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Regioselective 1,4- and 1,6-Conjugate Additions of Grignard Reagent-Derived Organozinc(II)ates to Polyconjugated Esters

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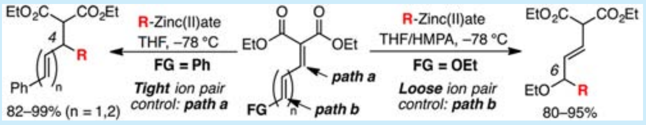
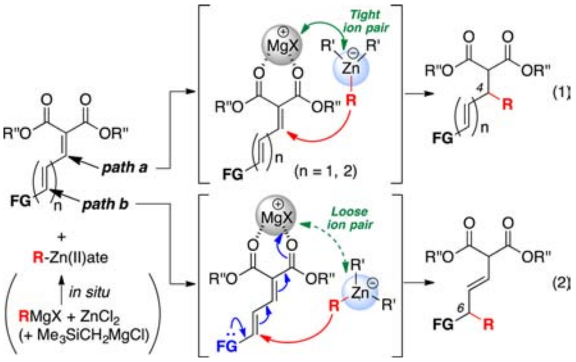
Supporting Information

ABSTRACT: Regioselective synthetic methods were developed for 1,4- and 1,6-conjugate additions of Grignard reagent-derived organozinc(II)ates to malonate-derived polyconjugated esters. By taking advantage of the tight ion-pair control of organozinc(II)ates, it was possible to switch between 1,4- and 1,6-conjugate additions by introducing a terminal ethoxy moiety in the conjugation.



Regioselective conjugate addition to α,β-unsaturated carbonyl compounds with organometallic reagents, which are usually prepared in situ from commercially available Grignard reagents[1] and transition-metal salts, is one of the most important carbon−carbon bond-forming reactions.[2] In particular, organocuprates(I) from Grignard, organozinc(II), and organoaluminum(III) reagents have been traditionally used for enantio- and regioselective 1,4-conjugate addition, and seminal breakthroughs have been achieved in the last 10 years.[3−6] Moreover, several advanced examples of 1,6- and 1,8-conjugate additions of Grignard reagents have begun to be reported with the use of copper(I) and other transition-metal salts.[7] Traditional organozinc(II)ates, $[R_3Zn]^-[Li]^+$ or $[R_3Zn]^-[MgX]^+$,[8,9] have also been used for 1,4-conjugate addition of α,β-unsaturated enones,[10] and recently, Dieter developed a regioselective 1,4-conjugate addition to nitrodienes.[11] However, the use of organozinc(II)ates for a regioselective 1,4-conjugate addition to *less reactive α,β-unsaturated esters* is rather limited. Unlike strongly π-coordinatable organocuprates(I) with high-lying d-orbitals, organozinc(II)ates with relatively low-lying d-orbitals would not act as metal-centered nucleophiles.[9a,b] Alternatively, however, a tight ion pair of the hard nucleophilic $[R_3Zn]^-$ moiety and the hard Lewis acidic $[Li]^+$ or $[MgX]^+$ moiety, which would selectively coordinate to the carbonyl moiety through a pathway of carbozincation,[9a] might be promising. Accordingly, organozinc(II)ates would recognize the carbonyl moiety better than the π-conjugated moiety, and we envisioned that organozinc(II)ates might be practical alkylating reagents for *α,β-unsaturated esters*, if the substrates could be designed to fully match the character of the organozinc(II)ates. In this context, we report here the transition-metal-free highly regioselective 1,4- and 1,6-conjugate additions of Grignard reagent-derived organozinc(II)ates to malonate-derived polyconjugated esters[5] for the first time (eqs 1 and 2). In particular, chelation to the $Mg(II)^+$ center with a 1,3-dicarbonyl moiety would promote 1,4-conjugate addition (path a) at the activation site close to the cationic $[MgX]^+$ moiety due to the tight ion pair between the cationic $[MgX]^+$ moiety and anionic $[R_3Zn]^-$ moiety (eq 1). Moreover, if we introduce an electron-donating group to the substrates, it might weaken the tight ion pair of the organozinc(II)ates and selectively activate the terminal conjugated carbon, so that 1,6-conjugate addition (path b) might occur selectively (eq 2).



