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Iron-Mediated Intramolecular Metalative Cyclization of α,β-Unsaturated Esters and Amides. Versatile One-Pot Preparation of Bicyclic Ketoesters

Takeshi Hata, Naoki Hirone, Shiro Sujaku, Kirihiro Nakano, 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

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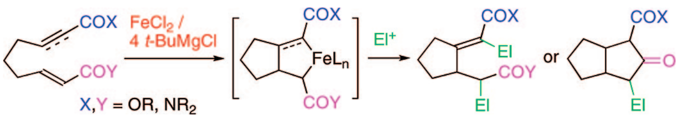
ABSTRACT



2-Nonen-7-ynedioic or 2-decen-8-ynedioic acid derivatives were treated with an iron reagent generated from FeCl$_2$ and *t*-BuMgCl in a ratio of 1:4 to give cyclized products after hydrolysis, deuteriolysis, or the addition of carbonyl compounds. Upon reaction with the same iron reagent, 2,7-nonadienedioates afforded bicyclic ketoesters (and their enol forms) after the addition of *s*-BuOH or carbonyl compounds.

Cyclization of enynes and dienes derived from unsaturated carbonyl compounds with a stoichiometric amount of a metal species may produce synthetically useful functionalized organometallic compounds, but reactions belonging to this class are still limited, probably because of the poor compatibility of a reactive metallic portion and the carbonyl group.[1] Here, we report that an iron reagent, generated from FeCl$_2$ and *t*-BuMgCl, is particularly useful for this type of cyclization, in conjunction with another advantage that iron is abundant, inexpensive, and nontoxic, which should contribute to economical and sustainable organic synthesis.[2]

Treatment of (*E*)-2-nonen-7-ynedioic acid derivative **2** with reagent **1** generated from FeCl$_2$ and *t*-BuMgCl in a ratio of 1:4[3,4] afforded cyclized product **4** in good yield after aqueous workup, with both carbonyl groups remaining untouched (Scheme 1).[5−8] When the aqueous workup was replaced with deuteriolysis, dideuterated product **4**-*d*$_2$ was obtained, showing the presence of the dimetalated intermediate **3**. This intermediate regioselectively reacted with carbonyl compounds to give carbon chain-elongated products **5−7** in one pot.[9]

Other products prepared from various (*E*)-2-nonen-7-ynedioic acid derivatives according to Scheme 1 by hydrolysis are shown in Figure 1, where a dotted line refers to a newly formed carbon−carbon bond. Cyclopentanes **4** and **8−10** having various ester and amide side chains were obtained in good yields. While a benzyloxymethyl group in the tether portion was not effective enough to control the stereochemistry of product **11**, a highly diastereoselective

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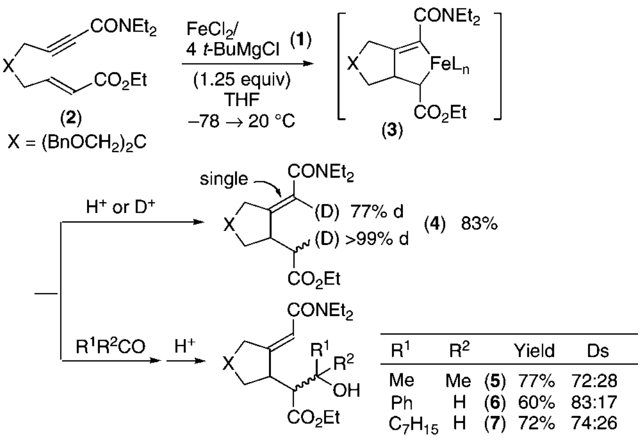
[1] For functionalized titanacycles and their synthetic applications, see: (a) Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 319−354. (b) Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759–784. (c) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835–2886. (d) Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014–10027. (e) Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7774–7780. For functionalized nickelacycles, see: (f) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467–473. (g) Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 13481–13485.

[2] For reviews on iron-mediated organic reactions, see: (a) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317–3321. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. For enyne cyclization, see: (c) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315. For coupling reactions, see: (d) Fürstner, A.; Rubén, M. *Chem. Lett.* **2005**, *34*, 624–629. For iron carbonyl complexes, see: (e) Semmelhack, M. F. In *Organometallics in Organic Synthesis. A Manual*, 2nd ed.; Schlosser, M., Ed.; John Wiley & Sons: Chichester, 2002; pp 1006−1121.

10.1021/ol802170z CCC: $40.75

Scheme 1. Cyclization of Enynedioic Acid Derivative and Subsequent Reactions



R^1	R^2		Yield	Ds
Me	Me	(**5**)	77%	72:28
Ph	H	(**6**)	60%	83:17
C_7H_{15}	H	(**7**)	72%	74:26

cyclization giving a single bicyclic compound **12** should be also noted. Substituted cyclohexane **13** was similarly produced from the corresponding (*E*)- and (*Z*)-2-decen-8-ynedioic acid derivatives in good yields, regardless of their olefinic geometries.

