

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**

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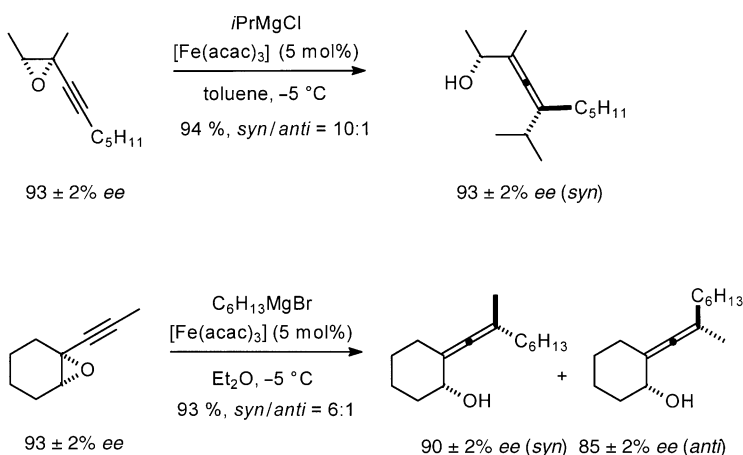
Allenes in general and 2,3-allenol derivatives in particular are versatile building blocks for advanced organic synthesis because of the reactivity inherent to their axially chiral backbones.^[1] They are usually prepared by S_N2' -type reactions of propargylic substrates with organocopper reagents. 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.^[1,4,5] 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 -MeOC₆H₄MgBr 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 foremost, 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 (≤ 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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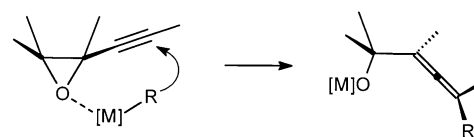
Table 1: Iron-catalyzed synthesis of 2,3-allenols from propargyl epoxides.^[a]

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

[a] The reactions were carried out at -5°C in the presence of $[\text{Fe}(\text{acac})_3]$ (3–5 mol%) precatalyst and Grignard reagent (1.3 equiv), unless stated otherwise. [b] Fe–salen precatalyst. [c] -30°C . [d] -60°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 Et₂O. 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).

The reasons, however, why the diastereoselectivity *decreases* upon lowering the reaction temperature are far



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

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 $[\text{Fe}(\text{acac})_3]$ 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

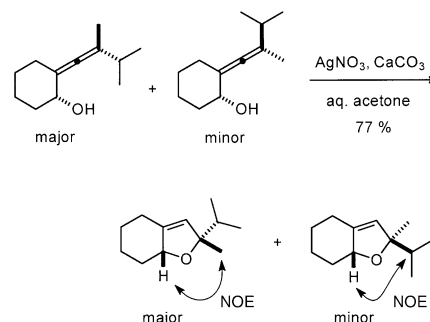
*i*PrMgCl (2 M in Et₂O, 0.42 mL, 0.83 mmol) was transferred by syringe into a solution of 1-prop-1-ynyl-9-oxa-bicyclo[6.1.0]nonane (105 mg, 0.64 mmol) and [Fe(acac)₃] (11 mg, 0.03 mmol) in toluene (14 mL) at –5 °C under Ar, causing an immediate color change from bright red to dark brown/black. After stirring for 5 min, the mixture was quenched with NH₄Cl (5 mL) and diluted with Et₂O (10 mL), the layers were separated, and the aqueous phase was extracted with Et₂O (3 × 5 mL). The combined organic layers were dried over MgSO₄, and the residue was purified by flash chromatography (5:1 pentane/Et₂O) 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; ¹H NMR (400 MHz, CD₂Cl₂): δ = 4.10 (dd, *J* = 7.9, 3.7 Hz, 1 H; *anti*), 4.07 (dd, *J* = 8.8, 4.0 Hz, 1 H; *syn*), 2.30–2.10 (m, 2 H), 2.05 (m, 1 H), 1.87 (m, 1 H), 1.71 (s, 3 H), 1.70–1.05 (m, 10 H), 1.05 (d, *J* = 1.9 Hz, 3 H; *syn*), 1.04 (d, *J* = 1.9 Hz, 3 H; *syn*), 1.03 (d, *J* = 1.9 Hz, 3 H; *anti*), 1.01 ppm (d, *J* = 1.9 Hz, 3 H; *anti*); *syn* isomer: ¹³C NMR (100 MHz, CD₂Cl₂; DEPT) δ = 197.27 (C), 109.91 (C), 109.67 (C), 72.81 (CH), 33.36 (CH₂), 32.99 (CH), 29.66 (CH₂), 29.84 (CH₂), 26.50 (CH₂), 25.92 (CH₂), 23.24 (CH₂), 22.17 (CH₃), 22.04 (CH₃), 17.33 ppm (CH₃); *anti* isomer: ¹³C NMR (100 MHz, CD₂Cl₂; DEPT): δ = 196.67 (C), 110.58 (C), 110.04 (C), 71.97 (CH), 33.29 (CH₂), 33.08 (CH), 29.45 (CH₂), 29.18 (CH₂), 26.61 (CH₂), 26.04 (CH₂), 22.92 (CH₂), 22.04 (CH₃), 21.97 (CH₃), 17.37 ppm (CH₃); MS (EI, 70 eV): *m/z* (%): 208 (10) [*M*⁺], 193 (30), 165 (13), 137 (38), 110 (27), 95 (100); HMRS: calcd for C₁₄H₂₄O: 208.1828; found: 208.1827.

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- [15] The stereochemical assignment was corroborated by NOE measurements of the dihydrofuran derivatives formed from selected allenols upon treatment with AgNO₃.^[16c] All other compounds were assigned by analogy. A representative example is shown below.



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