e]	3.0/1.0	—	120	0.32	5	98 : 2
2	3.0/1.0	—	120	0.82	61	66 : 34
3	3.0/1.0	TMEDA/20	120	0.99	85	49 : 51
4	3.0/1.0	TMEDA/20	15	0.94	81	63 : 37
5	3.0/1.0	TMEDA/20, PPh_3/10	15	0.97	83	57 : 43
6	1.5/1.0	TMEDA/20, PPh_3/10	15	0.97	88	51 : 49
7	1.5/1.0	TMEDA/20, PPh_3/10	1	0.12	4	98 : 2
8	1.0/1.5	TMEDA/20, PPh_3/10	15	0.96	64	92 : 8
9	1.0/1.5	TMEDA/20, PPh_3/10, Zn/20	15	0.99	85	90 : 10
10	1.0/1.0	TMEDA/20, PPh_3/10, Zn/20	15	0.96	88	65 : 35
11	1.0/1.2	TMEDA/20, PPh_3/10, Zn/20	15	0.97	85	85 : 15
12	1.0/2.0	TMEDA/20, PPh_3/10, Zn/20	15	1.06	72	94 : 6
13[f]	3.0/1.0	TMEDA/20, PPh_3/10	120	0.63	< 1	—

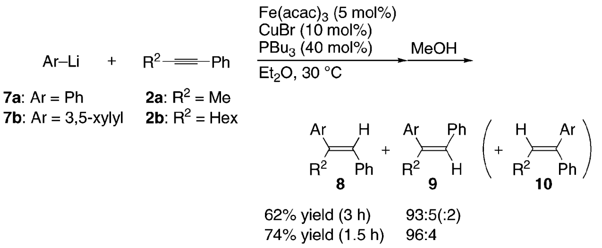
[a] The reaction was carried out in Et_2O (1.0 mL) at −20 °C under a nitrogen atmosphere using BuLi (**1a**: 1.53–1.66 M in hexane) and 1-phenylpropyne (**2a**) in the presence of $FeCl_3$ (0.020 mmol). [b] The amount of consumed **2a**. [c] Determined by GC. [d] The yield based on **2a** (entries 1–7 and 13) or **1a** (entries 8–12). [e] $Fe(acac)_3$ and toluene were used instead of $FeCl_3$ and Et_2O, respectively. [f] In the absence of $FeCl_3$.

Table 2 Iron-catalyzed alkyllithiation of alkynes followed by methanolysis[a]



Entry	Method	R^1	R^2	R^3	t/h	Yield[b] (%)	Ratio **5** : **6**[c]
1	A	Bu	Bu	Ph	1.5	81	—
2	A	Bu	Bu	$3\text{-}CF_3C_6H_4$	1.5	82	—
3	A	Bu	Bu	$4\text{-}ClC_6H_4$	3	79	—
4	A	Bu	Bu	$2\text{-}MeC_6H_4$	24	65	—
5	A	Bu	Bu	$3\text{-}MeOC_6H_4$	1.5	96	—
6	A	Bu	Bu	$2\text{-}MeOC_6H_4$	1.5	82	—
7	B	Bu	Bu	Ph	0.25	84	—
8	B	Bu	Hex	Ph	0.25	79	93 : 7
9	B	Bu	*i*-Bu	Ph	1.0	82	94 : 6
10	B	Bu	Et	Ph	1.0	81	92 : 8
11	B	Hex	Me	Ph	1.0	75	95 : 5
12	B	*i*-Bu	Me	Ph	0.25	72	> 99 : 1

[a] The reaction was carried out in Et_2O at −20 °C under a nitrogen atmosphere using an alkyllithium (**1**) and an alkyne (**2**) in the presence of $FeCl_3$, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and PPh_3. Method A: **1** = 0.68 mmol, **2** = 0.45 mmol, $FeCl_3$ = 23 μmol, TMEDA = 90 μmol, PPh_3 = 45 μmol. Method B: **1** = 0.40 mmol, **2** = 0.60 mmol, $FeCl_3$ = 20 μmol, TMEDA = 80 μmol, PPh_3 = 40 μmol, in combination with Zn (0.080 mmol). [b] Isolated yield based on **2** (entries 1–6) or **1** (entries 7–12). [c] Determined by GC.

