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Iron-Mediated and -Catalyzed Metalative Cyclization of Electron-Withdrawing-Group-Substituted Alkynes and Alkenes with Grignard Reagents

Takeshi Hata, Shiro Sujaku, Naoki Hirone, Kirihiro Nakano, Junsuke Imoto, Haduki Imade, and Hirokazu Urabe*[a]

Abstract: Treatment of ethyl (*E*)-5,5-bis[(benzyloxy)methyl]-8-(*N*,*N*-diethylcarbamoyl)-2-octen-7-ynoate with an iron reagent generated from $FeCl_2$ and *t*BuMgCl in a ratio of 1:4 (abbreviated as $FeCl_2$/4 *t*BuMgCl) afforded ethyl [4,4-bis[(benzyloxy)methyl]-2-[(*E*)-(*N*,*N*-diethylcarbamoyl)methylene]cyclopent-1-yl]acetate in good yield. Deuteriolysis of an identical reaction mixture afforded the bis-deuterated product ethyl [4,4-bis[(benzyloxy)methyl]-2-[(*E*)-(*N*,*N*-diethylcarbamoyl)deuteriomethylene]cyclopent-1-yl]deuterioacetate, thus confirming the existence of the corresponding dimetalated intermediate. The latter intermediate can react with halogens or aldehydes to facilitate further synthetic transformations. The amount of $FeCl_2$ was reduced to catalytic levels (10 mol% relative to enyne), and catalytic cyclizations of this sort proceeded with yields comparable to those of the aforementioned stoichiometric reactions. The cyclization of diethyl (*E*,*E*)-2,7-nonadienedioate with a stoichiometric amount of $FeCl_2$/4 *t*BuMgCl, followed by the addition of *s*BuOH as a proton source, afforded a mixture of 2-(ethoxycarbonyl)-3-bicyclo[3.3.0]octanone and its enol form in good yield. The use of aldehyde or ketone in place of *s*BuOH afforded 2-(ethoxycarbonyl)-3-bicyclo[3.3.0]octanone, which has an additional hydroxyalkyl side chain. Additionally, the metalation of a carbon–carbon unsaturated bond in *N*,*N*-diethyl-5,5-bis[(benzyloxy)methyl]-7,8-epoxy-2-octynamide or (*E*)-3,3-dimethyl-6-(*N*,*N*-diethylcarbamoyl)-5-hexenyl *p*-toluenesulfonate with $FeCl_2$/4 *t*BuMgCl or $FeCl_2$/4 PhMgBr was followed by an intramolecular alkylation with an epoxide or alkyl *p*-toluenesulfonate to afford 5,5-bis[(benzyloxy)methyl]-3-[(*E*)-(*N*,*N*-diethylcarbamoyl)methylene]-1-cyclohexanol or *N*,*N*-diethyl(3,3-dimethylcyclopentyl)acetamide after hydrolysis. In both cases, the remaining metalated portion α to the amide group was confirmed by deuteriolysis and could be utilized for an alkylation with methyl iodide.

Keywords: alkenes • alkynes • Grignard reaction • iron • metallacycles

Introduction

When the intramolecular cyclization of acetylenes and olefins is performed with a stoichiometric amount of metal species, the metal portion may be incorporated into the cyclized products, producing new and versatile organometallic compounds.[1] However, the applicability of this process to functionalized olefins and acetylenes is limited, probably because of the poor compatibility of the reactive metallic portion and the functional group.[2] Recently, iron compounds have attracted much attention as safe, abundant, and economical reagents for a wide range of organic reactions, including coupling reactions, cyclizations, isomerizations, metalations, oxidations, reductions, and other types of reactions.[3] Considering the current rapid growth in the number of iron-mediated reactions, we were also prompted to explore a new utility of iron, particularly in the formation of metallacycles from unsaturated compounds. Herein, we report a synthetic methodology, according to which, an iron salt is utilized for the metalation of functionalized carbon–carbon multiple bonds to enable the aforementioned cyclization and even alkylation with an electrophile. (Scheme 1). Another advantage is that iron-mediated reactions constitute synthetic methods that are economical and sustainable.[3]

Results and Discussion

Stoichiometric enyne and diene cyclizations:[4] We first investigated the cyclization of doubly functionalized enyne **1** with iron reagents generated by the reduction of $FeCl_2$ with

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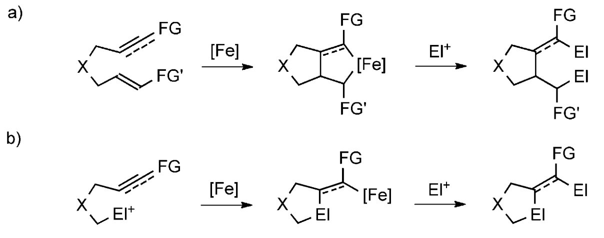
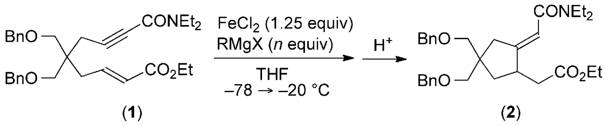


Scheme 1. Iron-mediated formation of metallacycles or metalated species from functionalized unsaturated compounds. FG = functional group, [Fe] = iron reagent or iron moiety, El+ = electrophile.

various Grignard reagents.[5] Scheme 2 summarizes its outcome. Among the Grignard reagents tested, the combination of $FeCl_2$ and *t*BuMgCl in a molar ratio of 1:4[6] was optimal, giving the desired cyclization product **2** in 83 % yield with the functional groups intact.[7–9]

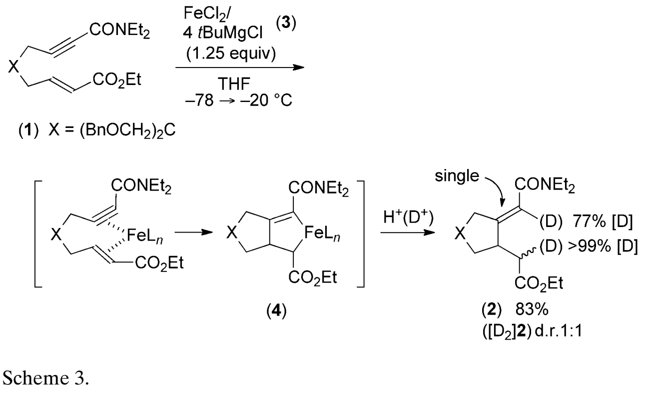


RMgX	*n*	Yield [%][a]
MeMgBr	5	(0)
EtMgCl	5	(trace)
*i*PrMgCl	5	(15)
*t*BuMgCl	2.5	22
*t*BuMgCl	5	83
PhMgBr	5	(37)

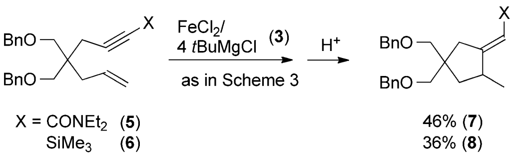
[a] Yields in parentheses are those determined by ^{1}H NMR spectroscopy.

Scheme 2. Bn = benzyl.

