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Iron-catalyzed addition of Grignard reagents to activated vinyl cyclopropanes†‡

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A highly regioselective iron-catalyzed addition of branched primary, secondary or tertiary alkyl Grignard reagents to activated vinyl cyclopropanes is described, which likely proceeds by a direct addition mechanism as opposed to single electron transfer or an iron-allyl based process.

Iron-catalyzed reactions are gaining prominence in synthetic chemistry due to the associated economic and environmental benefits.[1] Amongst the various transformations of π-bonds effected by low-valent iron,[1,2] alkene carbometalation[3,4] and allylic substitution reactions[5] have received considerable attention. A juxtaposition of the reported systems for these two processes reveals several features unique to each reaction class. In the recorded allylic substitution reactions, the leaving group is a stabilized oxygen (phosphate, carboxylate, alkoxide) or halide atom, and the unsaturated system is frequently an α-olefin.[5] In contrast, alkene carbometalation is generally reported within the context of strained systems.[3] The latter reactions benefit, however, from the generation of a reactive carbon–metal bond, allowing further functionalization after the iron-catalyzed step. A desire to bridge these two systems, and in so doing capitalize on the advantages of each, led us to consider the reaction of suitably activated vinyl cyclopropanes with low-valent iron-catalysts.[6–9] Such a process could conceivably take place with simple unstrained alkenes, and through scission of the carbon–carbon σ-bond, provide a reactive carbon nucleophile for additional bond-forming reactions.

The study commenced with an examination of the reaction between vinyl cyclopropane **1** and organomagnesium reagents (Table 1). Aryl nucleophiles reacted efficiently but displayed poor regioselectivity (entries 1 and 2). Transitioning to primary alkyl Grignard reagents resulted in an increase in the relative amount of 1,7-addition (**a**), with a further enhancement in the selectivity observed with more sterically hindered nucleophiles (entries 3–6). Secondary and tertiary alkyl Grignard reagents displayed excellent regioselectivity, affording the 1,7-addition products in good yield as predominately the *E*-isomers (entries 7–9).

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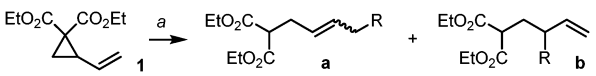
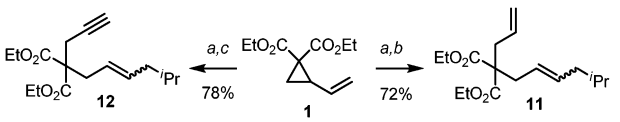
‡ Electronic supplementary information (ESI) available: Experimental section and characterization data for all new compounds. See DOI: 10.1039/b918818e

Table 1 Examination of Grignard reagents in iron-catalyzed addition reactions



Entry	RMgX, cosolvent	Product	**a** : **b**[b]	**a***E* : *Z*[b]	Yield[c] (%)
1	PhMgCl, THF	**2a**,**b**	1.5 : 1	5.7 : 1	75
2	(Mesityl)MgBr, THF	**3a**,**b**	1.4 : 1	2.7 : 1	84
3	MeMgCl, THF	**4a**,**b**	4.3 : 1	4.3 : 1	79
4	*n*PrMgCl, THF	**5a**,**b**	8.9 : 1	5.6 : 1	48
5	*i*BuMgCl, THF	**6a**,**b**	11.9 : 1	7.2 : 1	82
6	*t*BuCH$_2$MgBr, THF	**7a**,**b**	8.6 : 1	8.4 : 1	83
7	*i*PrMgCl, THF	**8a**	>20 : 1	5.8 : 1	79
8	*c*C$_5$H$_9$MgCl, Et$_2$O	**9a**	>20 : 1	6.5 : 1	61
9	*t*BuMgCl, Et$_2$O	**10a**	>20 : 1	8.2 : 1	78

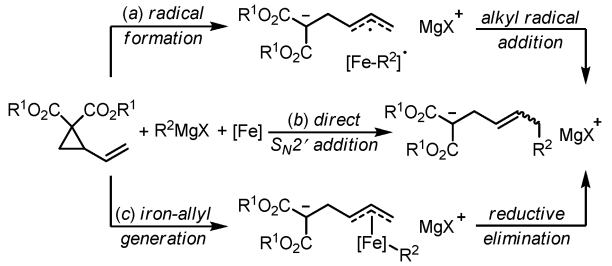
[a] Fe(acac)$_3$ (10 mol%, 99.9 + % purity), RMgX (1.5 equiv.), toluene, −30 °C, 30 min. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of regio- and stereoisomeric mixture after chromatography.



