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Chromium-Catalyzed Arylmagnesiation of Alkynes

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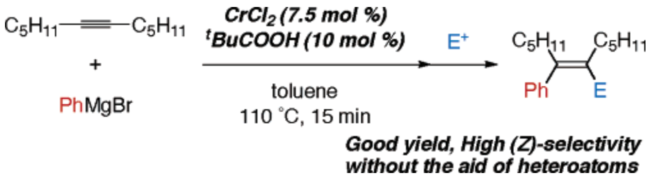
ABSTRACT



Good yield, High (Z)-selectivity without the aid of heteroatoms

Arylmagnesiation of unfunctionalized alkynes in the presence of catalytic amounts of chromium(II) chloride and pivalic acid proceeds with high stereoselectivity. The alkenylmagnesium intermediate reacts with various electrophiles to afford the corresponding tetrasubstituted olefins in good yields.

Carbometalation of alkynes is a straightforward method for the synthesis of multisubstituted olefins in organic synthesis.[1] To date, most studies of the process have focused on employing heteroatom-containing alkynes such as homopropargyl ethers and propargyl alcohols as substrates.[2] As for the carbometalation of unfunctionalized alkynes, however, much less progress has been made.[3−5] The development of facile, efficient, and general methods for the carbometalation of unfunctionalized alkynes remains an important challenge. Herein, we wish to report that a simple chromium salt promotes arylmagnesiation of unfunctionalized alkynes with high efficiency.

Treatment of 6-dodecyne (**1**, 1.0 mmol) with phenylmagnesium bromide (**2**, 3.0 mmol, 2 M diethyl ether solution) in toluene (3 mL) at 110 °C in the presence of chromium(II) chloride (0.075 mmol) for 18 h provided 6-phenyl-6-dodecene (**3**) in an *E*/*Z* ratio of 91:9 in 81% yield (Table 1, entry 1). We screened several transition metal catalysts such as iron, cobalt, and nickel salts, none of which did show any catalytic activity under similar reaction conditions.[6] The choice of reaction solvent is crucial. The use of THF instead of toluene resulted in recovery of the starting material **1**.

We next explored several additives to improve the yield and the *E*/*Z* selectivity (Table 1). Surprisingly, the addition of a catalytic amount of protic additives led to higher yield, better stereoselectivity, and faster reaction rate.[7] Although

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[1] (a) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 4.4, pp 865−911. (b) Marek, I.; Normant, J. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 271−337. (c) Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed.* **1997**, *36*, 93−95.

[2] For a review on metal-mediated carbometalation of alkynes and alkenes containing heteroatoms, see: (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899−5913. For a recent example on transition metal-catalyzed carbometalation of alkynes containing heteroatoms, see: (b) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15050−15051.

[3] The arylmetalation of unfunctionalized alkynes is very difficult to achieve: Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 17164−17165 and references cited therein.

[4] For recent examples on transition metal-catalyzed carbometalation of unfunctionalized alkynes, see: (a) Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221−10222. (b) Suginome, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc.* **2006**, *128*, 14438−14439.

[5] (a) Nishikawa, T.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 4629−4630. (b) Nishikawa, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2795−2797. In these reports, we described chromium-catalyzed annulation reactions of acetylenic compounds with methallylmagnesium chloride, probably initiated by carbometalation of alkyne units. However, the carbometalation processes suffered from limitations as to the scope of the alkynes and Grignard reagents. The alkynes available for use are limited to 1,6-diynes and 1,6-enynes. In other words, the intramolecular carbomagesiation of unfunctionalized alkynes did not proceed at all. Additionally, we obtained promising results only with methallylmagnesium chloride of high nucleophilicity. (c) Molander, G. A.; Sommers, E. M. *Tetrahedron Lett.* **2005**, *46*, 2345−2349.

[6] The use of chromium(III) chloride afforded **3** in a yield similar to the chromium(II) chloride catalyst in the absence of pivalic acid. In the presence of pivalic acid, chromium(II) chloride was superior to other chromium salts.