Scheme 3 shows detailed data on the highest-yielding reaction depicted in Scheme 2. Upon reaction with $FeCl_2$/4 *t*BuMgCl (**3**), enyne **1** afforded **2** as a single olefinic isomer as depicted in Scheme 3. Deuteriolysis after the reaction gave the deuterated product [D_2]**2**, confirming the presence of a bismetalated intermediate **4**.[10] Interestingly, less extensively functionalized enynes **5** and **6**, shown in Scheme 4, underwent cyclization to give **7** and **8** in lower yields, suggesting that the iron reagent **3** prefers functionalized to unfunctionalized enynes. Therefore, the electron-rich, low-valent iron reagent probably interacts more strongly with electron-deficient unsaturated bonds in **1** during the cyclization process.



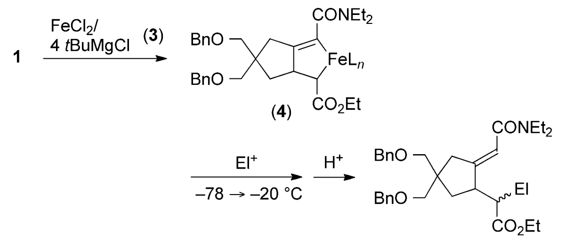
Scheme 3.



Scheme 4.

Overall results of the enyne cyclization are summarized in Table 1. Functionalized enynes with *tert*-butyl ester **9**, nitrile **10**, amide **11**, or sulfone **12** moieties reacted equally well to afford the corresponding cyclopentanes **19**–**22** after aqueous workup (Table 1, entries 2–5). Substitution to the tether portion did not impede cyclization, and thus compounds **13** and **14** afforded **23** and **24**, respectively (Table 1, entries 6 and 7), with bicyclic heterocycle **24** notably being produced as a single stereoisomer. Enyne **15**, which incorporates two ethyl ester appendages, generated diester **25** (Table 1, entry 8) through a cyclization process. The cyclohexane framework **26** was formed in good yield, regardless of the *cis*- or *trans*-olefinic stereochemistry of the starting materials **16** and **17** (Table 1, entries 9 and 10). Finally, the cyclization of functionalized dienyne **18** produced vinyl-substituted cyclopentane **27** in good yield (Table 1, entry 11).

The intermediate metallacycle **4**, which yielded the cyclic products shown in Table 1 below through the hydrolysis route, was additionally able to react with external electrophiles (such as halogens, aldehydes, or ketones) selectively at the position shown in Scheme 5 to give the coupling products **28**–**32**.[11] Thus, further synthetic transformations, such as functionalization and carbon–carbon bond formation, are possible from the intermediate metallacycles, demonstrating their utility as versatile organometallic compounds.

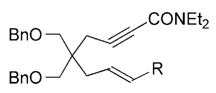
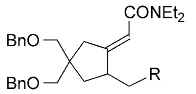
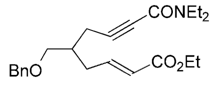
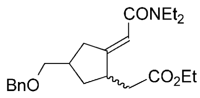
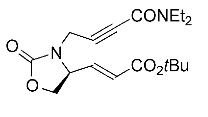
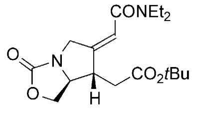
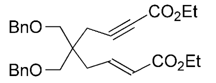
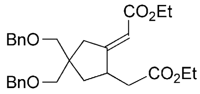
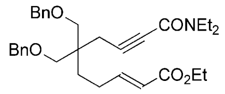
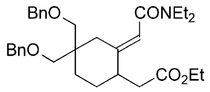
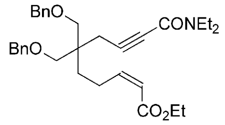
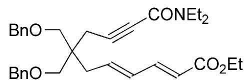
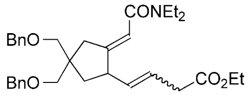


El+ = Br_2	El = Br	61% (d.r. 89:11) (**28**)
I_2	I	67% (d.r. 82:18) (**29**)
PhCHO	PhCH(OH)-	60% (d.r. 83:17) (**30**)
C_7H_{15}CHO	C_7H_{15}CH(OH)-	72% (d.r. 74:26) (**31**)
Me_2CO	Me_2C(OH)-	77% (d.r. 72:28) (**32**)

Scheme 5.

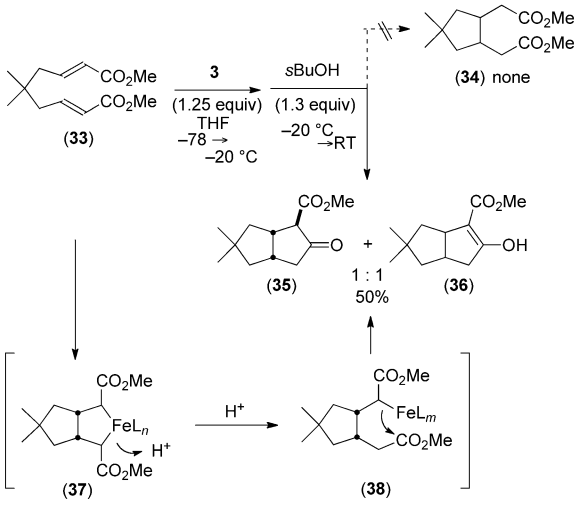
Cyclization of dienedioate **33** with the same iron reagent **3** took a different reaction course, through which the expected cyclopentane **34** was not isolated after aqueous workup (Scheme 6). Instead, bicyclic ketoester **35** was formed as a 1:1 mixture of tautomeric keto and enol forms (**35** and

Table 1. Cyclization of functionalized enynes according to the reaction shown in Scheme 3.

Entry	Substrate		Period [h]	Product[a]		Isolated yield [%]
						
1	R = CO_2Et	**(1)**	3.5	R = CO_2Et	**(2)**	83
2	CO_2tBu	**(9)**	4	CO_2tBu	**(19)**	85
3	CN	**(10)**	2	CN	**(20)**	49
4	$CONEt_2$	**(11)**	4.5	$CONEt_2$	**(21)**	92
5	SO_2Ph	**(12)**	3	SO_2Ph	**(22)**	76
6		**(13)**	4		**(23)**	66 (d.r. = 2:1)[b]
7		**(14)**	0.5		**(24)**	64[c]
8		**(15)**	3		**(25)**	61
9		**(16)**	4.5		**(26)**	65
10		**(17)**	2		**(26)**	71
11		**(18)**	3		**(27)**	73 (*E*/*Z* = 1:1)[d]

[a] Products were isolated after workup with aqueous HCl. [b] d.r. = diastereomeric ratio. [c] Reagent **3** (1.57 equiv) was used. [d] For the disubstituted double bond.