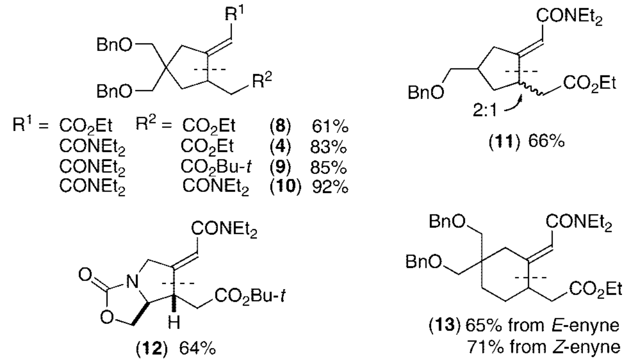


Figure 1. Products formed according to Scheme 1.

When we attempted the cyclization of dienedioate **14** with iron reagent **1** under the same conditions, the expected cyclopentane **15** was not isolated after aqueous workup (Scheme 2). Instead, the isolable product here was a bicyclic ketoester **16** as a 1:1 mixture of tautomeric keto and enol forms[10] in varying yields between 17 and 32%. The ketoester itself was a single isomer, which should have a thermodynamically stable *exo*-alkoxycarbonyl group. The proposed reaction course from **14** to **16** involves the iron-mediated cyclization to form metallacycle **17**, protonation to one of its carbon−metal bonds, and Dieckmann condensation of **18** to **16**. Proper choice of the proton source regarding its reactivity and equivalents appeared critical for the efficient conversion from **14** to **16**, and we found that *s*-BuOH as indicated in Scheme 2 attained a satisfactory and stable product yield of **16** (50%).[8,11−13]

Figure 2 shows ketoesters prepared from various *E*,*E*-dienedioates according to Scheme 2. The type of alcohol portion of the starting esters did not affect the efficiency of cyclization to give **19-21** in comparable yields. The yields of **20** from the corresponding *E*,*E*- and *Z*,*E*-dienedioates (61 and 35%, respectively) show that the former is a more preferable starting material than the latter. Differently substituted ketoesters **16** and **22** and those having an oxa- or aza-heterocycle **23** and **24** were produced in satisfactory yields.

In the transformation of Scheme 2, the carbon−metal bond in **17** is cleaved by a proton, which is followed by the second cyclization. However, this proton may be replaced by another electrophile. In fact, when a ketone or aldehyde was added

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(3) For our recent work on iron-catalyzed addition of Grignard reagents to dienoates and dienamides, see: (a) Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603–606. (b) Okada, S.; Arayama, K.; Murayama, R.; Ishizuka, T.; Hara, K.; Hirone, N.; Hata, T.; Urabe, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6860–6864.

(4) The use of fewer equivalents of *t*-BuMgCl resulted in considerable decrease in the product yield. It has been reported that $FeCl_2$ and 4 equiv of RCH_2CH_2MgX form a species of the formal composition of $[Fe(MgX)_2]_n$. To the best of our knowledge, the use of *t*-BuMgCl for this purpose has not been mentioned. (a) Bogdanović, B.; Schwickardi, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610–4613. (b) Fürstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863. (c) Fürstner, A.; Krause, H.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 440–444.

(5) Even with the metal species listed in ref 1, cyclization of enynedioic acid derivatives to the products such as those in Scheme 1 and Figure 1 has not been reported.

(6) Other iron-mediated cyclizations of enynes and dienes are as follows. In these reports, α,β-unsaturated carboxylic acid derivatives are not included as the starting material. For the Pauson−Khand-type enyne cyclization, see: (a) Pearson, A. J.; Dubbert, R. A. *Organometallics* **1994**, *13*, 1656–1661. For [2 + 2] cyclization and polymerization of dienes, see: (b) Bouwkamp, M. W.; Bowman, A. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 13340–13341. (c) Takeuchi, D.; Matsuura, R.; Park, S.; Osakada, K. *J. Am. Chem. Soc.* **2007**, *129*, 7002–7003. Cyclization of diynes initiated by iron-catalyzed carbometalation was recently reported: (d) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 1505–1506.

(7) Iron-catalyzed Diels−Alder and Alder−ene reactions are also known. (a) Genet, J. P.; Ficini, J. *Tetrahedron Lett.* **1979**, 1499–1502. (b) tom Dieck, H.; Diercks, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 778–779. (c) Baldenius, K.-U.; tom Dieck, H.; König, W. A.; Icheln, D.; Runge, T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 305–307. (d) Takacs, J. M.; Anderson, L. G.; Madhavan, G. V. B.; Seely, F. L. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1013–1015. (e) Takacs, J. M.; Anderson, L. G.; Newsome, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 2542–2544. (f) Fürstner, A.; Majima, K.; Martin, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992–2004.

(8) For experimental details, see the Supporting Information.