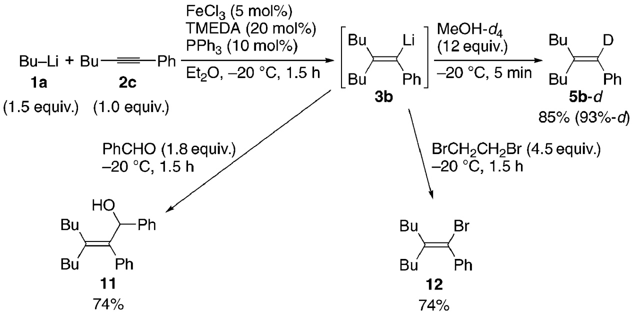


Scheme 1

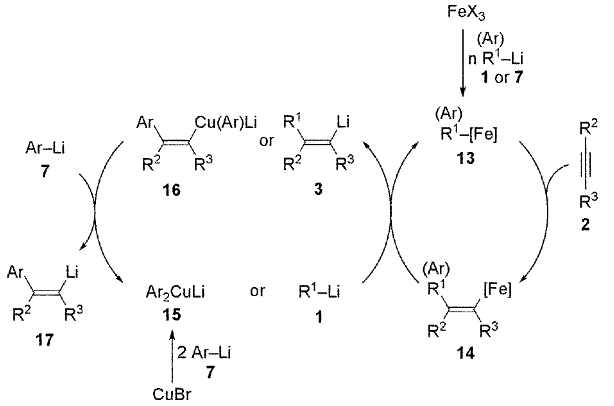
stereo- and regioselectivities also between 3,5-xylyllithium (**7b**) and 1-phenyl-1-octyne (**2b**).

Quenching the reaction mixture from addition of butyllithium (**1a**) to 1-phenyl-1-hexyne (**2c**) with MeOH-d_4 gave alkene **5b**-*d* having a deuterium atom on the phenyl-substituted alkene carbon, showing that alkenyllithium **3b** was actually produced by the alkyllithium (Scheme 2). Transformation of butyllithiation product **3b** upon reaction with other electrophiles demonstrates synthetic utility of the carbolithiation reactions. Thus, the reaction mixture above was treated with benzaldehyde or 1,2-dibromoethane to give allyl alcohol **11** or alkenyl bromide **12**, respectively, in a high yield (Scheme 2).

Production of *syn*-adducts is likely to show that insertion of alkynes into the Fe–C bond generated by the reaction of an iron complex with an organolithium compound is operative in the addition step. A plausible catalytic cycle based on that in the Fe–Cu-catalyzed arylmagnesiation of alkynes[10a] is shown



Scheme 2



Scheme 3

in Scheme 3. Alkyllithium **1**, which is more nucleophilic than aryl Grignard reagents, seems not to require a copper co-catalyst to transmetalate with alkenyliron complex **14** giving alkyllithiation product **3**. In contrast, it is likely that less nucleophilic aryllithium **7** does not have ability to transmetalate directly with **14** but with a copper complex to give diarylcuprate **15**, which undergoes transmetalation with alkenyliron **14** to regenerate aryliron complex **13**. The resulting cuprate (**16**) having an alkenyl group reacts with aryllithium **7** to give aryllithiation product **17** with regeneration of diarylcuprate **15**.

In conclusion, we have disclosed that alkyl- and aryllithium compounds undergo stereo- and regioselective carbometalation reactions with alkynes having no heteroatoms under iron or iron–copper catalysis.

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11 The reaction of **7a** with **2a** (*cf.* Scheme 1) under the conditions of method A in Table 2 at –20 or 30 °C gave only 5% (*E* : *Z* = >99 : 1) or 14% (*E* : *Z* = 85 : 15) yield of the adducts with 6 and 70% conversion of **2a**, respectively.