36)[12] in unstable yields up to 32%. The ketoester was produced as a single stereoisomer with a thermodynamically stable *exo*-alkoxycarbonyl group. The *cis* junction of bicyclic compound **35** was spectroscopically confirmed in comparison to data of an authentic sample. A rationalization for the formation of **35** is also shown in Scheme 6. The iron-mediated cyclization of **33** generated metallacycle **37**, one carbon–metal bond of which was protonated during aqueous workup to give **38**. The monoenolate of diester **38** rapidly underwent Dieckmann condensation to give the observed product **35**. Because the usual workup is not an appropriate way to perform controlled protonation of **37**, the proper choice of the proton source, regarding its reactivity and stoichiometry, appeared critical for the efficient conversion of **37** to **38**. After investigations along this line, we found that the use of *s*BuOH under the conditions shown in Scheme 6 led to a stable and improved yield of **35** (50%).[13–15]

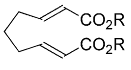
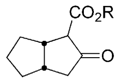
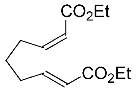
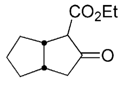
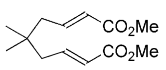
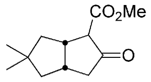
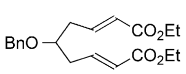
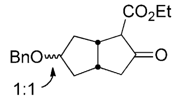
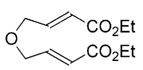
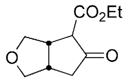
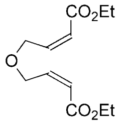
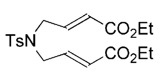
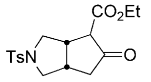


Scheme 6. Tandem cyclization of dienedioate.

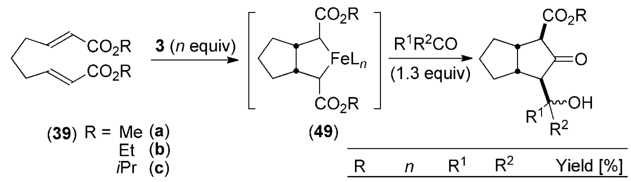
Table 2 shows various ketoesters prepared from dienedioates according to Scheme 6. The yields of **45b** from the corresponding *E*,*E*- and *Z*,*E*-dienes **39b** and **40** (61 and 35%, respectively) show that the former is a more preferable starting material than the latter (Table 2, entries 2 and 4). This was again seen in the cyclization of *E*,*E*- and *Z*,*Z*-dienedioates **42** and **43**, for which the latter no longer produced the desired compound **47** in an acceptable yield (Table 2, entries 7 and 8). A substituted ketoester **46** and those fused to oxa- or aza-heterocycles **47** and **48** were produced from **41**, **42**, and **44**, respectively, in satisfactory yields (Table 2, entries 6, 7, and 9).[16]

While the transformation shown in Scheme 6 is triggered by protonation of metallacycle **37**, this proton could be replaced by other electrophiles. In fact, when a ketone or aldehyde was added to metallacycle **49** (Scheme 7), an aldol-type reaction took place instead of a protonation, which was followed by Dieckmann condensation to give bicyclic compounds **50**–**53**. Ketoester **50** was generated as a single stereoisomer with the hydroxyisopropyl group at the *exo* position, and the stereochemistry assigned to products **51**–**53**

Table 2. Bicyclic ketoesters prepared according to the reaction shown in Scheme 6.

Entry	Dienedioate	Product[a]	Isolated yield [%][b]
			
1	R = Me (**39a**)	R = Me (**45a**)	53
2	Et (**39b**)	Et (**45b**)	61
3	*i*Pr (**39c**)	*i*Pr (**45c**)	47[c]
4	 (**40**)	 (**45b**)	36[d]
5	 (**33**)	 (**35**)	50
6	 (**41**)	 (**46**)	57[c]
7	 (**42**)	 (**47**)	50
8	 (**43**)	(**47**)	9
9[e]	 (**44**)	 (**48**)	62

[a] Only the keto form is shown. [b] Yield of a mixture of keto and enol forms. [c] Reagent **3** (1.5 equiv) was used. [d] Reagent **3** (1.42 equiv) was used. [e] Ts = tosyl.



R	*n*	R^1	R^2	Yield [%]
Et	1.5	Me	Me	(**50**) 55
Me	1.25	Et	H	(**51**) 70
Et	1.5	Et	H	(**52**) 46
*i*Pr	1.5	Et	H	(**53**) 62

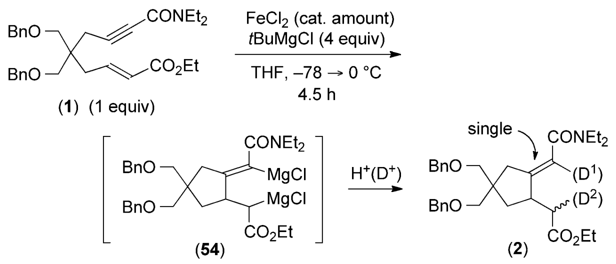
Scheme 7.

was based on that of **50**. This transformation could be considered as analogous to the generation and reaction of the dianion of ketoesters **45a–c**,[17] which gives derivatives that have a side chain.

Catalytic enyne cyclization: The iron reagent used in this study is suitable for stoichiometric reactions, because of its low cost and abundance, as described in the Introduction. Nonetheless, its catalytic use is still attractive from the following points of view: 1) to minimize transition-metal waste and 2) to modify the reactivity of the resultant organometallic intermediates. At the outset, we theorized that the reduction of the amount of iron would facilitate the 1,2- and 1,4-addition of the highly nucleophilic Grignard reagents and, as a result, inhibit cyclization.[18] In fact, when we attempted the enyne cyclization of **1** with 1 mol% of $FeCl_2$ (and 4 equiv of *t*BuMgCl relative to **1**), only a small amount of the desired compound **2** was observed (Scheme 8). However, to our delight, when the quantity of iron was increased to 5 mol%, the yield of **2** was significantly improved. Eventually, with 10 mol% of $FeCl_2$, the yield was further amplified to reach a level comparable to that of the stoichiometric reaction (cf. 125 mol% of $FeCl_2$).

Under the optimum conditions given in Scheme 8, the cyclization generally took place in good yields, as seen from the results in Table 3. A variety of functional groups survived these catalytic conditions to give desired products **2** and **19**–**22** (Table 3, entries 1–5). Diester **15** cyclized to **25** in a somewhat better yield than the corresponding stoichiometric reaction (Table 3, entry 6 vs. Table 1, entry 8). The cyclization of **16** to **26** (containing a six-membered ring) and the dienyne cyclization of **18** to **27** were as efficient as the stoichiometric reactions (Table 3, entries 7 and 8 vs. Table 1, entries 9 and 11).

Because the content of iron is low in the catalytic reactions, the metalated intermediates mostly consist of magnesium derivatives such as **54** (Scheme 9). Whereas the aforementioned stoichiometric iron-based metallacycle **4** in Scheme 5 reacted once with halogens, aldehydes, or ketones to

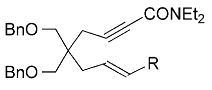
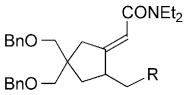
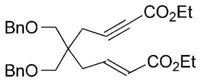
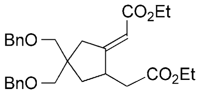
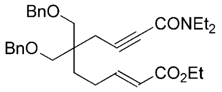
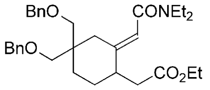
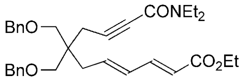
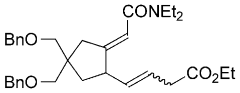


$FeCl_2$ [mol%]	Yield [%]	D^1 [%]	D^2 [%]	d.r.[a]
1	5			
5	39			
10	82	69	>99	1:1
Cf.[b] 125	83	77	>99	1:1

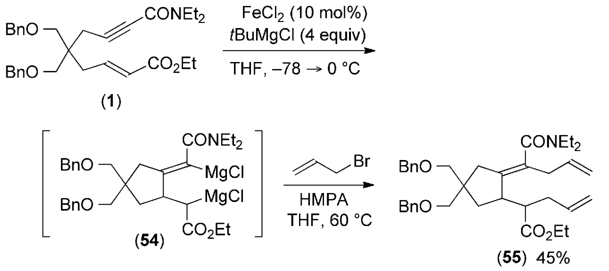
[a] Diastereoselectivity with respect to D^2. [b] Cited from Scheme 3, in which *t*BuMgCl (5 equiv to **1**) was used.

