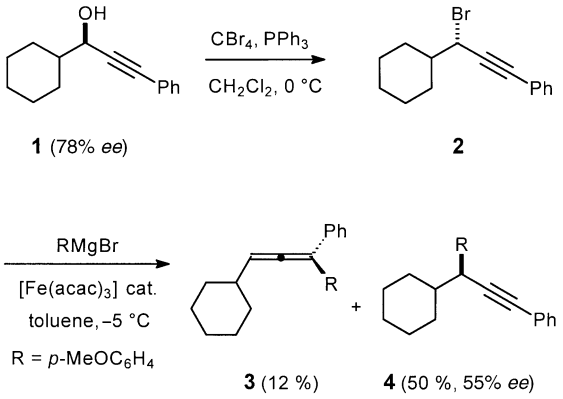


Scheme 1. Preparation and iron-catalyzed reaction of a nonterminal propargyl bromide with a Grignard reagent.

Iron-Catalyzed Allenol Formation

Iron-Catalyzed Cross-Coupling Reactions: Efficient Synthesis of 2,3-Allenol Derivatives**

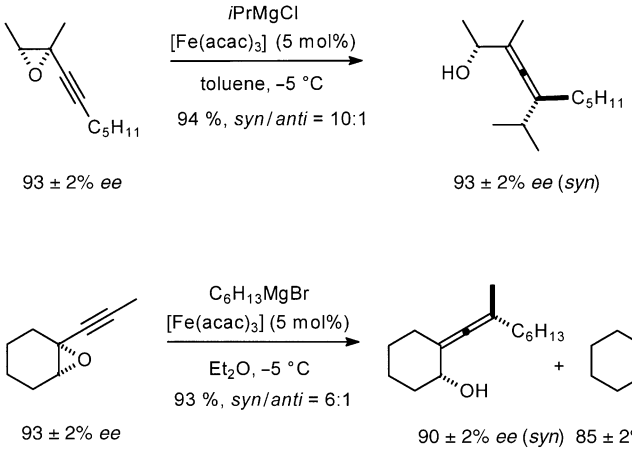
Alois Fürstner and María Méndez*

Allenes in general and 2,3-allenol derivatives in particular are versatile building blocks for advanced organic synthesis because of the reactivity inherent to their axially chiral backbones.[1] They are usually prepared by S_N2'-type reactions of propargylic substrates with organocopper reagents. Although this methodology has reached a high degree of sophistication and met with considerable success,[2] a literature survey shows that the stoichiometric regimen continues to prevail over the catalytic manifold in most applications.[1–3] Furthermore, strongly donating ligands to copper such as PBu_3 or $P(OMe)_3$ are required for efficient chirality transfer from the propargylic substrate to the incipient allene and/or to avoid the formation of reduction products derived from formal hydride delivery.[1f,4,5] Finally, a certain propensity of cuprates to racemize enantiomerically enriched allenes has been documented on several occasions.[6]

During our recent studies on iron-catalyzed cross-coupling reactions,[7] we became aware of an early, yet virtually inconsequential, report of Pasto et al. on the use of simple iron salts as precatalysts for the formation of allenes from propargylic halides and Grignard reagents.[8–10] In an attempt to apply this method, however, its limitations became immediately apparent (Scheme 1). Specifically, conversion of the scalemic propargyl alcohol **1** (78% *ee*)[11] into the corresponding bromide **2** followed by reaction with *p*-$MeOC_6H_4MgBr$ in the presence of $[Fe(acac)_3]$ catalyst furnished the desired allene **3** as the minor product only, together with compound **4** formed by direct S_N2-substitution. The *ee* of the latter was only 55%, thus showing that a considerable loss in enantiomeric purity accompanied this overall transformation.

Convinced of the preparative advantages of iron salts as user-friendly, inexpensive, and virtually nontoxic precatalysts,[7] however, various propargyl derivatives were screened in the search for better substrates. Gratifyingly, we found that propargyl epoxides perform exquisitely well. They are easily prepared in optically active form[12] and react with different Grignard reagents with exceptional efficiency in the presence of catalytic amounts of simple iron salts, preferentially the nonhygroscopic $[Fe(acac)_3]$. First and utmost, the central chirality of these substrates is transferred to the axial chirality of the resulting 2,3-allenols with high fidelity, as can be seen from the examples compiled in Scheme 2.