First, we examined ethyl addition to dienyl esters **1a**−**c** in tetrahydrofuran (THF) at −78 °C (Table 1). The reaction of diethyl malonate-derived **1a** (0.3 mmol) with ethylzinc(II)ate (1.5 equiv), which was prepared in situ from EtMgCl (1.5 equiv), Me_3SiCH_2MgCl (3 equiv), and $ZnCl_2$ (1.5 equiv) (method A),[8c−f] proceeded quickly, and the corresponding 4-Et-adduct **2a** was obtained in 91% yield within 1 h (entry 1). On the other hand, 1.5 equiv of EtMgCl for **1a** without $Me_3SiCH_2MgCl/ZnCl_2$ (method B) provided a mixture of **2a** (56% yield) and undesired 6-Et adduct **3a** (28% yield) (entry 2). Di-*tert*-butyl malonate **1b** showed much lower reactivity than **1a**, although the ratio of **2b**/**3b** was still high when ethylzinc(II)ate was used (entry 3). In sharp contrast, no products were obtained from much less reactive monoester **1c** (entries 5 and 6). This result would indicate that even highly nucleophilic $[Et(Me_3SiCH_2)_2Zn]^-$ does not easily add to the nonchelatable ester **1c**, since a lack of possible chelation to the labile Lewis acid $Mg(II)^+$ would lead failure in keeping the nucleophilic $[Et(Me_3SiCH_2)_2Zn]^-$ close to the appropriate reaction site such as the 4-position.[12] Moreover, to avoid the synthetic limitation of malonates, hydrolysis and decarboxylation of **2a** was performed to give **2a′** in 90% yield.

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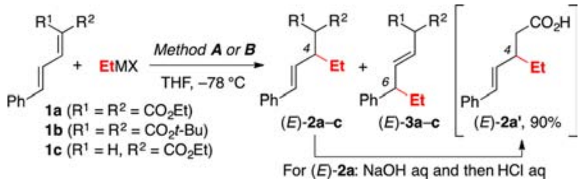
Table 1. Ethyl Addition of Dienyl Esters 1a−c[a]



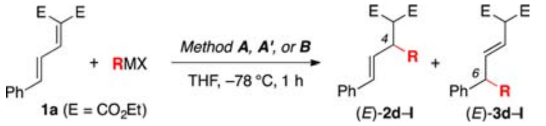
entry	1	*method*	reaction time (h)	2/3	yield (%)	
					2	**3**
1	**1a**	*A*	1	**2a/3a**	**91** (70)[b]	7 (26)[b]
2	**1a**	*B*	1	**2a/3a**	56	28
3	**1b**	*A*	24	**2b/3b**	71	5
4	**1b**	*B*	24	**2b/3b**	38	10
5	**1c**	*A*	5	**2c/3c**	0	0
6	**1c**	*B*	5	**2c/3c**	0	0

[a]The reaction was conducted in THF at −78 °C with method A or **B** on a 0.3 mmol scale of **1**, and isolated yields are shown. Method A: EtMgCl (1.5 equiv), Me_3SiCH_2MgCl (3 equiv) and $ZnCl_2$ (1.5 equiv). Method B: EtMgCl (1.5 equiv). [b]EtMgCl (1.5 equiv), Me_3SiCH_2MgCl (0.2 equiv) and $ZnCl_2$ (0.1 equiv) were used.

Unfortunately, a catalytic amount of ethylzinc(II)ate was not effective, and undesired **3a** was obtained in significant amounts (entry 1, also see the Supporting Information).

We next investigated the generality of organozinc(II)ates for the 1,4-conjugate addition to **1a** (Table 2). As a result, alkyl-, alkenyl-, and alkynylzinc(II)ates (method A or A′),[13] which were derived from Me-, *n*-Bu-, *n*-octyl-, allyl-, and vinylMgCl and PhC≡CMgBr, could be used, and the corresponding 4-alkyl adducts **2d**−**i** were obtained in 84−97% yields with high regioselectivities (entries 1−12). Moreover, phenylzinc(II)ate (method A′)[13] could also be used, and **2j** was obtained in 99% yield with a formation of a small amount (<10% yield) of biphenyl (entry 13), which is sometimes observed in the reactions with phenylzinc(II)ate.[9j,11] Encouraged by these results, we further investigated the generality of 1,4-conjugate addition to trienyl ester **4** with 1°-alkylzinc(II)ates (Table 3).