Scheme 8.

Table 3. Iron-catalyzed cyclization of functionalized enynes according to the reaction shown in Scheme 8.

Entry	Substrate		Period [h]	Product		Isolated yield [%]
						
1	R = CO_2Et	(**1**)	4.5	R = CO_2Et	(**2**)	82
2	CO_2tBu	(**9**)	4.5	CO_2tBu	(**19**)	80
3	CN	(**10**)	3.5	CN	(**20**)	54
4	$CONEt_2$	(**11**)	4.5	$CONEt_2$	(**21**)	70
5	SO_2Ph	(**12**)	3.5	SO_2Ph	(**22**)	70
6		(**15**)	3.5		(**25**)	80
7		(**16**)	3.5		(**26**)	71
8		(**18**)	3.5		(**27**)	80 (*E*/*Z* = 1:1)[a]

[a] For the disubstituted double bond.

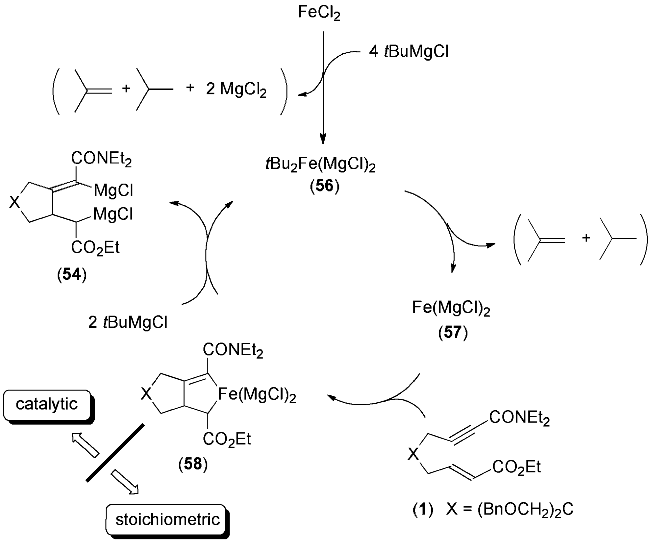


Scheme 9. HMPA = hexamethylphosphoric triamide.

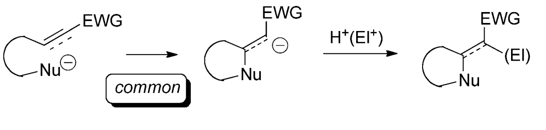
give mono-adducts **28–32**, the magnesium derivative **54** underwent alkylation twice with allyl bromide to give triene **55** as a 1:1 mixture of two isomers arising from the olefin geometry or diastereomeric sp^3-carbon centers. Alkylations are generally less efficient than halogenations or aldehyde additions, and thus, the double alkylation of **54** serves to prove that **54** is more reactive than the iron-based metallacycle **4** generated by stoichiometric reaction.

The proposed catalytic cycle accompanied by the stoichiometric reaction pathway is shown in Scheme 10. In the stoichiometric reaction, for which four equivalents of *t*BuMgCl are essential for good yields of products, the active iron species is probably **57**, which is generated from $FeCl_2$ via **56**.[6] The low-valent iron compound **57** reductively combines two electron-deficient unsaturated bonds of enyne **1** to give the metallacycle **58**, which is analogous to **4** ($L_n = (MgCl)_2$) in Scheme 3 or **37** ($L_n = (MgCl)_2$) in Scheme 6. Subsequently, the excess *t*BuMgCl expels the iron portion from **58** to generate the magnesium compound **54** and the iron species **56**, which enters a new catalytic cycle to produce **54**. As seen in Scheme 10, the catalytic reaction requires only two equivalents of the Grignard reagent. However, higher amounts of Grignard reagent (up to 4 equiv) are necessary in practice to break metallacycle **58**, which is stabilized by iron-centered chelation, into its constituents parts **54** and **56**.[19]

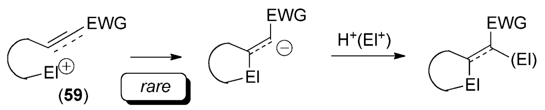
Stoichiometric cyclization by alkylation: Besides the cyclization of bis-unsaturated compounds described above, the alkylation of metalated carbon–carbon multiple bonds in an intramolecular manner constitutes an alternative method to prepare cyclic compounds. Whereas intramolecular conjugate addition of a nucleophile to electron-deficient unsaturated bonds, followed by addition of an appropriate electrophilic trap, is a well-established cyclization method (Scheme 11),[20] the reverse version, which would involve the addition of an electrophile to **59** (Scheme 12 and thus, Scheme 1 b), has not



Scheme 10. Proposed mechanism of iron-mediated and -catalyzed metalative cyclization.



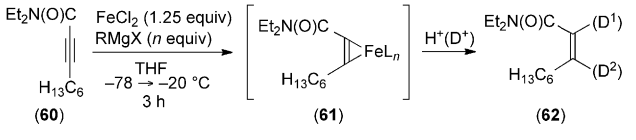
Scheme 11. Cyclization by addition of nucleophile to electron-deficient unsaturated carbonyl compounds.



Scheme 12. Cyclization by addition of electrophile to electron-deficient unsaturated carbonyl compounds.

been documented,[21] even though both of these transformations are conceptually and practically of equal importance.

To assess the feasibility of the reaction given in Scheme 12, we first investigated whether the iron reagent utilized in the preceding sections could actually metalate a functionalized acetylenic bond (Scheme 13). Among several Grignard reagents tested, the combination of $FeCl_2$ and *t*BuMgCl in a molar ratio of 1:4 again proved to be the best. Thus, treatment of acetylenic amide **60** with **3** (1.25 equiv) produced *cis*-olefinic amide **62** in 57 % yield after aqueous workup. Deuteriolysis of the same reaction mixture afforded the deuterated product [D_2]**62**, confirming the presence of a dimetallic species **61**, which could be formally drawn as an iron-containing metallacyclopropene.[22]

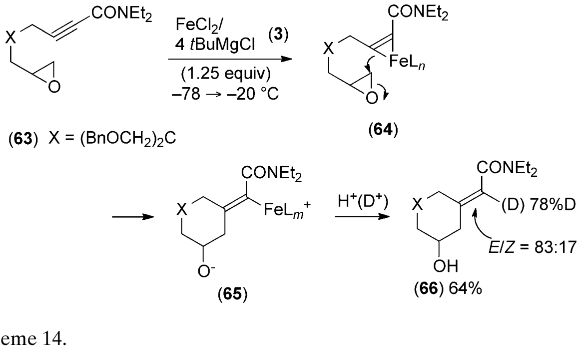


RMgX	*n*	Yield [%][a]	D^1 [%]	D^2 [%]
MeMgBr	5	(0)		
EtMgCl	5	(0)		
*i*PrMgCl	5	(0)		
*t*BuMgCl	2.5	(trace)		
*t*BuMgCl	5	57	95	70
PhMgBr	5	(0)		

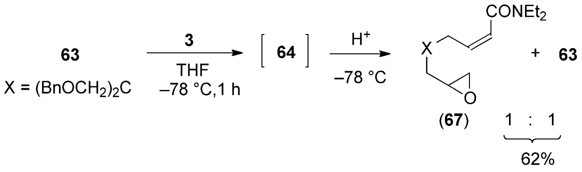
[a] Yields in parentheses are those determined by ^1H NMR spectroscopy.