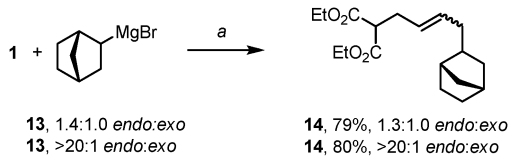
Scheme 1 *Reagents and conditions*: (a) Fe(acac)$_3$ (10 mol%, 99.9 + % purity), *i*PrMgCl (1.5 equiv.), toluene, −30 °C, 30 min; (b) allyl bromide (3 equiv.), DMPU, room temperature, 23 h; (c) propargyl bromide (3 equiv.), DMPU, room temperature, 23 h.

As secondary alkyl Grignard reagents provided high levels of regiocontrol, a more thorough study with this class of nucleophiles was conducted. We initially sought to utilize the putative magnesium enolate generated upon cleavage of the cyclopropane. Addition of an alkyl halide and DMPU to the reaction mixture once **1** was consumed allowed telescoping of the iron-catalyzed process with traditional malonate chemistry, and thereby opened convenient access to dialkylated malonates *via* this two-step one-pot approach (Scheme 1).

We next turned our attention to the iron-catalyzed bond-forming event itself. Three potential mechanisms were considered (Scheme 2): (*a*) single electron transfer from a reduced iron complex to afford a malonate anion and delocalized allyl radical, followed by recombination of the allyl radical with an alkyl group from iron (*b*) nucleophilic displacement, potentially involving an iron-ate type intermediate, (*c*) oxidative insertion of iron into the strained carbon–carbon bond to afford an iron-allyl intermediate with expulsion of the malonate anion, followed by reductive elimination.



Scheme 2 Three conceivable pathways for iron-catalyzed addition.

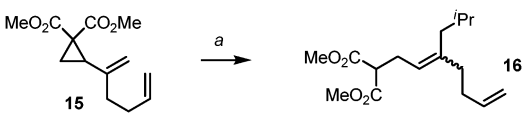


Scheme 3 *Reagents and conditions*: (a) $Fe(acac)_3$ (10 mol%, 99.9 + % purity), **13** (1.5 equiv.), toluene, −30 °C, 30 min.

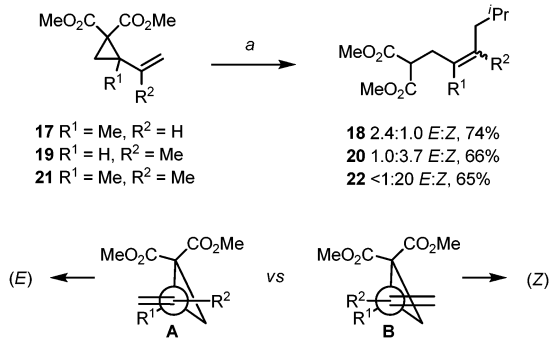
To interrogate pathway (*a*) the reaction was first conducted in the presence of *H*-atom donor γ-terpinene, the Grignard addition proceeded unperturbed, and no reduced product was detected by ^{1}H NMR. Radical generation in the nucleophilic component of the reaction was further investigated using 2-norbornylmagnesium bromide as a stereochemical probe (Scheme 3).[10] The addition of a diastereomeric mixture of Grignard reagent **13** (1.4 : 1.0 *endo* : *exo*) afforded an essentially identical mixture of diastereomers in the product malonate **14**. However, when diastereomerically enriched *endo*-2-norbornylmagnesium bromide was employed, a >20 : 1 mixture of *endo* : *exo* diastereomers was generated, providing evidence against alkyl radical generation during the reaction.

To examine radical generation in the vinyl cyclopropane component, alkene tethered substrate **15** was examined.[11] No 5-*exo*-trig radical cyclization was observed suggesting that if single electron transfer occurs the delocalized radical is trapped at a rate greater than intramolecular cyclization (Scheme 4).

Alkene stereochemistry is not established in the iron-allyl mechanism until after cleavage of the cyclopropane,[12] whereas non-bonding interactions in the substrate are expected to influence the product alkene geometry in a direct addition process. Therefore, substituent effects may allow one to distinguish pathways *b* and *c*. Substrate **17**, which bears a methyl group on the cyclopropane, was found to be less *E*-selective than the unsubstituted system **1** (Scheme 5). Reaction of **19**, carrying a methyl group at the internal alkene carbon, resulted in a modest preference for the *Z*-olefin. As shown with **21**, these substituent effects work in concert to provide tetrasubstituted alkene **22** solely as the *Z*-isomer in 65% yield. This observation is noteworthy, as the stereoselective formation of



Scheme 4 *Reagents and conditions*: (a) $Fe(acac)_3$ (10 mol%, 99.9 + % purity), *i*PrMgCl (1.5 equiv.), toluene, −30 °C, 30 min, 61%, *E* : *Z* = 1 : 4.9.