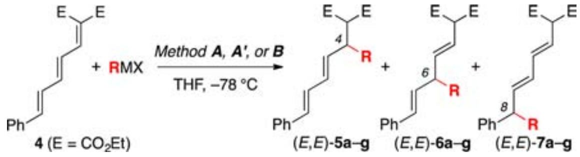
Table 2. Regioselective Alkyl Addition at the 4-Position of Dienyl Ester 1a[a]



entry	RMgX	*method*	2/3	yield (%)	
				2	**3**
1	MeMgCl	*A'*	**2d/3d**	**85**	6
2	MeMgCl	*B*	**2d/3d**	23	2
3	*n*-BuMgCl	*A*	**2e/3e**	**88**	10
4	*n*-BuMgCl	*B*	**2e/3e**	47	27
5	*n*-octylMgCl	*A*	**2f/3f**	**90**	7
6	*n*-octylMgCl	*B*	**2f/3f**	46	24
7	allylMgCl	*A*	**2g/3g**	**84**	9
8	allylMgCl	*B*	**2g/3g**	33	14
9	vinylMgCl	*A*	**2h/3h**	**97**	0
10	vinylMgCl	*B*	**2h/3h**	53	0
11[b]	PhC≡CMgBr	*A'*	**2i/3i**	**97**	0
12[b]	PhC≡CMgBr	*B*	**2i/3i**	33	0
13[c]	PhMgBr	*A'*	**2j/3j**	**99**	0
14[c]	PhMgBr	*B*	**2j/3j**	64	0
15	*c*-HexMgCl	*A*	**2k/3k**	39	60
16	*c*-HexMgCl	*B*	**2k/3k**	48	47
17[d]	*t*-BuMgCl	*A*	**2l/3l**	25	18
18[d]	*t*-BuMgCl	*B*	**2l/3l**	23	18

[a]The reaction was conducted in THF at −78 °C with Method A, A′, or B on a 0.3 mmol scale of **1a** unless otherwise noted. Method A: Grignard reagent (1.5 equiv), Me_3SiCH_2MgCl (3 equiv) and $ZnCl_2$ (1.5 equiv). Method A′: Grignard reagent (4.5 equiv) and $ZnCl_2$ (1.5 equiv). Method B: Grignard reagent (1.5 equiv). [b]Reaction temperature was gradually increased from −78 °C to −20 °C over 13 h. [c]The reaction time was 24 h. [d]The reaction time was 20 h.

Table 3. Regioselective Alkyl Addition at the 4-Position of Trienyl Ester 4[a]



entry	RMgX	*method*	reaction time (h)	5/6/7	yield (%)		
					5	**6**	**7**
1	MeMgCl	*A'*	3	**5a/6a/7a**	**88**	7	1
2	MeMgCl	*B*	3	**5a/6a/7a**	20	0	0
3	EtMgCl	*A*	1	**5b/6b/7b**	**92**	5	2
4	EtMgCl	*B*	1	**5b/6b/7b**	51	20	24
5	*n*-BuMgCl	*A*	1	**5c/6c/7c**	**88**	7	3
6	*n*-BuMgCl	*B*	1	**5c/6c/7c**	51	21	26
7	*n*-octylMgCl	*A*	17	**5d/6d/7d**	**82**	4	4
8	*n*-octylMgCl	*B*	17	**5d/6d/7d**	53	20	26
9	allylMgCl	*A*	1	**5e/6e/7e**	**89**	5	2
10	allylMgCl	*B*	1	**5e/6e/7e**	44	13	14
11	vinylMgCl	*A*	4	**5f/6f/7f**	**87**	1	1
12	vinylMgCl	*B*	4	**5f/6f/7f**	27	6	1
13	PhMgBr	*A'*	24	**5g/6g/7g**	**99**	0	0
14	PhMgBr	*B*	24	**5g/6g/7g**	41	0	0

[a]The reaction was conducted in THF at −78 °C with method A, A′, or B on a 0.3 mmol scale of **4** unless otherwise noted.

As a result, a highly selective 1,4-conjugate addition to **4** occurred with the use of 1°-alkyl, vinyl-, and phenylzinc(II)ate (method A or A′). In contrast, when we used Grignard reagent alone (method B), a mixture of alkyl adducts at the 4-, 6-, and 8-positions (**5**, **6**, and **7**, respectively) was obtained. However, unlike the above less hindered organozinc(II)ates, sterically demanding 2°- and 3°-alkylzinc(II)ates (*c*-Hex- and *t*-Bu, respectively) were not effective, and the desired 1,4-adducts **2k** and **2l** were obtained from **1a** with low regioselectivities (Table 2, entries 15 and 17).