Scheme 13.

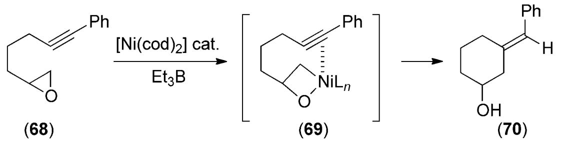
Encouraged by the above result, we returned to the reaction shown in Scheme 12 and performed the cyclization of acetylenic amide **63**, which contains an epoxide moiety, with **3** (Scheme 14).[23,24] This reaction afforded cyclohexanol **66** with an *E*/*Z* ratio of 83:17 in good yield after aqueous workup. Quenching of the reaction mixture with DCl in D_2O afforded the deuterated product [D]**66**, confirming the presence of a metalated intermediate such as **65**. Moreover, when the reaction was terminated at a low temperature, *cis*-olefinic amide **67**, which maintained an epoxide moiety, was recovered as an isolable product (Scheme 15). These observations are consistent with the reaction course shown in Scheme 14. It is worth noting that this proposed pathway, involving a substitution of the epoxide group in **63** with the intermediate acetylene–iron complex **64**, is mechanistically different from that of a similar nickel-catalyzed reaction of unfunctionalized acetylene **68** (Scheme 16). In this case, to account for the formation of cyclohexanol **70**,[25] it was presumed that the nickel complex was inserted to the epoxide C–O bond to form **69**.



Scheme 14.



Scheme 15.



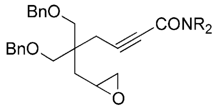
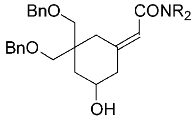
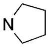
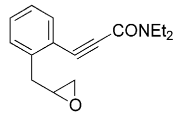
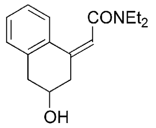
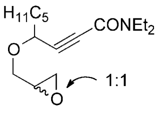
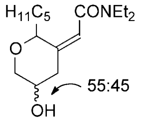
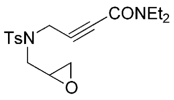
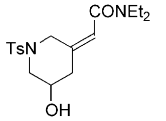
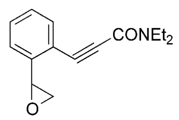
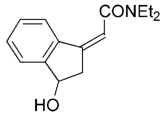
Scheme 16. COD = 1,5-cyclooctadiene.

Table 4 shows overall results of the intramolecular substitution of epoxide with functionalized acetylenes. Substrate **72**, which had a benzo-fused tether, afforded the bicyclic product **77** (Table 4, entry 3), and those substrates with an oxa or aza tether (**73** and **74**, respectively) afforded the corresponding heterocyclic compounds **78** and **79** (Table 4, entries 4 and 5). The elimination of the heteroatom group β to the carbon–iron bond in the intermediates **73** and **74** did not appear to be a serious side reaction, as judged by the product yields of **78** and **79**. The ring closure always occurs in 6-*endo-Tet* (or *Trig*) fashion, and this *endo* selectivity was also observed for the cyclopentane annulation of **75** to **80** (Table 4, entry 6).[16]

Alkyl tosylates **81** and **82**[23] behaved similarly to give cyclopentanes **83** and **84** (Scheme 17). Upon deuteriolysis of the reaction mixture of **81**, product [D]**83** was formed with a high deuterium content, which showed that this reaction also followed the route illustrated in Scheme 12.[16]

Extension of the above tosylate cyclization to an olefinic substrate **85** was not so straightforward and we could not obtain the desired product **86** with **3** (Scheme 18). We subsequently employed an array of Grignard reagents (Scheme 18) and found that $FeCl_2$/4 PhMgBr (**3′**), which did not promote the cyclization of acetylenic substrates

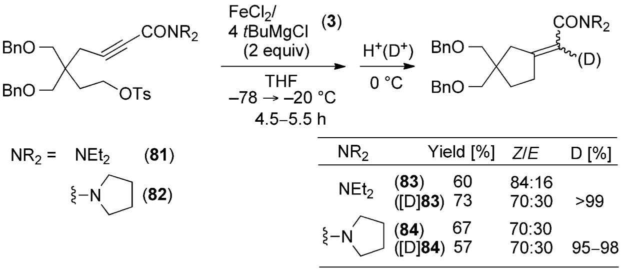
Table 4. Cyclization of functionalized acetylene and epoxide according to the reaction shown in Scheme 14.

Entry	Substrate		Period [h]	Product[a,b]		Isolated yield [%][c]	E/Z[d]
							
1	$NR_2 = NEt_2$	**(63)**	3		**(66)**	64	83:17
2		**(71)**	5		**(76)**	46	75:25
3		**(72)**	2		**(77)**	47	14:86
4		**(73)**	4		**(78)**	46	–[e]
5		**(74)**	4		**(79)**	47	17:83
6		**(75)**	3		**(80)**	37	21:79

[a] Products were isolated after workup with aqueous HCl. [b] Structure of the major isomer is shown. [c] Combined yields of E and Z isomers. [d] Olefinic stereochemistry was assigned by ^{1}H NMR spectroscopic analysis in all cases except for entry 2. [e] An exact E/Z ratio could not be determined because of the presence of diastereoisomers.

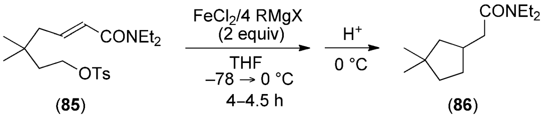
(Scheme 17) or the enyne cyclization shown in Scheme 2, reacted smoothly with olefins to give the corresponding cyclization products in excellent yields.

Scheme 19 shows more details on the cyclization of **85**. The olefin–iron complex **87** formed from **85** and **3′** underwent cyclization to generate **89**, the hydrolysis (or deuteriolysis) of which, gave [D]**86**. Interception of **87** at a low temperature with DCl in D_2O afforded the saturated amide **88**, which bore two deuterium atoms, and thus, verified the role of intermediate dimetalated species **87**. Interestingly, the metalation of the olefinic bond of **85** with **3′** and the subsequent intramolecular alkylation were faster than the iron-catalyzed phenylation of the tosylate moiety,[3,27] because no phenylated product was isolated in this transformation. Other examples of this cyclization are listed in Schemes 20 and 21.



