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Iron-Catalyzed Regio- and Stereoselective Substitution of γ,δ-Epoxy-α,β-unsaturated Esters and Amides with Grignard Reagents

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ABSTRACT

When γ,δ-epoxy-α,β-unsaturated esters or amides were treated with 2 equiv of Grignard reagents in the presence of 10−24 mol % $FeCl_2$, regio- and stereoselective substitution of the epoxide moiety with the Grignard reagent occurred to give exclusively δ-hydroxy-γ-alkyl or aryl-α,β-unsaturated esters or amides in good yields.

Diene monoepoxides are useful building blocks in organic synthesis, and their utility has been explored by many research groups.[1] Although their functionalized counterparts, such as γ,δ-epoxy-α,β-unsaturated carboxylic acid derivative **1** in eq 1, are often more useful than simple compounds,[2] their reaction with organometallic reagents has not been amply reported, probably because of the poor compatibility of the functional group with metallic reagents.[3,4] Here we report that iron-catalyzed substitution of these diene monoe-

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[1] (a) Olofsson, B.; Somfai, P. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; pp 315−347. For substitution of epoxides with Grignard reagents, see: (b) Urabe, H.; Sato, F. In *Handbook of Grignard Reactions*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; pp 577−632.

[2] Substitution of functionalized diene monoepoxides with various nucleophiles has been reported. With oxygen or nitrogen nucleophiles: (a) Yu, X.-Q.; Yoshimura, F.; Ito, F.; Sasaki, M.; Hirai, A.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 750–754. (b) Miyashita, M.; Mizutani, T.; Tadano, G.; Iwata, Y.; Miyazawa, M.; Tanino, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5094–5097. (c) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319–2321. (d) Tsuda, T.; Horii, Y.; Nakagawa, Y.; Ishida, T.; Saegusa, T. *J. Org. Chem.* **1989**, *54*, 977–979. With active methylene compounds under Pd catalysis (which shows different regioselection to form allyl alcohols rather than homoallyl alcohols): (e) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575–2578. (f) Nemoto, H.; Ibaragi, T.; Bando, M.; Kido, M.; Shibuya, M. *Tetrahedron Lett.* **1999**, *40*, 1319–1322. With hydride under Pd catalysis: (g) Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280–6287. With electron: (h) Molander, G. A.; Bella, B. E. L.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259–5264. (i) Yadav, J. S.; Shekharam, T.; Srinivas, D. *Tetrahedron Lett.* **1992**, *33*, 7973–7976.

[3] With methyl- or ethylaluminum reagents: (a) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6483–6485. (b) Shanmugam, P.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3265–3268. For application to natural product synthesis, see: (c) Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4341–4353. (d) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3579–3582.

[4] With organocopper reagents (which shows different regioselection to form allyl alcohols rather than homoallyl alcohols): Hirai, A.; Matsui, A.; Komatsu, K.; Tanino, K.; Miyashita, M. *Chem. Commun.* **2002**, 1970–1971.

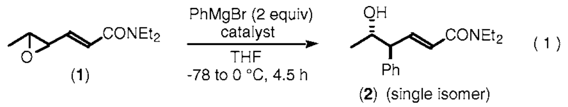
[5] For reviews on iron-promoted organic reactions, see: (a) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108–1117. (b) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317–3321. (c) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. For diene, enyne, and diyne cyclizations, see: (d) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem.Int. Ed* **2008**, *47*, 4268–4315. For coupling reactions, see: (e) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500–1511. (f) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624–629.

[6] For iron-catalyzed or -mediated reactions from our laboratory, see: (a) Okada, S.; Arayama, K.; Murayama, R.; Ishizuka, T.; Hara, K.; Hirone, N.; Hata, T.; Urabe, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6860–6864. (b) Hata, T.; Hirone, N.; Sujaku, S.; Nakano, K.; Urabe, H. *Org. Lett.* **2008**, *10*, 5051–5053. (c) Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603–606.