To overcome this drawback in 2°- and 3°-alkyl additions to dienyl ester **1a**, we tried using less hindered enynyl ester **8a** (Table 4).[14] As a result, not only 1°-alkylzinc(II)ates (entries 1 and 3) but also alkynylzinc(II)ate (entry 5), phenylzinc(II)ate (entry 7), and 2°-alkylzinc(II)ates, which were derived from *i*-Pr- and *c*-HexMgCl (entries 9, 11, and 13), could be used with method A or A′. Remarkably, 3°-alkylzinc(II)ates derived from *t*-BuMgCl could be used without serious problems (entry 15). Notably, a terminal Ph moiety (see **8a**) could be replaced by $t\text{-BuMe}_2\text{Si}$ (TBS) (see **8b**), and the corresponding 4-*i*-Pr-adduct **9f** was obtained in 99% yield (entry 11).

By taking advantage of the high reactivity of enynyl ester **8a**, we transformed the obtained alkynyl ester **9g** to the corresponding olefin (*E*)-**2k** (eq 3). After the hydrogenation of **9g** with Lindlar's catalyst, compound (*Z*)-**2k** was obtained in 91% yield. Subsequent treatment of (*Z*)-**2k** with iodine gave (*E*)-**2k** in 72% yield. Since (*E*)-**2k** was not successfully obtained directly from **1a** due to steric reasons (eq 4), we could demonstrate the synthetic utility of such enyne-derived products.

Finally, we investigated the reaction of dienyl ester **11**, which has a terminal EtO group[15] (Table 5). As shown in eq 2, electron-donation from the EtO group would provide the most activated

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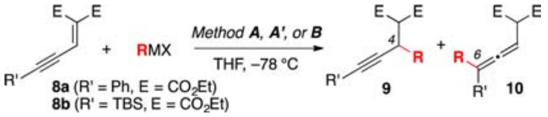
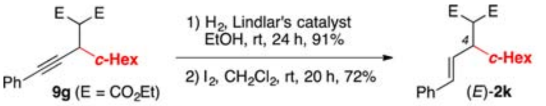
Table 4. Regioselective Alkyl Addition at the 4-Position of Enynyl Esters 8a and 8b[a]



entry	8	RMgX	*method*	Reaction time (h)	9/10	yield (%)	
						9	10
1	**8a**	EtMgCl	*A*	1	**9a/10a**	92	0
2	**8a**	EtMgCl	*B*	1	**9a/10a**	35	0
3	**8a**	BnMgCl	*A*	2	**9b/10b**	94	0
4	**8a**	BnMgCl	*B*	2	**9b/10b**	30	3
5[b]	**8a**	PhC≡CMgCl	*A*	14	**9c/10c**	98	0
6[b]	**8a**	PhC≡CMgCl	*B*	14	**9c/10c**	50	0
7	**8a**	PhMgBr	*A'*	18	**9d/10d**	95	0
8	**8a**	PhMgBr	*B*	18	**9d/10d**	43	0
9	**8a**	*i*-PrMgCl	*A*	4	**9e/10e**	93	0
10	**8a**	*i*-PrMgCl	*B*	4	**9e/10e**	53	14
11	**8b**	*i*-PrMgCl	*A*	4	**9f/10f**	99	0
12	**8b**	*i*-PrMgCl	*B*	4	**9f/10f**	29	3
13	**8a**	*c*-HexMgCl	*A*	18	**9g/10g**	74	0
14	**8a**	*c*-HexMgCl	*B*	18	**9g/10g**	44	9
15	**8a**	*t*-BuMgCl	*A*	2	**9h/10h**	94	0
16	**8a**	*t*-BuMgCl	*B*	2	**9h/10h**	38	17

[a] The reaction was conducted in THF at −78 °C with method A, A′, or B on a 0.3 mmol scale of **8** unless otherwise noted. [b] Reaction temperature was gradually increased from −78 to −20 °C over 14 h.