NR_2		Yield [%]	Z/E	D [%]
NEt_2	**(83)**	60	84:16	
	([D]**83**)	73	70:30	>99
	(84)	67	70:30	
	([D]**84**)	57	70:30	95–98

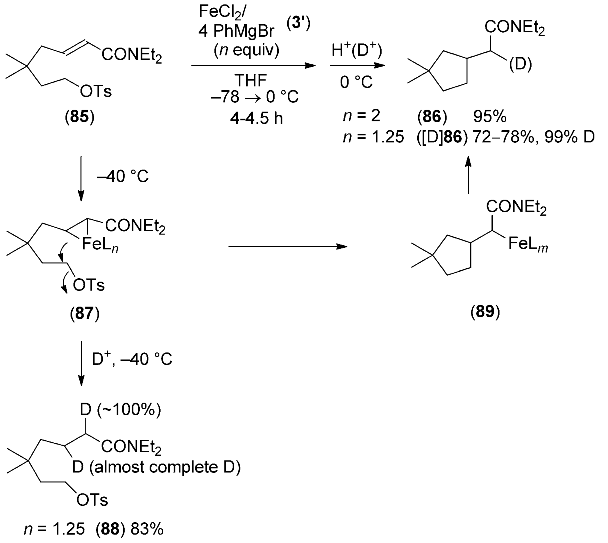
Scheme 17.



RMgX	Yield [%][a]
MeMgBr	(0)
EtMgCl	(0)
iPrMgCl	(0)
tBuMgCl	(trace)
PhMgBr	95

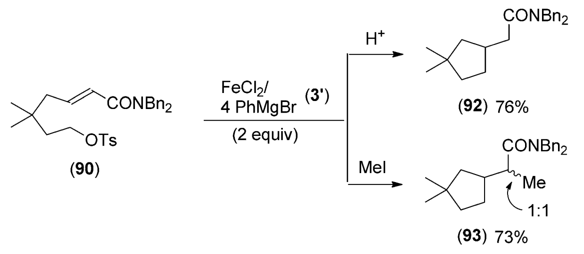
[a] Yields in parentheses are those determined by ^{1}H NMR spectroscopy.

Scheme 18.

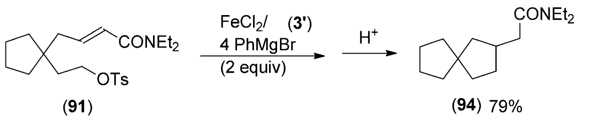


Scheme 19. Alkylation of functionalized olefin with iron reagent **3′**.

Scheme 20 exemplifies that the intermediate metalated species generated from **90** (similar to **89** in Scheme 19) was successfully alkylated to give the carbon-elongated product **93** in good yield.



Scheme 20.



Scheme 21.

Conclusion

We reported a series of effective metalative cyclizations of functionalized enynes and dienes with a simple iron reagent, **3**. The enyne cyclization could be made catalytic with respect to iron. In addition, intramolecular alkylation of functionalized acetylenes and olefins with an epoxide or tosylate was achieved through metalation with analogous iron reagents. Further investigations into new synthetic applications of iron reagents are now in progress.

Experimental Section

Typical procedure for compounds included in Table 1: Compound 2: *t*BuMgCl (0.500 mL, 1.00 M solution in THF, 0.500 mmol) was added to a solution of **1** (50.6 mg, 0.100 mmol) and $FeCl_2$ (15.8 mg, 0.125 mmol) in THF (1.0 mL) at −78 °C under argon. The resulting solution was slowly warmed to −20 °C over 3.5 h, followed by termination of the reaction by the addition of aqueous HCl (1.0 mL, 1.00 N). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2.0 mL), dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, the ^1H NMR spectroscopic analysis of which did not show signals of the olefinic stereoisomer. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate as the eluent) to afford **2** as an oil (42.3 mg, 83 %).

Typical procedure for compounds included in Table 2: A 1:1 mixture of keto and enol forms of 45b from 39b: *t*BuMgCl (0.495 mL, 1.01 M solution in THF, 0.500 mmol) was added to a solution of **39b** (24.0 mg, 0.100 mmol) and $FeCl_2$ (15.8 mg, 0.125 mmol) in THF (1.0 mL) at −78 °C under argon. The solution was warmed to −20 °C over 1 h, 2-butanol (0.012 mL, 0.130 mmol) was added, and the reaction mixture was warmed to room temperature over 1 h. The reaction was terminated by addition of aqueous HCl (3 mL, 1.00 N). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed successively with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, which was purified by chromatography on silica gel (hexane/ethyl acetate as the eluent) to afford **45b** as an oil (12.0 mg, 61 %).

Typical procedure for compounds included in Table 3: Compound 2: *t*BuMgCl (0.392 mL, 1.02 M solution in THF, 0.400 mmol) was added to a solution of **1** (50.6 mg, 0.100 mmol) and $FeCl_2$ (1.3 mg, 0.010 mmol) in THF (1.0 mL) at −78 °C under argon. The solution was slowly warmed to 0 °C over 4.5 h and the reaction was terminated by addition of aqueous HCl (1.0 mL, 1.00 N). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2.0 mL), dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, the ^1H NMR spectroscopic analysis of which did not show the signals of another olefinic stereoisomer. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate as the eluent) to afford **2** as an oil (41.7 mg, 82 %).

Typical procedure for compounds in Table 4: An 83:17 *E*/*Z* mixture of 66: *t*BuMgCl (0.500 mL, 1.00 M solution in THF, 0.500 mmol) was added to a solution of **63** (45.0 mg, 0.100 mmol) and $FeCl_2$ (15.8 mg, 0.125 mmol) in THF (1.0 mL) at −78 °C under argon. The solution was gradually warmed to −20 °C over 3 h, followed by termination of the reaction by addition of aqueous HCl (2.0 mL, 1.00 N). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2.0 mL), dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, the ^1H NMR spectroscopic analysis of which revealed that the olefinic stereoselectivity was 83:17. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate as the eluent) to afford **66** as an oil of the same isomeric composition (28.9 mg, 64 %).

Typical synthetic procedure for compounds in Scheme 17: An 84:16 *Z*/*E* mixture of 83: *t*BuMgCl (0.784 mL, 1.02 M solution in THF, 0.800 mmol) was added to a solution of **81** (59.2 mg, 0.100 mmol) and $FeCl_2$ (25.4 mg, 0.200 mmol) in THF (1.0 mL) at −78 °C under argon. The solution was slowly warmed to −20 °C over 5 h, followed by termination of the reaction by addition of aqueous HCl (1 mL, 1.00 N). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were neutralized with a saturated aqueous solution of $NaHCO_3$ (2 mL), dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, the ^1H NMR spectroscopic analysis of which revealed that the *Z*/*E* ratio of the product was 60:40. The crude oil was purified by chromatography on silica gel (hexane/ethyl acetate as the eluent) to afford **83** as an oil (38.9 mg, 60 %; 84:16 mixture of *Z* and *E* isomers).

Typical synthetic procedure for compounds in Scheme 19: Compound 86: PhMgBr (0.730 mL, 1.09 M solution in THF, 0.800 mmol) was added to a solution of **85** (38.2 mg, 0.100 mmol) and $FeCl_2$ (25.4 mg, 0.200 mmol) in THF (1.0 mL) at −78 °C under argon. The solution was slowly warmed to 0 °C over 4 h, followed by termination of the reaction by addition of aqueous HCl (1 mL, 1.00 N). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were neutralized with a saturated aqueous solution of $NaHCO_3$ (2 mL), dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, which was purified by chromatography on silica gel (hexane/ethyl acetate as the eluent) to afford **86** as an oil (20.2 mg, 95 %).

