

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

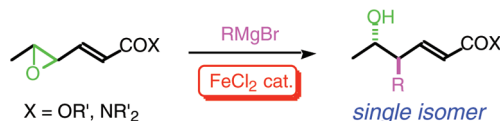
Takeshi Hata, Rie Bannai, Mamoru Otsuki, and Hirokazu Urabe*

Department of Biomolecular Engineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259-B-59 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501, Japan

hurabe@bio.titech.ac.jp

Received January 5, 2010

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 mono-

(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.

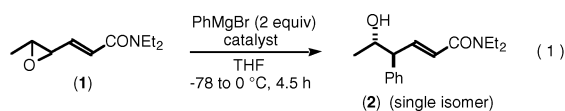
(4) With organocopper reagents (which shows different regioselection to form allyl alcohols rather than homoallyl alcohols): Hirai, A.; Matsui, A.; Komatsu, K.; Tanino, K.; Miyashita, M. *Chem. Commun.* **2002**, 1970–1971.

(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 Pailh, 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.

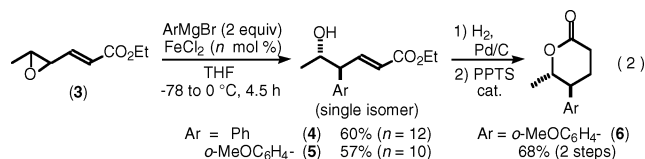
poxides with Grignard reagents satisfactorily took place to give homoallyl alcohols as single isomers.^{5,6}

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 FeCl₂ as the best catalyst and obtained the desired homoallyl alcohol **2** in 62% isolated yield and as a single isomer (entry 4).⁸



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



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

(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 ¹H 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.

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

entry	epoxide	Grignard reagent	FeCl ₂ (mol %)	product	yield (%) ^a
1		RMgBr	12		60
2			10		57
3			11		81
4		PhMgBr	12		68
5		ArMgBr	12		62
6			22		57
7		PhMgBr	10		77
8			20		59
9			12		77 ^b
10		RMgBr	21		89
11			21		49
12		RMgBr ^c	24		60
13			21		78
14		MeMgBr	21		86
15		MeMgBr	10		63
16			21		76
17		MeMgBr	21		88
18		MeMgBr	21		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.

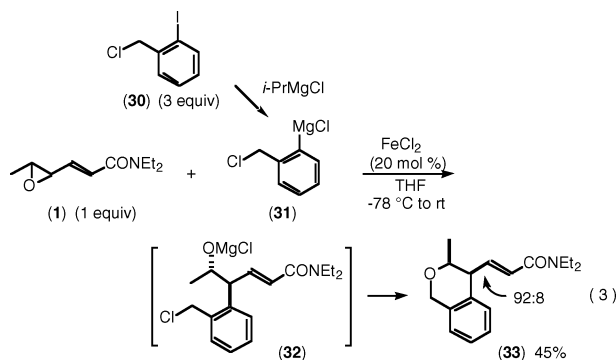
smoothly with a Grignard reagent to produce the desired products **28** and **29** in high yields (entries 17 and 18).

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-

(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.

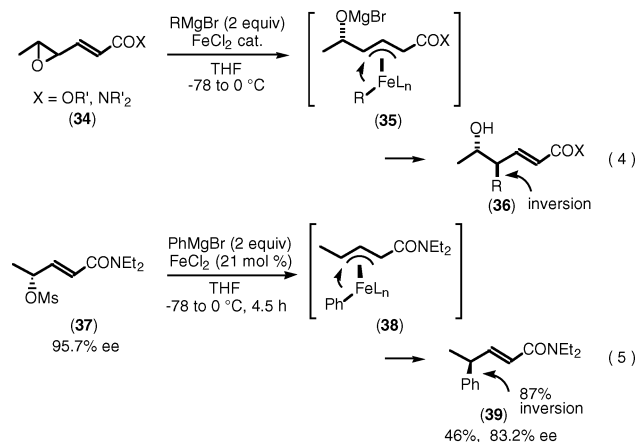


The present reaction should proceed via π -allyliron intermediate **35**^{12,13} generated from **34** with inversion of configuration of the allylic epoxide carbon (eq 4). Subsequent migration of the R group from iron to the allyl ligand with retention of configuration should have resulted in the exclusive 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

(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.; Kattinig, 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) Åkermarck, 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.

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>.

OL100022W

(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.