10.1021/ol100022w

poxides with Grignard reagents satisfactorily took place to give homoallyl alcohols as single isomers.[5,6]

The outcome of the preliminary investigation is shown by eq 1, in which amide **1** was allowed to react with PhMgBr in the presence of iron salts or other metallic catalysts. While a few iron salts proved particularly useful for this reaction (entries 2−5), routine catalysts[1,2] were found ineffective (entries 6−12).[7] Considering its cost and simplicity (free from organic ligands), we adopted 10−20 mol % of FeCl$_2$ as the best catalyst and obtained the desired homoallyl alcohol **2** in 62% isolated yield and as a single isomer (entry 4).[8]

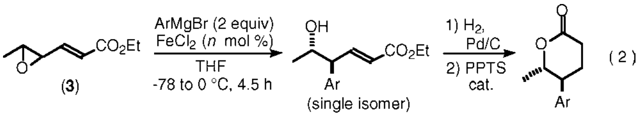


(**1**)

(**2**) (single isomer)

entry	catalyst (mol %)	isolated yield (%)	entry	catalyst (mol %)	isolated yield (%)
1	none	0	7	PdCl$_2$ (10)	0
2	Fe(acac)$_3$ (20)	61	8	Pd(PPh$_3$)$_4$ (10)	0
3	FeCl$_2$ (22)	61	9	NiCl$_2$ (10)	0
4	FeCl$_2$ (12)	62	10	NiCl$_2$(PPh$_3$)$_2$ (10)	0
5	FeCl$_2$ (5)	32	11	MnCl$_2$ (20)	0
6	CuI (10)	0	12	CoCl$_2$ (20)	0

This reaction is also applicable to ester **3** as shown in eq 2. The stereochemistry of product **5** was unambiguously verified by its derivatization to known lactone **6**.[9]



(**3**)

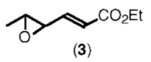
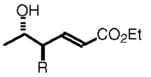
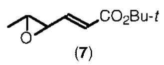
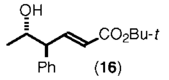
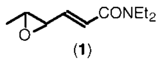
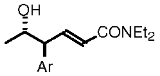
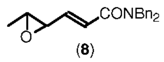
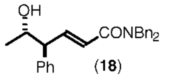
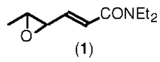
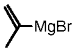
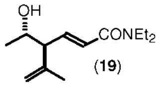
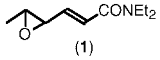
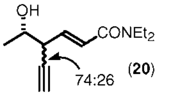
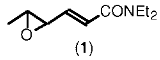
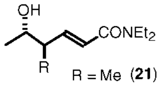
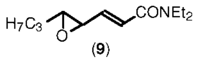
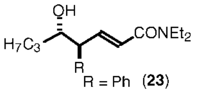
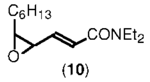
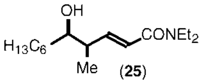
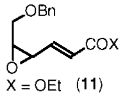
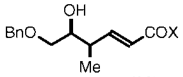
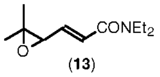
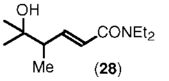
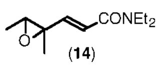
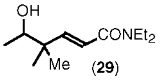
(single isomer)

Ar = Ph (**4**) 60% (n = 12)
o-MeOC$_6$H$_4$- (**5**) 57% (n = 10)

Ar = o-MeOC$_6$H$_4$- (**6**)
68% (2 steps)

The high selectivity observed above is valid to various γ,δ-epoxy-α,β-unsaturated carboxylic acid derivatives and Grignard reagents as shown in Table 1, thus affording the desired products as virtually single isomers. Besides ethyl ester **3** and diethylamide **1**, *t*-butyl ester **7** and *N*,*N*-dibenzylamide **8** participated in the substitution as well to give **16** and **18** (entries 4 and 7). In addition to aryl delivery (entries 1, 2, 4−7, and 12), alkyl or alkenyl Grignard reagents afforded single homoallyl alcohols in good yields (entries 3, 8, 10, 11, and 13−18). One exception was ethynyl Grignard reagent (entry 9), which gave the coupling product **20** in good yield, but its diastereoselectivity was moderate. While the reactions of entries 1−13 always started with *trans*-epoxides, *cis* epoxides **10**−**12** could be utilized equally well to give the homoallyl alcohols **25**−**27** as single isomers (entries 14−16), among which product **26** is a known compound.[3a] Even trisubstituted epoxides **13** and **14** reacted smoothly with a Grignard reagent to produce the desired products **28** and **29** in high yields (entries 17 and 18).