Products **2**, **45b**, **66**, **83**, and **86** were fully characterized by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and elemental analysis.

Acknowledgements

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[1] Group 4 metal (Ti, Zr)-mediated reactions are representative of these stoichiometric transformations among many metal-promoted cyclizations; a) *Titanium and Zirconium in Organic Synthesis* (Ed.: I. Marek), Wiley-VCH, Weinheim, **2002**; b) Symposia-in-Print (Eds.: K. Suzuki, P. Wipf): *Tetrahedron* **2004**, *60*, 1269–1424; c) Symposia-

in-Print (Ed.: E. Negishi): *Tetrahedron* **1995**, *51*, 4255–4570; for the latest reviews on other metal-catalyzed cyclizations, see: d) *Handbook of Cyclization Reactions, Vols. 1 and 2* (Ed.: S. Ma), Wiley-VCH, Weinheim, **2010**; e) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem.* **2008**, *120*, 4338–4386; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; f) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813–834.

[2] Hereafter, the term "functionalized" refers to "electron-withdrawing-group-substituted" and particularly to "ester- and amide-substituted". Synthetically useful functionalized metallacycles are known; for titanacycles, see: a) A. Wolan, Y. Six, *Tetrahedron* **2010**, *66*, 3097–3133; b) F. Sato, H. Urabe in *Titanium and Zirconium in Organic Synthesis* (Ed.: I. Marek), Wiley-VCH, Weinheim, **2002**; pp. 319–354; c) F. Sato, S. Okamoto, *Adv. Synth. Catal.* **2001**, *343*, 759–784; d) F. Sato, H. Urabe, S. Okamoto, *Chem. Rev.* **2000**, *100*, 2835–2886; e) H. Urabe, K. Suzuki, F. Sato, *J. Am. Chem. Soc.* **1997**, *119*, 10014–10027; f) R. Tanaka, A. Yuza, Y. Watai, D. Suzuki, Y. Takayama, F. Sato, H. Urabe, *J. Am. Chem. Soc.* **2005**, *127*, 7774–7780; for nickelacycles, see: g) J. Montgomery, *Acc. Chem. Res.* **2000**, *33*, 467–473; h) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980–3998; *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908; for tantalacycles, see: i) Y. Kataoka, J. Miyai, M. Tezuka, K. Takai, K. Utimoto, *J. Org. Chem.* **1992**, *57*, 6796–6802.

[3] For reviews on iron-mediated organic reactions, see: a) *Iron Catalysis in Organic Chemistry: Reactions and Applications* (Ed.: B. Plietker), Wiley-VCH, Weinheim, **2008**; b) A. Correa, O. G. Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108–1117; c) E. B. Bauer, *Curr. Org. Chem.* **2008**, *12*, 1341–1369; d) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363–3367; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321; e) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254; for enyne cyclization, see: f) Ref. [1e]; for coupling reactions, see: g) B. Plietker, *Synlett* **2010**, 2049–2058; h) B. Plietker, A. Dieskau, *Eur. J. Org. Chem.* **2009**, 775–787; i) W. M. Czaplik, M. Mayer, J. Cvengros, A. J. von Wangelin, *ChemSusChem* **2009**, *2*, 396–417; j) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500–1511; k) A. Fürstner, M. Rubén, *Chem. Lett.* **2005**, *34*, 624–629; for iron carbonyl complexes, see: l) M. F. Semmelhack in *Organometallics in Organic Synthesis. A Manual*, 2nd ed. (Ed.: M. Schlosser), Wiley, New York, **2002**, pp. 1006–1121; m) *Comprehensive Organometallic Chemistry, Vol. 4* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, pp. 243–649.

[4] Portions of this section have been preliminarily communicated, see: T. Hata, N. Hirone, S. Sujaku, K. Nakano, H. Urabe, *Org. Lett.* **2008**, *10*, 5031–5033.

[5] For our relevant work on iron-catalyzed reactions of functionalized unsaturated compounds and Grignard reagents, see: a) K. Fukuhara, H. Urabe, *Tetrahedron Lett.* **2005**, *46*, 603–606; b) S. Okada, K. Arayama, R. Murayama, T. Ishizuka, K. Hara, N. Hirone, T. Hata, H. Urabe, *Angew. Chem.* **2008**, *120*, 6966–6970; *Angew. Chem. Int. Ed.* **2008**, *47*, 6860–6864; c) T. Hata, R. Bannai, M. Otsuki, H. Urabe, *Org. Lett.* **2010**, *12*, 1012–1014.

[6] For some reactions using an iron catalyst and *tert*-butyl Grignard reagents, see: a) R. S. Smith, J. K. Kochi, *J. Org. Chem.* **1976**, *41*, 502–509; b) E. C. Ashby, T. L. Wiesemann, *J. Am. Chem. Soc.* **1978**, *100*, 189–199; c) G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199–1205; d) H. Guo, K. Kanno, T. Takahashi, *Chem. Lett.* **2004**, *33*, 1356–1357; e) L. K. Ottesen, F. Ek, R. Olsson, *Org. Lett.* **2006**, *8*, 1771–1773; f) B. D. Sherry, A. Fürstner, *Chem. Commun.* **2009**, 7116–7118; it has been reported that $FeCl_2$ and 4 equiv of RCH_2CH_2MgX form a species of the formal composition of $[Fe(MgX)_2]_n$; g) B. Bogdanović, M. Schwickardi, *Angew. Chem.* **2000**, *112*, 4788–4790; *Angew. Chem. Int. Ed.* **2000**, *39*, 4610–4612; h) A. Fürstner, A. Leitner, M. Mendez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863; i) A. Fürstner, H. Krause, C. W. Lehmann, *Angew. Chem.* **2006**, *118*, 454–458; *Angew. Chem. Int. Ed.* **2006**, *45*, 440–444 and references cited therein; some ate complexes of iron with *t*BuMgCl are also possible for the iron intermediates in Scheme 10, see: j) T. Kauffmann, *Angew. Chem.* **1996**, *108*, 401–418; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 386–403.

[7] Even with the metal species listed in Ref. [2], the cyclization of bisfunctionalized enynes, such as those in Tables 1 and 3, has not been reported.

[8] Other recently reported iron-mediated cyclizations of (unfunctionalized)dienes, enynes, and diynes are as follows: for [2+2] cyclization and polymerization of dienes, see: a) M. W. Bouwkamp, A. C. Bowman, E. Lobkovsky, P. J. Chirik, *J. Am. Chem. Soc.* **2006**, *128*, 13340–13341; b) D. Takeuchi, R. Matsuura, S. Park, K. Osakada, *J. Am. Chem. Soc.* **2007**, *129*, 7002–7003; for a few types of enyne cyclizations, see: c) A. J. Pearson, R. A. Dubbert, *Organometallics* **1994**, *13*, 1656–1661; d) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677–1693; for tandem carbometalation of diynes, see: e) D. Zhang, J. M. Ready, *J. Am. Chem. Soc.* **2006**, *128*, 15050–15051; for the Reppe-type alkyne trimerization, see: f) C. Breschi, L. Piparo, P. Pertici, A. M. Caporusso, G. Vitulli, *J. Organomet. Chem.* **2000**, *607*, 57–63.