(9) Products **6** and **7** consisted of only two diastereoisomers out of four. These diastereoisomers should be attributable to the stereochemistry between the cyclopentane carbon and the carbon α to the ester group as similarly observed for **5**. In these cases, the assignment of stereochemistries to major and minor isomers has not been done.

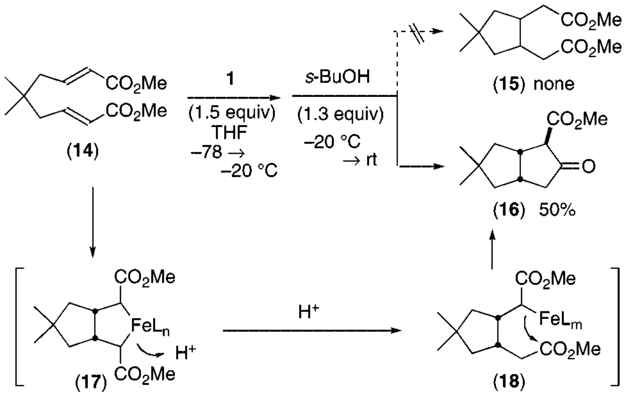
(10) Ketoesters in Scheme 2, Figure 2, and eq 1 are always an approximately 1:1 mixture of keto and enol forms, of which only the former is depicted for simplicity.

(11) Bicyclic ketoester **16** is a known key compound to pentalenolactone F: Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295–5303.

(12) For reviews on the preparation and synthetic utility of five-membered bicyclic compounds, see: Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671–719. Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647–3692.

(13) Dimerization of cinnamate esters to ketoesters has been reported: (a) Kise, N.; Iitaka, S.; Iwasaki, K.; Ueda, N. *J. Org. Chem.* **2002**, *67*, 8305–8315, and references cited therein. (b) Takaki, K.; Beppu, F.; Tanaka, S.; Tsubaki, Y.; Jintoku, T.; Fujiwara, Y. *J. Chem. Soc., Chem. Commun.* **1990**, *n/a*, 516–517. (c) Jensen, S. R.; Kristiansen, A.-M.; Munch-Petersen, J. *Acta Chem. Scand.* **1970**, *24*, 2641–2647. For intramolecular cyclization of α,β-olefinic esters, see: (d) Shinohara, I.; Okue, M.; Yamada, Y.; Nagaoka, H. *Tetrahedron Lett.* **2003**, *44*, 4649–4652. However, these methods did not realize the concomitant incorporation of a second constituent such as a carbonyl compound to the products as can be seen in **27**−**30**.

Scheme 2. Tandem Cyclization of Dienedioate



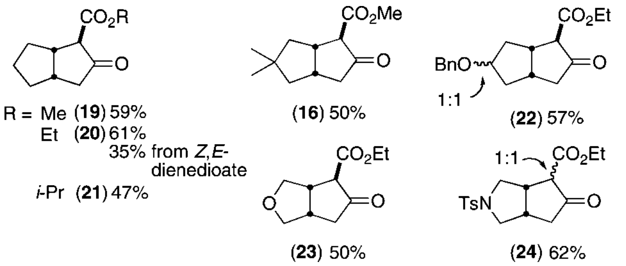
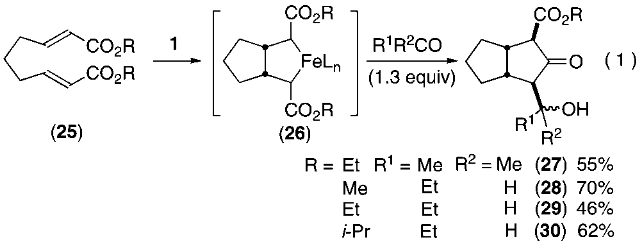


Figure 2. Bicyclic ketoesters prepared according to Scheme 2.

to metallacycle **26** generated from **25** and **1** (eq 1), an aldol-type reaction followed by the Dieckmann condensation took place to give bicyclic compounds **27**−**30** having an additional hydroxyalkyl side chain. The ketoester **27** was virtually a single stereoisomer having the hydroxyisopropyl group at the *exo* position,[8] and the same stereochemistry was assigned to other products **28**−**30** based on that of **27**. This transformation could be considered as an equivalent of the generation and reaction of the dianion of ketoesters **19**−**21**[14] and is a new entry to the existing methods.[13]



R =	R^1 =	R^2 =		
Et	Me	Me	(**27**)	55%
Me	Et	H	(**28**)	70%
Et	Et	H	(**29**)	46%
i-Pr	Et	H	(**30**)	62%

In conclusion, we reported new metalative cyclizations of doubly functionalized enynes and dienes with a simple iron reagent, which enable a tandem cyclization of dienedioates affording bicyclic ketoesters in one pot. Further investigations on the utility of the iron reagent and synthetic application of the products are now in progress.

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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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(14) For the generation and reactions of dianions of ketoesters, see: Thompson, C. M.; Green, D. L. C. *Tetrahedron* **1991**, *47*, 4223–4285.