ORGANIC LETTERS

2007
Vol. 9, No. 6
1045−1048

Iron-Catalyzed Arylmagnesiation of Aryl(alkyl)acetylenes in the Presence of an *N*-Heterocyclic Carbene Ligand

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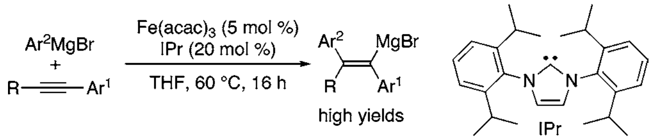
Received December 27, 2006

ABSTRACT



Addition of arylmagnesium bromides to aryl(alkyl)acetylenes proceeded in the presence of an iron catalyst and a *N*-heterocyclic carbene ligand to give high yields of the corresponding alkenylmagnesium reagents, which were transformed into tetrasubstituted alkenes by subsequent treatment with electrophiles.

Carbometalation of alkynes generating alkenylmetal species is one of the most powerful methods of synthesizing multisubstituted alkenes,[1] and the use of iron catalysis for this transformation has attracted increasing attention owing to its high activity toward the reactions of organomagnesium reagents.[2] However, although heteroatom-containing alkynes are known to undergo the carbometalation with high reactivity and selectivity due to the stabilizing effects caused by their coordination,[3] the carbometalation of those lacking the heteroatoms remains to be developed.[4] We have recently reported the arylmagnesiation of simple dialkylacetylenes that is realized for the first time by an iron/copper cocatalyst system.[5] Herein we report that the iron-catalyzed arylmagnesiation of aryl(alkyl)acetylenes is greatly improved by addition of a catalytic amount of an *N*-heterocyclic carbene ligand to give high yields of the corresponding trisubstituted alkenylmagnesiums that are convertible into tetrasubstituted alkenes by reaction with electrophiles.[6,7]

For the addition of 4-methoxyphenylmagnesium bromide (**2m**) to 1-phenyl-1-hexyne (**1a**) in the presence of Fe(acac)$_3$ as a catalyst, several additives were examined for their effects on the catalytic activity and selectivity, and it was found that the addition of a catalytic amount of an *N*-heterocyclic

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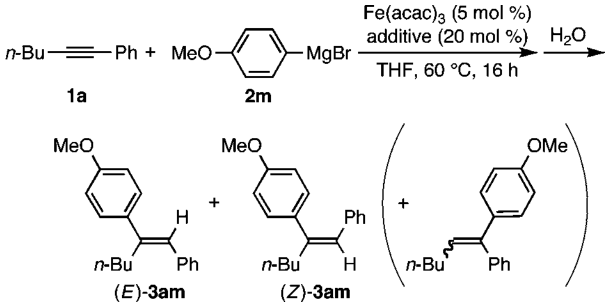
10.1021/ol063132r CCC: $37.00

carbene ligand greatly improved the yield of the arylmagnesiation (Table 1). Thus, the reaction of **1a** with **2m** (2 equiv) in the presence of Fe(acac)$_3$ (5 mol %) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr)[8] (20 mol %) in THF at 60 °C for 16 h gave, after addition of H_2O, 91% yield of the addition product, which consists of (*E*)-2-(4-methoxyphenyl)-1-phenyl-1-hexene ((*E*)-**3am**) and its (*Z*) isomer ((*Z*)-**3am**) in a ratio of 88/11 together with a small amount (1%) of its regioisomer (entry 1).[9] The amount of the carbene ligand IPr can be reduced to 10 mol % with a small decrease of the yield of the addition product **3am** (entry 2). The reaction without IPr ligand under otherwise the same reaction conditions gave only 23% yield of **3am** (entry 3), demonstrating the high efficiency of the carbene ligand in the present arylmagnesiation. Use of phosphine ligands, P(*n*-Bu)$_3$, P(*t*-Bu)$_3$, and PPh$_3$ in place of the carbene IPr did not improve the yield (entries 4−6), the yields being as low as that without ligand. The Fe/Cu cocatalyst system consisting of Fe(acac)$_3$ (5 mol %), P(*n*-Bu)$_3$ (40 mol %), and CuBr (10 mol %), which we have reported previously for arylmagnesiation,[5] was as effective as the present Fe/IPr catalyst, giving the addition products in 79% yield (entry 7).