[9] Iron-catalyzed Diels–Alder and Alder–ene reactions are also known, see: a) J. P. Genet, J. Ficini, *Tetrahedron Lett.* **1979**, *20*, 1499–1502; b) H. tom Dieck, R. Diercks, *Angew. Chem.* **1983**, *95*, 801–802; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 778–779; c) K.-U. Baldenius, H. tom Dieck, W. A. König, D. Icheln, T. Runge, *Angew. Chem.* **1992**, *104*, 338–340; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 305–307; d) J. M. Takacs, L. G. Anderson, G. V. B. Madhavan, F. L. Seely, *Angew. Chem.* **1987**, *99*, 1073–1075; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1013–1015; e) J. M. Takacs, L. G. Anderson, P. W. Newsome, *J. Am. Chem. Soc.* **1987**, *109*, 2542–2544; f) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992–2004; g) B. Moreau, J. Y. Wu, T. Ritter, *Org. Lett.* **2009**, *11*, 337–339. See also: h) J. R. Cabrero-Antonino, A. Leyva-Pérez, A. Corma, *Adv. Synth. Catal.* **2010**, *352*, 1571–1576.

[10] A metalated carbon α to a carbonyl group is in equilibrium with its enolate form, but the latter is not drawn for simplicity throughout this article.

[11] Two diastereoisomers out of four were exclusively formed for **30** and **31**. These diastereoisomers should be attributable to the stereochemistry between the cyclopentane carbon and the carbon α to the ester group, as also observed for products **28**, **29**, and **32**. Assignment of stereochemistry to major and minor isomers has not been carried out.

[12] Ketoesters in Scheme 6, Table 2, and Scheme 7 exist as approximately a 1:1 mixture of keto and enol forms, of which only the former is depicted for simplicity.

[13] Bicyclic ketoester **35** is a known key compound to pentalenolactone F, see: D. E. Cane, P. J. Thomas, *J. Am. Chem. Soc.* **1984**, *106*, 5295–5303.

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

[15] The dimerization of cinnamate esters to ketoesters has been reported, see: a) N. Kise, S. Iitaka, K. Iwasaki, N. Ueda, *J. Org. Chem.* **2002**, *67*, 8305–8315 and references cited therein; b) K. Takaki, F. Beppu, S. Tanaka, Y. Tsubaki, T. Jintoku, Y. Fujiwara, *J. Chem. Soc. Chem. Commun.* **1990**, 516–517; c) S. R. Jensen, A.-M. Kristiansen, J. Munch-Petersen, *Acta Chem. Scand.* **1970**, *24*, 2641–2647; for intramolecular cyclizations of α,β-olefinic esters, see: d) I. Shinohara, M. Okue, Y. Yamada, H. Nagaoka, *Tetrahedron Lett.* **2003**, *44*, 4649–4652; for a related coupling of chalcones with titanocene dicarbonyl, see: e) R. Schobert, F. Maaref, S. Dürr, *Synlett* **1995**, 83–84; however, these methods did not result in the concomitant incorporation of a second constituent, such as a carbonyl compound, to give products **50**–**53** (Scheme 7).

[16] Our attempts to execute the diene cyclization (Scheme 6), the cyclizations with epoxides (Scheme 14), and tosylates (Scheme 17) with

catalytic amounts of the iron reagent have so far proven unsuccessful.

[17] For the generation and reactions of dianions of ketoesters, see: C. M. Thompson, D. L. C. Green, *Tetrahedron* **1991**, *47*, 4223–4285.

[18] This was what we actually experienced in the titanium alkoxide-based metalative cyclizations of enynes, where attempted catalytic reactions with respect to titanium were always unsuccessful (Ref. [2a–d]).

[19] When the catalytic cyclization of **1** (Table 3, entry 1) was attempted with 2 equiv of *t*BuMgCl, the desired product **2** was not obtained. The similar tendency is also seen in Scheme 2 and Scheme 13.

[20] For reviews on three-component coupling reactions based on conjugate addition of nucleophiles, see: a) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**, pp. 48–218; b) H.-C. Guo, J.-A. Ma, *Angew. Chem.* **2006**, *118*, 362–375; *Angew. Chem. Int. Ed.* **2006**, *45*, 354–366; c) M. J. Chapdelaine, M. Hulce in *Organic Reactions, Vol. 38* (Ed.: L. A. Paquette), Wiley, New York, **1990**, pp. 225–653.

[21] This transformation could be executed by the metalation of unsaturated bond and a suitable electrophilic trap. Despite their limited number, such examples can be found for unfunctionalized olefins and acetylenes (see the Ref. below), but the cyclization of functionalized acetylenes or olefins shown in Scheme 12 has no precedent. For carbonyl compounds, see: a) Ref. [2a–d]; for halides, see: b) N. Suzuki, D. Y. Kondakov, M. Kageyama, M. Kotora, R. Hara, T. Takahashi, *Tetrahedron* **1995**, *51*, 4519–4540; for tosylates, see: c) R. R. Cesati, III, J. de Armas, A. H. Hoveyda, *Org. Lett.* **2002**, *4*, 395–398.

[22] Acetylene–iron carbonyl complexes are known, but they react with nucleophiles rather than electrophiles: D. L. Reger, E. Mintz, L. Lebioda, *J. Am. Chem. Soc.* **1986**, *108*, 1940–1949; see also Ref. [3m].

[23] We chose epoxides and tosylates as the electrophiles for this study because other typical electrophiles, such as alkyl halides, are readily converted to carbanions by halogen/metal exchange and can be utilized along the traditional reactions given in Scheme 11 rather than that in Scheme 12.

[24] For ring-opening reactions of epoxides, see: *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**.

[25] a) C. Molinaro, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 8076–8077; for its synthetic application, see: b) J. D. Trenkle, T. F. Jamison, *Angew. Chem.* **2009**, *121*, 5470–5472; *Angew. Chem. Int. Ed.* **2009**, *48*, 5366–5368. In this nickel-catalyzed reductive coupling of acetylene and epoxide, functionalized acetylenes were not reported as the substrate; and the reaction shown in Scheme 14 did not proceed with a low-valent nickel catalyst in our laboratory. Thus, the successful ring-opening reaction of the epoxide with a functionalized acetylene in this study may stem from the mechanistic differences between the Ni- and Fe-mediated reactions.

[26] For Baldwin's rule, see: a) J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734–736. The epoxide moiety is claimed to behave in an intermediate sense between the *Tet* and *Trig* categories. As 6-*endo-Tet* is disfavored and other possible 6-*endo-Trig*, 5-*exo-Tet*, *and* 5-*exo-Trig* are favored, the alternative *exo* opening of the epoxide moiety, which was not seen in the reaction shown in Scheme 14, seems more common; b) R. J. Madhushaw, C.-L. Li, K.-H. Shen, C.-C. Hu, R.-S. Liu, *J. Am. Chem. Soc.* **2001**, *123*, 7427–7428. Analogously, the reaction of **75**→**80** (Table 4, entry 6) is anomalous because both 5-*endo-Tet* or -*Trig* modes are disfavored, whereas another set of 4-*exo-Tet* and -*Trig* is favored by this rule.

[27] H. Urabe, F. Sato in *Handbook of Grignard Reactions* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**, pp. 577–632.

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