Scheme 5 *Reagents and conditions*: (a) $Fe(acac)_3$ (10 mol%, 99.9 + % purity), *i*PrMgCl (1.5 equiv.), toluene, −30 °C, 30 min; bottom: hypothetical reactive conformations.

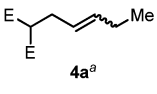
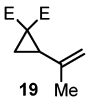
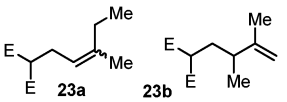
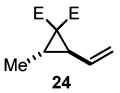
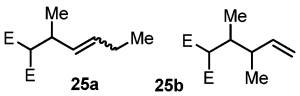
tetrasubstituted olefins remains a challenge to modern synthetic technologies.[13]

The preceding observations, assuming alkene generation is under kinetic control, are most consistent with a transition state where overlap of the π-system with the cyclopropane σ-bond is required. Two reactive conformations, **A** and **B**, fulfill this stereoelectronic constraint, and lead to opposite alkene geometry (Scheme 5, bottom). In the unsubstituted case ($R^1 = R^2 = H$), reaction through conformer **A** minimizes non-bonding interactions; this conformation becomes progressively less favorable relative to **B** upon substitution. In the disubstituted system ($R^1 = R^2 = Me$), $A^{1,3}$-strain resulting from methyl substitution on the cyclopropane and an eclipsing interaction between R^2 and the cyclopropane ring apparently destabilize **A** to the extent that the reaction occurs exclusively through **B**.[14]

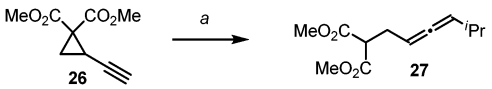
The correlation between the bulk of the incoming nucleophile and the reaction selectivity provides further evidence for a direct addition pathway (Table 1). Moreover, the reversal in regioselectivity observed in reactions between the slim and hence less selective MeMgBr and the differently substituted vinyl cyclopropanes **1**, **19** and **24** also speaks against an allyl mechanism (Table 2). Should the reaction proceed through an η^3-allyl-iron intermediate, the regiochemistry is not expected to be significantly altered by a methyl group at the central carbon of the π-allyl unit;[15] the product distribution obtained with substrates **1** and **19**, however, shows that the absence or presence of a methyl branch at this position exerts a strong effect. In line with the preceding observations, this result argues against an allyl-iron based process and single electron transfer, even though at present no single mechanism can be completely excluded.

Although a limited number of catalytic reactions of vinyl cyclopropanes with carbon nucleophiles have been reported,[7] the present study is the first example of the catalytic addition of a hard organometallic nucleophile, and benefits from the use of a cheap and benign precatalyst. The iron-catalyzed reaction effectively outcompetes the otherwise rapid 1,2-addition of the Grignard reagent to the substrate,[16] providing another illustration of the kinetic competence of reactions catalyzed by low-valent iron.[1] Moreover, though the structural details of the *in situ* generated catalyst are not known, the most convincing support to date for a direct addition mechanism is provided,[11] representing a rare case of mechanistic insight

Table 2 Product distribution in the iron-catalyzed ring opening of differently substituted vinyl cyclopropanes; E = COOMe unless stated otherwise[b]

Substrate	Products	**a** : **b**	Yield (%)
		3.4 : 1[c]	79
		1 : 2[e]	85
		13 : 1[d]	85

[a] E = COOEt. [b] $Fe(acac)_3$ (10 mol%, 99.9 + % purity), MeMgBr (1.5 equiv.), toluene, −30 °C, 30 min. [c] **a** isomer, *E* : *Z* = 8.7 : 1. [d] **a** isomer, *E* : *Z* = 15.2 : 1. [e] **a** isomer, *E* : *Z* = 1 : 1.7.



Scheme 6 *Reagents and conditions*: (a) $Fe(acac)_3$ (10 mol%, 99.9 + % purity), *i*PrMgCl (1.5 equiv.), toluene, −30 °C, 30 min, 60%.

into iron-catalyzed C–C-bond formations.[2,12,17–19] Furthermore, early studies indicate that this reaction can be extended to other π-systems such as **26** (Scheme 6), which is reminiscent of the *syn*-selective iron-catalyzed opening of propargyl epoxides previously described by our group.[20]

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