The reactions are virtually instantaneous, even at low temperatures ($\leqslant$5 min), the required catalyst loading is low (3–5 mol%),[13] no extra ligands are necessary, the yields are good to excellent, and the substrate scope is sufficiently broad. Importantly, propargyl epoxides with terminal or nonterminal alkyne units react with similar ease (Table 1). Moreover, the direct attack of the Grignard reagent at the epoxide ring[14] remains insignificant in all but the most activated cases (Table 1, entries 17 and 21).



Scheme 2. Chirality transfer experiments.

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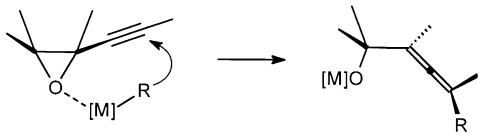
Table 1: Iron-catalyzed synthesis of 2,3-allenols from propargyl epoxides.[a]

Entry	Substrate	R^1	R^2MgX	Major product	Solvent	*syn*/*anti*	Yield [%]
1		H	$C_6H_{13}MgBr$		toluene	78:22	72[b]
2		H	PhMgBr		toluene	75:25	83
3		H	MeMgBr		toluene	55:45	71
4		Me	$C_6H_{13}MgBr$		Et_2O	86:14	93
5		Me	$C_6H_{13}MgBr$		Et_2O	78:22	75[c]
6		Me	$C_6H_{13}MgBr$		Et_2O	50:50	54[d]
7		Me	*i*PrMgCl		Et_2O	84:16	79
8		Me	*i*PrMgCl		toluene	90:10	70
9		Me	PhMgBr		Et_2O	66:34	98
10		Ph	MeMgBr		Et_2O	65:35	69
11		CH_2OH	$C_6H_{13}MgBr$		Et_2O	92:8	65[e]
12		Me	$C_6H_{13}MgBr$		toluene	80:20	73
13		Me	$C_6H_{13}MgBr$		toluene	88:12	80
14		Me	*i*PrMgCl		toluene	84:16	79
15		Me	$C_6H_{13}MgBr$		toluene	92:8	62
16		Me	$C_6H_{13}MgBr$		Et_2O	75:25	90
17		Me	*i*PrMgCl		toluene	86:14	75[f]
18		Me	*i*PrMgCl		Et_2O	60:40	89
19		C_5H_{11}	*i*PrMgCl		toluene	91:9	94
20		C_5H_{11}	*i*PrMgCl		Et_2O	75:5	64
21		C_5H_{11}	EtMgBr		toluene	82:18	55[g]

[a] The reactions were carried out at $-5\,^{\circ}C$ in the presence of $[Fe(acac)_3]$ (3–5 mol%) precatalyst and Grignard reagent (1.3 equiv), unless stated otherwise. [b] Fe–salen precatalyst. [c] $-30\,^{\circ}C$. [d] $-60\,^{\circ}C$. [e] Grignard reagent (2.3 equiv). [f] A by-product (9%) was isolated that is formed by direct attack of the Grignard at the epoxide ring of the substrate. [g] In addition to the allenol, approximately 15% of by-products were formed from direct attack of the Grignard reagent at the epoxide ring of the substrate.

As can be seen from Table 1, the *syn*-configured 2,3-allenols are invariably formed as the major products.[15] Remarkably, this stereochemical outcome is *opposite* to that usually observed in reactions of propargyl epoxides with organocopper reagents,[4,6,16] which furnish the *anti*-configured allenols, except when carried out under "ligand-free" conditions in the presence of excess TMSCl.[4] Although the efficiency of the iron-catalyzed allenol formation is largely independent of the solvent used, the diastereoselectivity is higher in toluene than in Et_2O. This consistent trend (Table 1, entries 7/8, 15/16, 17/18, 19/20) is tentatively interpreted in terms of a "directed" delivery of the nucleophile to the alkyne,[17] which occurs only after the catalyst and/or the Grignard reagent has been coordinated to the oxygen atom of the substrate. Such a precoordination is likely more pronounced in a hydrocarbon solvent than in an ether medium (Scheme 3).



Scheme 3. Proposed stereochemical rationale for the preferential formation of *syn*-configured 2,3-allenol derivatives by "directed" delivery of the nucleophile R.