Table 1. Iron-Catalyzed Arylmagnesiation of 1-Phenyl-1-hexyne (**1a**): Additive Effect[a]



entry	additive	yield (%)[b]	*E*:*Z*[c]
1	IPr	91	88:11 (:1)
2	IPr[d]	78	89:9 (:2)
3	none	23[f]	85:13 (:2)
4	P(*n*-Bu)$_3$	16[f]	72:21 (:7)
5	P(*t*-Bu)$_3$	23[f]	82:17 (:1)
6	PPh$_3$	33[f]	86:12 (:2)
7	P(*n*-Bu)$_3$[e] + CuBr[d]	79	92:7 (:1)

[a] The reaction was carried out in THF (1.0 mL) at 60 °C for 16 h under a nitrogen atmosphere using 4-methoxyphenylmagnesium bromide (**2m**, 0.40 mmol) and 1-phenyl-1-hexyne (**1a**, 0.20 mmol) in the presence of Fe(acac)$_3$ (0.010 mmol) and additive (0.040 mmol). [b] Isolated yield. [c] Determined by ^{1}H NMR and GC−MS. The values in parentheses show the ratio of regioisomers to **3am**. [d] The reaction was conducted with 10 mol % additive loading. [e] The reaction was conducted with 40 mol % additive loading. [f] Determined by ^{1}H NMR using an internal standard (MeNO$_2$).

The addition of D_2O to the arylmagnesiation product resulting from the reaction of **1a** with **2m** in the presence of the Fe(acac)$_3$/IPr catalyst (entry 1 in Table 1) gave the alkene **3am**-*d* where the olefinic carbon at the 1 position is incorporated with deuterium in 99%. The high content of deuterium demonstrates the formation of alkenylmagnesium species before hydrolysis.

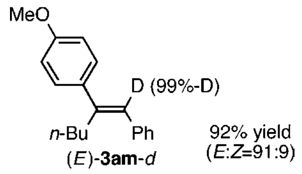
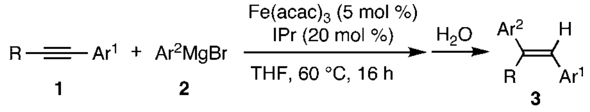


Table 2 summarizes the results obtained for arylmagnesiation of aryl(alkyl)acetylenes catalyzed by the Fe/IPr system. The addition of 4-methoxyphenylmagnesium bromide (**2m**) was successful for the alkynes **1a**−**1d** bearing primary and secondary alkyl groups at the alkyne terminal (entries 1−4). Unfortunately, the present Fe/IPr catalyst system was not as effective for the alkyne substituted with a *tert*-butyl group. Introduction of a methoxy group to the benzene ring on the alkyne at the ortho, meta, or para position

Table 2. Iron-Catalyzed Arylmagnesiation of Alkynes: Scope[a]



1a: R = *n*-Bu, Ar^1 = Ph
1b: R = Et, Ar^1 = Ph
1c: R = *i*-Bu, Ar^1 = Ph
1d: R = *i*-Pr, Ar^1 = Ph
1e: R = *n*-Bu, Ar^1 = 4-MeOC$_6$H$_4$
1f: R = *n*-Bu, Ar^1 = 3-MeOC$_6$H$_4$
1g: R = *n*-Bu, Ar^1 = 2-MeOC$_6$H$_4$
1h: R = *n*-Bu, Ar^1 = 4-ClC$_6$H$_4$

