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Iron-Catalyzed Carbometalation of Propargylic and Homopropargylic Alcohols

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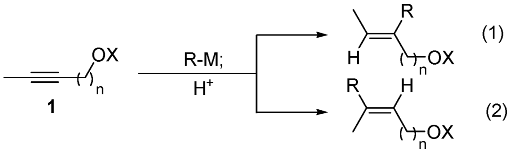
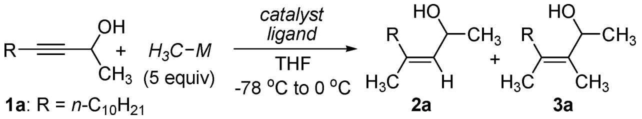
Olefins are fundamental building blocks for organic synthesis, and a multitude of methods exist for their preparation. Among various approaches, additions to alkynes offer the promise of convergence and stereoselectivity while leveraging the wealth of literature related to alkyne synthesis. Indeed, carbometalation of terminal alkynes represents a general method and has found widespread use in the synthesis of complex molecules.[1] In contrast, electronically unbiased internal alkynes react slowly and with poor regioselectivity. However, polar functionality near the alkyne has been found to affect both the rate and regioselectivity of carbometalation reactions (eqs 1, 2).[2] For example, addition of Grignard reagents to propargylic alcohols introduces an organic fragment proximal to the alcohol (eq 1).[2b,c] The opposite regioselectivity has been observed in reactions of homo-propargylic alcohols and ethers with vinyl titanium reagents,[2d] allyl magnesium bromide,[2e,f] butyl lithium[2g] and trimethyl aluminum[2h] (eq 2, $n = 2$; X = H or alkyl). Here we report an iron-catalyzed carbomagnesiation of propargylic and homopropargylic alcohols which generates tri- and tetrasubstituted olefins with high regio- and stereoselectivity (eq 2; $n = 1$, 2; X = H).



In the absence of catalysts, CH_3MgBr does not add to the internal propargylic alcohol **1a**. Accordingly, we evaluated a variety of first-row transition metal salts for their ability to catalyze methylmagnesiation (Table 1). While Cu(I) salts did not effect addition,[3] Co(II), Ni(II), and Fe(III) displayed promising catalytic activity (entries 2−4). In all cases regioselectivity and stereoselectivity were very high, but the desired trisubstituted olefin (**2a**) was contaminated with the dimethyl product **3a**. The formation of this side product was largely suppressed when bis(diphenylphosphino)ethane (dppe, 1 equiv to Fe) was included in the reaction mixture (entry 6). Interestingly, methyllithium proved totally unreactive in the presence or absence of catalyst (entry 7).[2g]

Table 2 presents the generality of the carbometalation. In the presence of $Fe(acac)_3$ or $Fe(ehx)_3$ (ehx = 2-ethyl hexanoate) propargylic alcohols react with methyl magnesium bromide to yield trisubstituted allylic alcohols as single regio- and stereoisomers.[4] Primary and secondary propargylic alcohols represent suitable substrates (entries 1−8), the latter reacting with complete conservation of optical purity (entry 7). Common oxygen protecting groups, olefins, and tertiary nitrogens appear well-tolerated. Furthermore, primary and secondary homopropargylic alcohols provide the corresponding homoallylic alcohols on treatment with methyl Grignard reagent (entries 9−10). In ongoing studies, we have found that the iron-catalyzed carbometalation can be extended to phenylation[5] (entries 11−12) and ethylation (entries 13−14). In the latter experiments, no diethylation products (analogous to **3**) were observed; instead, we obtained small amounts of the product arising from formal cis-hydrogenation (see below).[6,7]

Table 1. Catalytic Carbometalation of Propargylic Alcohol **1a**[a]



entry	CH_3M	catalyst[b]	ligand[b]	conversion (%)[c]	2a/3a[d]
1	CH_3MgBr	CuBr	none	<5	
2	CH_3MgBr	$Co(OAc)_2$	none	58	9/1
3	CH_3MgBr	$Ni(acac)_2$	none	63	9/1
4	CH_3MgBr	$Fe(acac)_3$	none	98	6/1
5[e]	CH_3MgBr	$Fe(ehx)_3$	none	98	5/1
6	CH_3MgBr	$Fe(acac)_3$	dppe	97	21/1
7	CH_3Li	$Fe(acac)_3$	none	0	

[a] Reactions were carried out on 0.1 mmol scale under a N_2 for 7 h. [b] Reaction run using 20 mol %. [c] Determined by GC using an internal standard. [d] Determined by GC analysis of crude reaction mixture. [e] ehx = 2-ethyl hexanoate.