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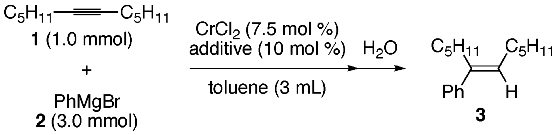
Table 1. Effect of Additives on the Chromium-Catalyzed Phenylmagnesiation of 6-Dodecyne (**1**)



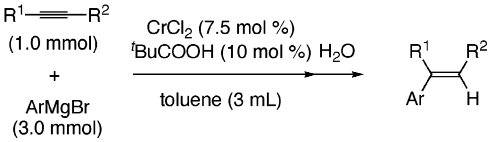
entry	additive	temp (°C)	time (h)	yield (%)[a]	*E*/*Z*[b]
1	none	110	18	81	91:9
2	none	60	18	0	
3	MeOH	110	2	77	95:5
4	PhOH	110	2	77	95:5
5	^{t}BuOH	110	2	75	95:5
6	AcOH	110	0.25	79	>99:1
7	PhCOOH	110	0.25	81	>99:1
8[c]	**^{t}BuCOOH**	**110**	**0.25**	**87**	**>99:1**
9	^{t}BuCOOH	60	18	75	96:4

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] When the reaction was performed in a 10-mmol scale, an 78% yield of 6-phenyl-6-dodecene (**3**) was obtained.

the reaction required 18 h at 110 °C when no additive was employed, the processes with alcohols (methanol, phenol, and *tert*-butyl alcohol) went to completion within 2 h (entries 1 vs 3−5). Further investigation revealed that the use of carboxylic acids not only resulted in faster reactions (0.25 h) but also increased the ratio of *E*/*Z* isomers to greater than 99:1 (entries 6 and 7). The yield depended on the steric bulkiness of the carboxylic acid, and pivalic acid showed the best result to provide (*E*)-6-phenyl-6-dodecene (**3**) in 87% yield after 0.25 h (entry 8). The chromium salt/pivalic acid system proceeded even at 60 °C to afford the corresponding phenylated product **3** in 75% yield albeit the reaction was slow. It is worth noting that the additive-free process did not produce **3** at all at the same temperature (entries 2 vs 9). This arylmagnesiation was readily scalable. Treatment of 10 mmol of 6-dodecyne (**1**) with phenylmagnesium bromide (**2**, 30 mmol) in the presence of chromium(II) chloride (0.75 mmol) and pivalic acid (1.0 mmol) in toluene (30 mL) in a similar manner provided **3** in an *E*/*Z* ratio of >99:1 in 78% yield. The reason for the dramatic effect of the additives is not clear at this stage.

Various combinations of alkynes and aryl Grignard reagents were examined in the chromium/pivalic acid-catalyzed process (Table 2). All the reactions afforded the corresponding *E* adducts exclusively or predominantly, except for the reaction of 1-(trimethylsilyl)propyne (entry 9). Arylmagnesium reagents having a methyl substitution at the ortho, meta, or para position effected the arylmagnesiation, and all the reactions afforded the corresponding *E* isomers exclusively (entries 1−3). 3-Methoxy- and 4-chlorophenylmagnesium bromides participated in the reaction (entries 4 and 5). The use of 2,2-dimethyl-3-decyne provided the corresponding product with complete regioselectivity (entry 6). The regioselectivity was simply governed by the steric factor of the two substituents of the alkyne. The reactions of the phenyl-substituted alkynes afforded modest yields of the arylmagnesiation products (entries 7 and 8). Diphenylacetylene also reacted with phenylmagnesium bro-

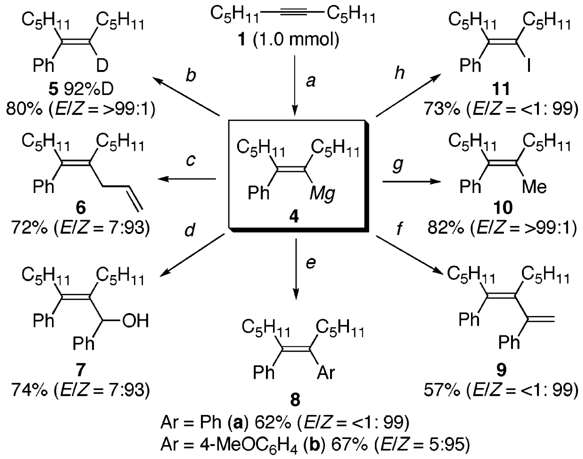
Table 2. Chromium-Catalyzed Arylmagnesiation of Alkynes