2m: Ar^2 = 4-MeOC$_6$H$_4$
2n: Ar^2 = 4-MeC$_6$H$_4$
2o: Ar^2 = 3,5-Me$_2$C$_6$H$_3$
2p: Ar^2 = 3-MeOC$_6$H$_4$
2q: Ar^2 = 2-MeOC$_6$H$_4$
2r: Ar^2 = 4-FC$_6$H$_4$
2s: Ar^2 = 1-Nap

entry	alkyne	Ar^2	product	yield (%)[b]	*E*:*Z*[c]
1	**1a**	**2m**	**3am**	91	89:11
2	**1b**	**2m**	**3bm**	91	85:15
3	**1c**	**2m**	**3cm**	87	95:5
4	**1d**	**2m**	**3dm**	84	78:22
5	**1a**	**2n**	**3an**	93[d]	89:11
6	**1e**	**2n**	**3en**	80	87:13
7	**1f**	**2n**	**3fn**	87	87:13
8	**1g**	**2n**	**3gn**	75[e]	92:8
9	**1h**	**2m**	**3hm**	69	83:17
10	**1e**	**2o**	**3eo**	73	82:18
11	**1a**	**2p**	**3ap**	75	76:24
12	**1a**	**2q**	**3aq**	59[e]	91:9
13	**1e**	**2r**	**3er**	73	82:18
14	**1e**	**2s**	**3es**	69[e]	94:6

[a] The reaction was carried out in THF (1.0 mL) at 60 °C for 16 h under a nitrogen atmosphere using an arylmagnesium bromide (0.40 mmol) and an alkyne (0.20 mmol) in the presence of Fe(acac)$_3$ (0.010 mmol) and IPr (0.040 mmol). [b] Isolated yield. [c] Determined by ^{1}H NMR and GC−MS. Formation of less than 3% of regioisomers was observed. [d] Determined by ^{1}H NMR using an internal standard (MeNO$_2$). [e] The reaction time is 24 h.

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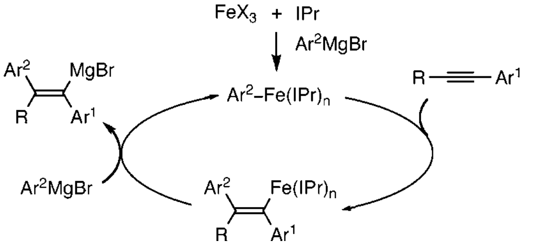
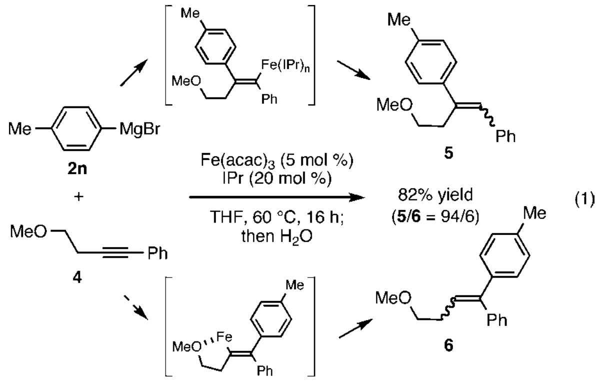
did not disturb the arylmagnesiation with 4-methylphenylmagnesium bromide (**2n**) (entries 6−8). The chloride substituent on the alkyne **1h** was intact under the present reaction conditions to give the corresponding arylation product **3hm** in a good yield (entry 9). Moderate to high yields of the addition products were obtained in the reaction of aryl Grignard reagents bearing methyl, methoxy, and fluoro **2o**−**2r** on the aryl ring (entries 10−13). In all the reactions shown in Table 2, the formation of regioisomers resulting from the arylmagnesiation in the opposite direction was observed in less than 3%. Although the arylmagnesiation of aryl(alkyl)acetylenes was thus realized by use of the Fe/IPr catalyst, that of dialkylacetylenes was not efficiently catalyzed by the present Fe/IPr system, 4-octyne giving only 19% yield of the addition product in the reaction with **2m**.