Iron(III) salts are proposed to undergo ligand exchange and reduction with CH_3MgBr to yield $L_nFe^{II}(CH_3)_2$ complexes at 0 °C.[8b] Lower oxidation states are available upon warming or in the presence of longer chain Grignard reagents.[9] Accordingly, the oxidation sate of the catalytically active species here remains ambiguous.[8a] Regardless, alkoxide-directed carbometalation likely yields an intermediate (vinyl)Fe species (Scheme 1). In principle, direct coordination to the iron center could occur (**4**). Alternatively, the interaction could be driven by association of iron with magnesium (**5**).[10] The (vinyl)Fe(R) species can undergo metathesis with Grignard reagent to provide the carbometalated product and regenerate catalyst, or it can suffer reductive elimination to yield the geminally dialkylated product **3**. β-Hydride elimination from an Fe(ethyl) intermediate could give rise to an Fe−H species **6**. Subsequent hydrometalation could lead to the hydrogenated side products observed in ethylation reactions.

The presumptive vinyl Grignard intermediate **7** can be trapped with a variety of electrophiles to yield tetrasubstituted allylic alcohols. For example, deuteration, formylation, allylation, and bromination proceed under the conditions indicated in Scheme 2. Likewise, trapping with benzaldehyde provides the allylic alcohols **8** and **9** as single olefin isomers. Finally, trapping the vinyl iron or magnesium species with a pendent alkyne yields the cyclic diene **10** in good yield.

Further studies of the iron-catalyzed carbomagnesiation may reveal intimate details of the reaction mechanism. In the meantime the method offers an efficient and stereoselective synthesis of tri- and tetrasubstituted olefins. Of note, the carbometalation reported here yields *Z*-configured allylic and homoallylic olefins. In contrast, the opposite olefin geometry is obtained from procedures based

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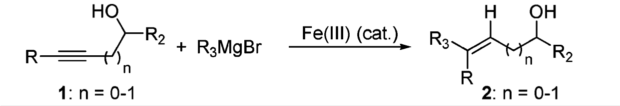
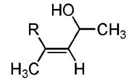
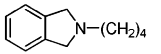
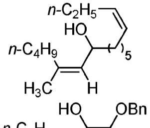
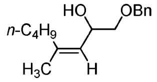
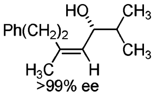
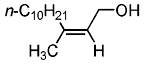
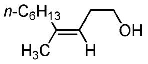
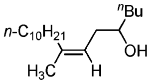
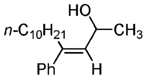
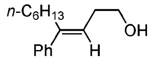
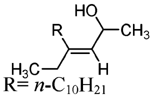
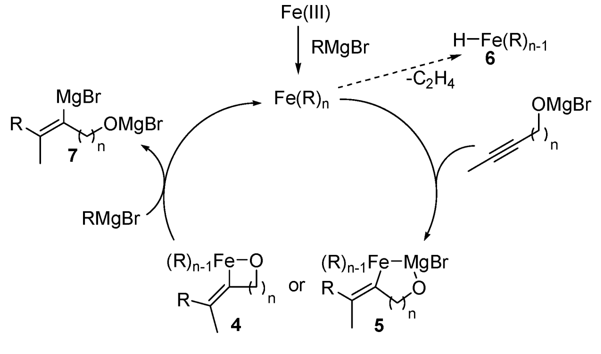
Table 2. Iron-Catalyzed Carbomagnesiation of Propargylic and Homopropargylic Alcohols[a]



entry	Conditions	Product	Yield (%)[b]
1	$Fe(ehx)_3$ (0.20 equiv) dppe (0.20 equiv)	 R = n-$C_{10}H_{21}$	75
2	$Fe(ehx)_3$ (0.20 equiv) dppe (0.20 equiv)	R = $TBSO(CH_2)_4$	80
3	$Fe(ehx)_3$ (0.20 equiv) dppe (0.20 equiv)	R = $BnO(CH_2)_3$	70
4	$Fe(acac)_3$ (0.20 equiv) dppe (0.20 equiv)	R = 	78
5	$Fe(acac)_3$ (0.30 equiv) dppe (0.30 equiv)		85
6	$Fe(acac)_3$ (0.15 equiv)		81
7	$Fe(acac)_3$ (0.30 equiv)	 >99% ee	61
8	$Fe(ehx)_3$ (0.30 equiv) dppe (0.30 equiv)		80
9[c]	$Fe(acac)_3$ (0.20 equiv)		75
10[c]	$Fe(acac)_3$ (0.20 equiv)		74
11	$Fe(acac)_3$ (0.50 equiv) CuBr (0.60 equiv)		69
12[c]	$Fe(acac)_3$ (0.40 equiv)		63
13[d]	$Fe(acac)_3$ (0.20 equiv) NMP (2.0 equiv)	 R= n-$C_{10}H_{21}$	70
14[d]	$Fe(acac)_3$ (0.20 equiv) NMP (2.0 equiv)	R= $TBSO(CH_2)_4$	74