The reasons, however, why the diastereoselectivity *decreases* upon lowering the reaction temperature are far less clear (Table 1, entries 4–6). Detailed mechanistic investigations will be necessary to shed light on this unusual behavior, which must include studies on the nature of the still elusive (and most likely highly reduced)[7] but exceptionally efficient iron catalyst formed in situ upon mixing of $[Fe(acac)_3]$ with an excess of an organomagnesium reagent. Investigations along these lines and further applications of iron-catalyzed cross-coupling reactions are currently underway and will be reported in due course.[18]

Experimental Section

*i*PrMgCl (2 M in Et_2O, 0.42 mL, 0.83 mmol) was transferred by syringe into a solution of 1-prop-1-ynyl-9-oxa-bicyclo[6.1.0]nonane (105 mg, 0.64 mmol) and [Fe(acac)$_3$] (11 mg, 0.03 mmol) in toluene (14 mL) at −5 °C under Ar, causing an immediate color change from bright red to dark brown/black. After stirring for 5 min, the mixture was quenched with NH_4Cl (5 mL) and diluted with Et_2O (10 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, and the residue was purified by flash chromatography (5:1 pentane/Et_2O) to provide 2-(2,3-dimethylbut-1-enylidene)-cyclooctanol as a colorless oil (100 mg, 75%, d.r. 86:14). IR (KBr): $\tilde{\nu}$ = 3402, 2931, 2858, 1943, 1115 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 4.10 (dd, J = 7.9, 3.7 Hz, 1H; *anti*), 4.07 (dd, J = 8.8, 4.0 Hz, 1H; *syn*), 2.30–2.10 (m, 2H), 2.05 (m, 1H), 1.87 (m, 1H), 1.71 (s, 3H), 1.70–1.05 (m, 10H), 1.05 (d, J = 1.9 Hz, 3H; *syn*), 1.04 (d, J = 1.9 Hz, 3H; *syn*), 1.03 (d, J = 1.9 Hz, 3H; *anti*), 1.01 ppm (d, J = 1.9 Hz, 3H; *anti*); *syn* isomer: ^{13}C NMR (100 MHz, CD_2Cl_2; DEPT) δ = 197.27 (C), 109.91 (C), 109.67 (C), 72.81 (CH), 33.36 (CH_2), 32.99 (CH), 29.66 (CH_2), 29.84 (CH_2), 26.50 (CH_2), 25.92 (CH_2), 23.24 (CH_2), 22.17 (CH_3), 22.04 (CH_3), 17.33 ppm (CH_3); *anti* isomer: ^{13}C NMR (100 MHz, CD_2Cl_2; DEPT): δ = 196.67 (C), 110.58 (C), 110.04 (C), 71.97 (CH), 33.29 (CH_2), 33.08 (CH), 29.45 (CH_2), 29.18 (CH_2), 26.61 (CH_2), 26.04 (CH_2), 22.92 (CH_2), 22.04 (CH_3), 21.97 (CH_3), 17.37 ppm (CH_3); MS (EI, 70 eV): m/z (%): 208 (10) [M^+], 193 (30), 165 (13), 137 (38), 110 (27), 95 (100); HMRS: calcd for $C_{14}H_{24}O$: 208.1828; found: 208.1827.

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Keywords: alkynes · allenes · cross-coupling · epoxides · iron

[1] For selected reviews, see: a) J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163–3185; b) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067–3125; c) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701–712; d) A. S. K. Hashmi, *Angew. Chem.* **2000**, *112*, 3737–3740; *Angew. Chem. Int. Ed.* **2000**, *39*, 3590–3593; e) A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2002**, *114*, 3057–3059; *Angew. Chem. Int. Ed.* **2002**, *41*, 2933–2935; f) N. Krause, A. Hoffmann-Röder, J. Canisius, *Synthesis* **2002**, 1759–1774; g) H. F. Schuster, G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, **1984**, and references therein.

[2] For a review, see: N. Krause, A. Hoffmann-Röder, in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 145–166, and references therein.

[3] For a recent exception, see: Z. Wan, S. G. Nelson, *J. Am. Chem. Soc.* **2000**, *122*, 10470–10471.

[4] For detailed studies on the effect of additives as well as for an in-depth mechanistic discussion, see the following for leading references: a) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *J. Am. Chem. Soc.* **1990**, *112*, 8042–8047; b) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, *47*, 1677–1696.

[5] C. Sahlberg, A. Claesson, *J. Org. Chem.* **1984**, *49*, 4120–4122.

[6] a) C. J. Elsevier, P. Vermeer, *J. Org. Chem.* **1989**, *54*, 3726–3730; b) H. Westmijze, I. Nap, J. Meijer, H. Kleijn, P. Vermeer, *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 154–157; c) A. Claesson, L.-I. Olsson, *J. Chem. Soc. Chem. Commun.* **1979**, 524–525.