In our previous report using the Fe/Cu cocatalyst system,[5] we proposed a catalytic cycle where the addition of an aryliron species to alkyne is a key step and the transmetalation between the resulting alkenyliron and arylmagnesium bromide is promoted through the formation of an organocopper species. In the present system, which is not assisted by the copper cocatalyst, strong coordination of the carbene ligand probably stabilizes low valent iron intermediates to prevent them from being decomposed, and as a result the alkenyliron intermediate has a chance to undergo the transmetalation with the arylmagnesium reagent before its decomposition forming iron metals[10] (Scheme 1).

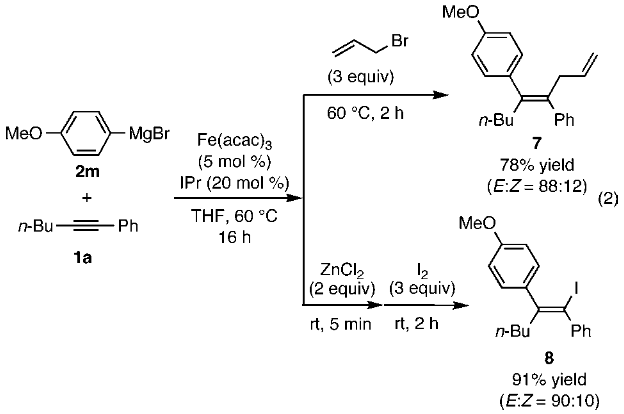
Scheme 1. Proposed Mechanism for Iron-Catalyzed Arylmagnesiation



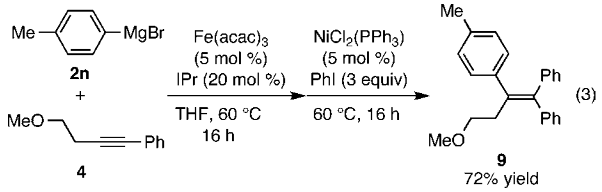
The addition of the Grignard reagent **2n** to a homopropargyl ether, 4-methoxy-1-phenyl-1-butyne (**4**), under the present conditions using the Fe/IPr catalyst gave, after hydrolysis, the product **5** arylated at the 2-position preferentially over its regioisomer **6** (eq 1). This regiochemistry is opposite to that expected from the results reported so far for the addition to homopropargyl ethers and alcohols, where intramolecular coordination of oxygen to iron is a decisive factor controlling the regiochemistry.[2d,h,3] In the present system, the strongly coordinating and sterically bulky carbene ligand may interfere with the intramolecular coordination of oxygen.



The alkenylmagnesium species generated by the iron-catalyzed arylmagnesiation can be trapped with electrophiles (eq 2). The addition of allyl bromide to the reaction mixture resulting from addition of the Grignard reagent **2m** to alkyne **1a** gave 78% yield of the tetrasubstituted alkene **7**. Iodination giving alkenyl iodide **8** was effected in high yield (91%) by treatment of the alkenylmagnesium with $ZnCl_2$ followed by addition of iodine to the alkenylzinc intermediate.[11]



Although the present Fe/IPr system did not catalyze the cross-coupling of the alkenylmagnesium species with an aryl halide, addition of a nickel catalyst realized the one-pot arylmagnesiation and cross-coupling sequence (eq 3). Thus, addition of phenyl iodide and $NiCl_2(PPh_3)_2$ catalyst[12] (5 mol %) to the alkenylmagnesium, generated from the Grignard reagent **2n** and alkyne **4**, brought about the alkenyl-aryl coupling to give 72% yield of triaryl-substituted alkene **9**.[13]



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In summary, we found that the iron-catalyzed arylmagnesiation of aryl(alkyl)acetylenes is efficiently realized by use of an *N*-heterocyclic carbene ligand. The alkenylmagnesium species formed with high regioselectivity were further transformed into tetrasubstituted alkenes by subsequent carbon−carbon bond-forming reactions.

Acknowledgment. Support has been provided in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan (21 COE on Kyoto University Alliance for Chemistry).

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL063132R