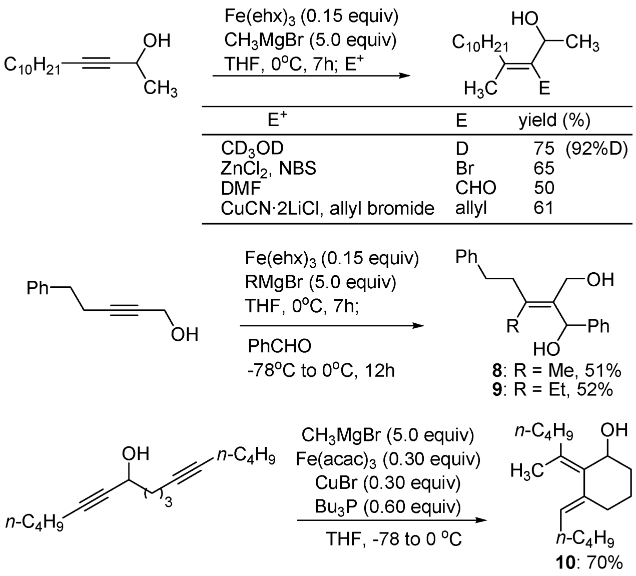
[a] Reactions carried out in THF (0.1 M in substrate) using 5.0 equiv of RMgBr at 0 °C for 7 h unless otherwise indicated. [b] Isolated yield. [c] In toluene at 23 °C. [d] NMP = N-methyl pyrrolidine.

Scheme 1



on carbometalation of terminal alkynes followed by trapping with aldehydes or epoxides.[1]

Scheme 2



E^+	E	yield (%)
CD_3OD	D	75 (92%D)
$ZnCl_2$, NBS	Br	65
DMF	CHO	50
$CuCN{\cdot}2LiCl$, allyl bromide	allyl	61

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Supporting Information Available: Complete experimental procedures and characterization data for Table 2 and Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65−72. (b) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631. (c) Marek, I.; Normant, J. In *Metal-Catalyzed Cross-Coupling Reactions;* Diederich, F.; Stang, P., Eds.; Wiley-VCH: U.K., 1998; pp 271−283. (d) Zhang, D.; Ready, J. M. *Org. Lett.* **2005**, *7*, 5681−5683. (e) see also Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853−12910.
(2) (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899−5913. (b) Forgione, P.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 11−15. (c) Forgione, P.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 17−20. (d) Ryan, J.; Micalizio, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 2764−2765. (e) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1996**, *118*, 6076−6077. (f) Eisch, J. J.; Merkley, J. H. J. *Organomet. Chem.* **1969**, *20*, P27−P31. (g) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621−623. (h) Ewing, J. C.; Ferguson, G. S.; Moore, D. W.; Schultz, F. W.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 2124−2128.
(3) (a) Douboudin, J. G.; Jousseaume, B.; Bonakdar, A.; Saux, A. *J. Organomet. Chem.* **1979**, *168*, 227−242. (b) Lu, Z.; Ma, S. *J. Org. Chem.* **2006**, *71*, 2655−2660.
(4) In some cases, dppe was not necessary.
(5) We speculate that the CuBr in Table 2, entry 11 facilitates transmetalation from (vinyl)Fe to (vinyl)Cu. See Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 17164−17165.
(6) (a) Snider, B.; Karras, M.; Conn, R. S. E. *J. Am. Chem. Soc.* **1978**, *100*, 4624−4626. (b) Sato, F.; Ishikawa, H.; Watanabe, H.; Miyake, T.; Sato, M. *Chem. Commun.* **1981**, 718−720. (c) Smith, J. M.; Lachicotte, R. J.; Holland, P. L. *J. Am. Chem. Soc.* **2003**, *125*, 15752−15753.
(7) Notes: (a) ^{i}PrMgCl provides the hydrogenated products in moderate yield. (b) No reaction is observed with ^{t}BuMgCl. (c) 4-Octyne does not react with CH_3MgBr in the presence of Fe(III) catalysts while cis-hydrogenation is observed with EtMgBr in the presence of $Fe(acac)_3$. (d) Reactions involving the methyl ether of **1a**, CH_3MgBr, and $Fe(acac)_3$ generate complex mixtures.
(8) (a) Treating the alkoxide of **1a** with 2 equiv $Fe(CH_3)_3$ (prepared as in ref 8b) afforded a 3:4 ratio of **2a**/**3a** (100% conversion). Fe(0), as prepared in ref 8b, did not catalyze the methylation of **1a**. (b) Krafft, M. E.; Holton, R. A. *J. Org. Chem.* **1984**, *49*, 3669−3670.
(9) Bogdanovic, B.; Schwickardi, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610−4612.
(10) (a) Aleandri, L. E.; Bogdanovic, B.; Bons, P.; Durr, C.; Gaidies, A.; Hartwig, T.; Huckett, S. C.; Lagarden, M.; Wilczok, U.; Brand, R. A. *Chem. Mater.* **1995**, *7*, 1153−1170. (b) Furstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856−13863.

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