entry	R^1	R^2	Ar	temp (°C)	time (h)	yield[a] (%)	*E*/*Z*[b]
1	C_5H_{11}	C_5H_{11}	2-MeC_6H_4	110	10	55	>99:1
2	C_5H_{11}	C_5H_{11}	3-MeC_6H_4	110	0.5	80	>99:1
3	C_5H_{11}	C_5H_{11}	4-MeC_6H_4	110	0.5	81	>99:1
4	C_5H_{11}	C_5H_{11}	4-ClC_6H_4	110	2	61	88:12
5[c]	C_5H_{11}	C_5H_{11}	3-$MeOC_6H_4$	110	18	69	87:13
6[d]	C_6H_{13}	^{t}Bu	Ph	110	4	53	>99:1
7	C_6H_{13}	Ph	Ph	110	2	68	92:8[e]
8	Me	Ph	Ph	60	18	51	95:5[e]
9	Me	Me_3Si	Ph	60	18	67	65:35
10	Ph	Ph	Ph	110	0.5	70	

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] The reaction was carried out without ^{t}BuCOOH. [d] $CrCl_2$ (20 mol %) and ^{t}BuCOOH (20 mol %) were used. [e] A small amount of the corresponding regioisomer was observed (entry 7; 10% yield, entry 8; 1% yield).

Scheme 1. Reactions of Various Electrophiles with the Arylmagnesiation Product **4**[a]



[a] Reagents and conditions: (a) $CrCl_2$ (7.5 mol %), ^{t}BuCOOH (10 mol %), PhMgBr (3.0 mmol), toluene, 110 °C, 0.25 h; (b) D_2O; (c) $CH_2{=}CHCH_2Br$ (4.0 mmol), CuCN·2LiCl (10 mol %), 0 °C, 3 h; (d) PhCHO (4.0 mmol), 0 °C, 3 h; (e) $Pd_2(dba)_3$ (2.5 mol %), P(*o*-tolyl)$_3$ (5 mol %), ArI (4.0 mmol), 25 °C, 3 h; (f) $Pd_2(dba)_3$ (2.5 mol %), P(*o*-tolyl)$_3$ (5 mol %), $PhC(Br){=}CH_2$ (4.0 mmol), 25 °C, 12 h; (g) MeI (4.0 mmol), CuCN·2LiCl (20 mol %), 0 °C, 3 h; (h) I_2 (4.0 mmol), 0 °C, 3 h.

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(7) (a) Vogl, E. M.; Groger, G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570. (b) Funabashi, K.; Jackmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5489−5492. (c) Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600−5601.

mide, giving triphenylethylene in 70% yield (entry 10). Unfortunately, the use of terminal alkynes resulted in failure.

With the reliable carbomagnesiation reaction in hand, we investigated the utility of the intermediary alkenylmagnesium compound **4** (Scheme 1). The intermediate reacted with various electrophiles such as deuterium oxide, allyl bromide, benzaldehyde, iodomethane, or iodine to give the corresponding tetrasubstituted alkenes with high stereoselectivity in good overall yield. As for trapping of **4** with allyl bromide or iodomethane, the addition of a catalytic amount of CuCN·2LiCl improved the yield of the corresponding products **6** and **10**. The alkenylmagnesium intermediate **4** was useful for palladium-catalyzed cross-coupling reactions of aryl iodides such as iodobenzene and 4-iodoanisole, and the two aryl groups were introduced smoothly with high stereoselectivity. The conjugated diene **9** was also prepared from the arylmagnesiation product **4** via palladium-catalyzed cross-coupling reaction.

In summary, the arylmagnesiation of unfunctionalized alkynes has been achieved by using a chromium salt. Notably, the addition of a catalytic amount of pivalic acid dramatically enhanced the reactivity and stereoselectivity. The procedure is highly efficient to construct multisubstituted ethene units.

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

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