[7] a) A. Fürstner, A. Leitner, *Angew. Chem.* **2002**, *114*, 632–635; *Angew. Chem. Int. Ed.* **2002**, *41*, 609–612; b) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863; c) A. Fürstner, A. Leitner, *Angew. Chem.* **2003**, *115*, 320–323; *Angew. Chem. Int. Ed.* **2003**, *42*, 308–311.

[8] a) D. J. Pasto, G. F. Hennion, R. H. Shults, A. Waterhouse, S.-K. Chou, *J. Org. Chem.* **1976**, *41*, 3496; b) D. J. Pasto, S.-K. Chou, A. Waterhouse, R. H. Shults, G. F. Hennion, *J. Org. Chem.* **1978**, *43*, 1385–1388.

[9] A. S. K. Hashmi, G. Szeimies, *Chem. Ber.* **1994**, *127*, 1075–1089.

[10] For reports on the reaction of certain allylic substrates under iron catalysis, see: a) A. Yanagisawa, N. Nomura, H. Yamamoto, *Tetrahedron* **1994**, *50*, 6017–6028; b) A. Yanagisawa, N. Nomura, H. Yamamoto, *Synlett* **1991**, 513–514; c) M. Nakamura, K. Matsuo, T. Inoue, E. Nakamura, *Org. Lett.* **2003**, *5*, 1373–1375; d) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2000**, *122*, 978–979.

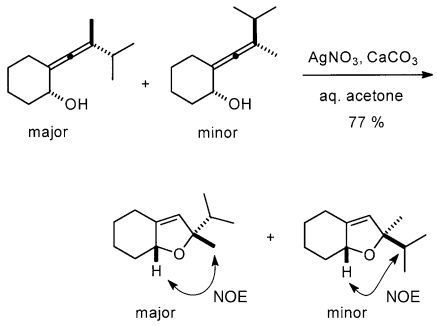
[11] D. E. Frantz, R. Fassler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.

[12] The enantiomerically enriched substrates used in this study were prepared by enantioselective oxidation of the corresponding enynes; see: Z.-X. Wang, G.-A. Cao, Y. Shi, *J. Org. Chem.* **1999**, *64*, 7646–7650.

[13] Control experiments showed that the iron catalyst is essential; no productive allenol formation is observed in the absence of [Fe(acac)$_3$].

[14] Organocopper reagents show a certain tendency to undergo direct nucleophilic substitution of the epoxide, in particular if the reaction is carried out with only catalytic amounts of copper, see comments in reference [1f].

[15] The stereochemical assignment was corroborated by NOE measurements of the dihydrofuran derivatives formed from selected allenols upon treatment with $AgNO_3$.[16c] All other compounds were assigned by analogy. A representative example is shown below.



[16] a) P. Vermeer, J. Meijer, C. de Graaf, H. Schreurs, *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 46–47; b) A. C. Oehlschlager, E. Czyzewska, *Tetrahedron Lett.* **1983**, *24*, 5587–5590; c) J. A. Marshall, K. G. Pinney, *J. Org. Chem.* **1993**, *58*, 7180–7184; d) C. Spino, S. Fréchette, *Tetrahedron Lett.* **2000**, *41*, 8033–8036; e) C. R. Johnson, D. S. Dhanoa, *J. Org. Chem.* **1987**, *52*, 1885–1888; f) A. Doutheau, A. Saba, J. Gore, G. Quash, *Tetrahedron Lett.* **1982**, *23*, 2461–2464; g) P. R. Ortiz de Montellano, *J. Chem. Soc. Chem. Commun.* **1973**, 709–710; h) R. K. Dieter, L. E. Nice, *Tetrahedron Lett.* **1999**, *40*, 4293–4296; i) F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold, B. L. Feringa, *Tetrahedron Lett.* **1999**, *40*, 4893–4896.

[17] a) A similar rationale has been proposed for the formation of bromoallenes from propargyl alcohols and CuBr: N. Bernard, F. Chemea, J. F. Normant, *Tetrahedron Lett.* **1998**, *39*, 8837–8840; b) for a review, see: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307–1370.

[18] For a recent application, see the following Communication in this issue: A. Fürstner, D. De Souza, L. Parra-Rapado, J. T. Jensen, *Angew. Chem.* **2003**, *115*, 5516–5518; *Angew. Chem. Int. Ed.* **2003**, *42*, 5358–5360.