Table 1. Preparation of Various Homoallyl Alcohols According to eqs 1 and 2

entry	epoxide	Grignard reagent	FeCl$_2$ (mol %)	product	yield (%)[a]
1	 (**3**)	RMgBr	12	 R = Ph (**4**)	60
2			10	o-MeOC$_6$H$_4$- (**5**)	57
3			11	Me (**15**)	81
4	 (**7**)	PhMgBr	12	 (**16**)	68
5	 (**1**)	ArMgBr	12	 Ar = Ph (**2**)	62
6			22	p-MeOC$_6$H$_4$- (**17**)	57
7	 (**8**)	PhMgBr	10	 (**18**)	77
8	 (**1**)		20	 (**19**)	59
9	 (**1**)	≡—MgBr	12	 74:26 (**20**)	77[b]
10	 (**1**)	RMgBr	21	 R = Me (**21**)	89
11			21	Et (**22**)	49
12	 (**9**)	RMgBr[c]	24	 R = Ph (**23**)	60
13			21	Me (**24**)	78
14	 (**10**)	MeMgBr	21	 (**25**)	86
15	 X = OEt (**11**)	MeMgBr	10	 X = OEt (**26**)	63
16	NEt$_2$ (**12**)		21	NEt$_2$ (**27**)	76
17	 (**13**)	MeMgBr	21	 (**28**)	88
18	 (**14**)	MeMgBr	21	 (**29**)	85

[a] Isolated yields. A single isomer was always produced, except for entry 9. [b] Same diastereoselectivity was observed before and after purification. Stereochemical assignment to the diastereoisomers has not been done. [c] PhMgBr (2.3 equiv) or MeMgBr (1.9 equiv) was used.

Synthetic versatility of Grignard reagents makes this transformation more attractive as illustrated in eq 3.[10] Coupling of functionalized Grignard reagent **31** generated from (chloromethyl)iodobenzene (**30**)[11] and diene monoep-

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(7) Unsuitable copper catalysis for this purpose was expected from the results of ref 4. See, for example: Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed* **2009**, *48*, 5586–5587.

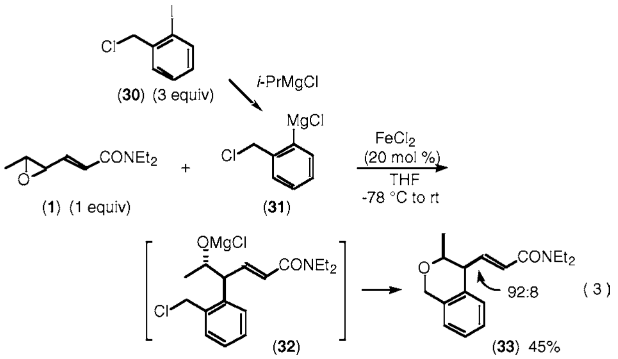
(8) Other regio- and stereoisomers were not detected in a crude reaction mixture after careful analysis by ^{1}H NMR spectroscopy.

(9) Nagumo, S.; Ono, M.; Kakimoto, Y.; Furukawa, T.; Hisano, T.; Mizukami, M.; Kawahara, N.; Akita, H. *J. Org. Chem.* **2002**, *67*, 6618–6622.

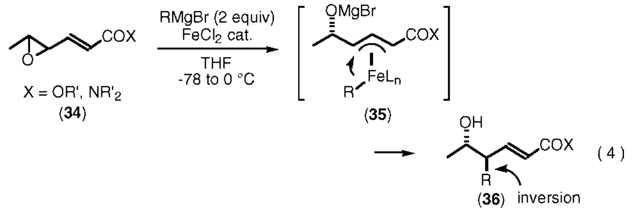
(10) As cited in reference 3 this type of carbon-carbon bond formation is so far viable with only methyl- or ethylaluminum reagents.

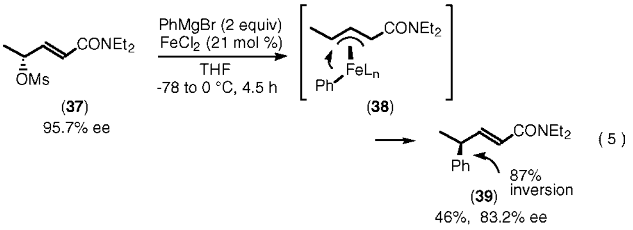
(11) Delacroix, T.; Bérillon, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 8108–8110.

oxide **1** afforded alkoxide **32**, which spontaneously underwent cyclization to yield the isochroman derivative **33**. The somewhat low diastereoselectivity (92:8) of **33** may arise from vinylogous enolization of intermediate **32** at a higher temperature necessary for the cyclization step.



The present reaction should proceed via π-allyliron intermediate **35**[12,13] generated from **34** with inversion of configuration of the allylic epoxide carbon (eq 4). Subsequent migration of the R group from iron to the allyl ligand with retention of configuration should have resulted in the exclusive production of **36** with the observed stereochemistry. To see the generality of this stereochemical outcome, we turned our attention to a similar substitution of an optically active, functionalized allyl mesylate **37**. As can be seen from eq 5, the stereochemical integrity of **37** was partially lost during the reaction through **38** to give product **39** as a single regioisomer with a lower ee value.[14] Thus, the highly selective overall inversion of stereochemistry in the reaction of the functionalized diene monoepoxide with a Grignard reagent is noteworthy from both synthetic and mechanistic points of view.





In conclusion, the iron-catalyzed substitution of γ,δ-epoxy-α,β-unsaturated esters and amides with Grignard reagents proceeded with inversion of configuration. As Grignard reagents are one of the most versatile organometallic reagents, this method is a novel entry to the practical preparation of stereodefined functionalized homoallyl alcohols.

Acknowledgment. This work was supported by a Grant-in-Aid for Young Scientists (B) (20750071, to T.H.) and a Grant-in-Aid for Scientific Research (B) (21350027) from JSPS.

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

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(12) Iron-catalyzed allylic substitution with Grignard reagents has been reported. (a) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 386–403. (b) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 513–514. (c) Urabe, H.; Inami, H.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1595–1597. (d) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373–1375. With functionalized (achiral) allyl bromide, see: (e) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787. With alkynylepoxides, see: (f) Fürstner, A.; Méndez, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355–5357. (g) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194–9204. With vinylcyclopropanes, see: (h) Sherry, B. D.; Fürstner, A. *Chem. Commun.* **2009**, 7116–7118.

(13) Regio- and stereochemical aspects of iron-catalyzed allylic substitution with soft nucleophiles such as malonates and amines have been disclosed. (a) Silverman, G. S.; Strickland, S.; Nicholas, K. M. *Organometallics* **1986**, *5*, 2117–2124. (b) Xu, Y.; Zhou, B. *J. Org. Chem.* **1987**, *52*, 974–977. (c) Zhou, B.; Xu, Y. *J. Org. Chem.* **1988**, *53*, 4419–4422. (d) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1469–1473. (e) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 6053–6056. (f) Åkermark, B.; Sjögren, M. P. T. *Adv. Synth. Catal.* **2007**, *349*, 2641–2646. (g) Plietker, B.; Dieskau, A.; Möws, K.; Jatsch, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 198–201. For review, see: (h) Plietker, B.; Dieskau, A. *Eur. J. Org. Chem.* **2009**, 775–787.

(14) To the best of our knowledge, this is the first example disclosing the stereochemical course of iron-catalyzed allylic substitution at an optically active system with Grignard reagent, which is categorized as a hard nucleophile.