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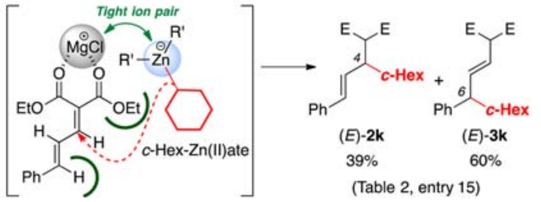
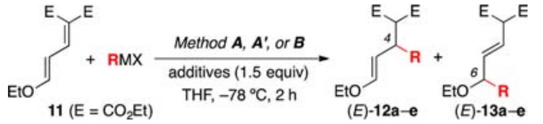


(4)

Table 5. Regioselective Alkyl Addition at the 6-Position of Dienyl Ester 11 with a Terminal Ethoxy Group[a]



entry	RMgX	*method*	additive	12/13	yield (%)	
					12	13
1	EtMgCl	*A*	–	**12a/13a**	20	80
2	EtMgCl	*A*	HMPA	**12a/13a**	12	86
3	EtMgCl	*A*	DMI	**12a/13a**	14	68
4	EtMgCl	*A*	TMEDA	**12a/13a**	2	9
5	EtMgCl	*B*	HMPA	**12a/13a**	6	39
6	EtMgCl	*B*	–	**12a/13a**	13	47
7	MeMgCl	*A*	HMPA	**12b/13b**	8	80
8	MeMgCl	*B*	–	**12b/13b**	3	65
9	vinylMgCl	*A*	HMPA	**12c/13c**	2	94
10	vinylMgCl	*B*	–	**12c/13c**	4	60
11	PhMgBr	*A'*	HMPA	**12d/13d**	0	95
12	PhMgBr	*B*	–	**12d/13d**	0	28
13	*i*-PrMgCl	*A*	HMPA	**12e/13e**	10	86
14	*i*-PrMgCl	*B*	–	**12e/13e**	4	10

[a] The reaction was conducted in THF at −78 °C with method A, A′, or B on a 0.3 mmol scale of **11** in the presence or absence of additive (1.5 equiv) unless otherwise noted. In method A′, Me_3SiCH_2Li was used in place of Me_3SiCH_2MgCl in Table 5.

electrophilic carbon center at the 6-position (also see the DFT calculation in the SI). However, the possible tight ion pair of organozinc(II)ates would still promote the nearest 1,4-conjugate addition. Based on this hypothesis, we examined the use of highly coordinating additives, such as HMPA (hexamethylphosphoramide), DMI (1,3-dimethyl-2-imidazolidinone), and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine),[16] in the presence of organozinc(II)ates to weaken the tight ion pair (Figure 1). As a result, HMPA (entry 2) was better than the other additives (entries 3 and 4).[17] Desired 6-Et adduct **13a** was obtained in 86% yield with 4-Et adduct **12a** in 12% yield (entry 2), whereas **13a** was obtained in 80% yield with **12a** in 20% yield in the absence of additives (entry 1). Since EtMgCl with HMPA did not switch the regioselectivity (entries 5 and 6), the combined use of ethylzinc(II)ate and HMPA should be necessary. Other organozinc(II)ates derived from Me- and vinylMgCl could be used with method A (or A′) with HMPA, and high **13** selectivities were observed (entries 7 and 9). Moreover, phenylzinc(II)ate and isopropylzinc(II)ate provided products **13d** and **13e** in respective yields of 95% and 86%.

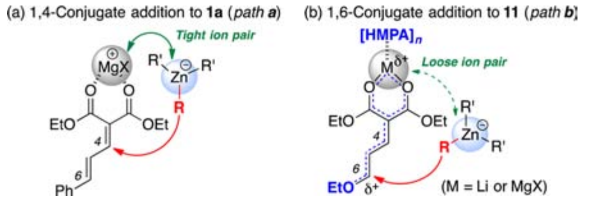
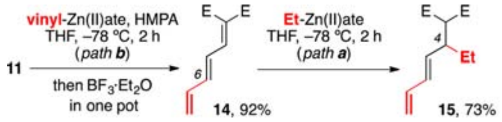


Figure 1. Control of regioselectivity with organozinc(II)ates.



(5)

Moreover, to demonstrate the utility of this synthetic method, we conducted a sequential path b−path a reaction (eq 5). First, compound **11** was transformed to a prolonged conjugate triene **14** with vinyl-Zn(II)ate/HMPA (path b, 1,6-addition) and the subsequent use of $BF_3 \cdot Et_2O$ in one pot. Next, compound **14** could be used for a new 1,4-conjugate addition (path a), and 4-Et-adduct **15** was selectively obtained as a major product.

In summary, we have developed highly regioselective 1,4- and 1,6-conjugate additions of Grignard reagent-derived organozinc(II)ates to malonate-derived polyconjugated esters. The tight ion-pair control of organozinc(II)ates could promote 1,4-conjugate addition to dienyl, trienyl, and enynyl esters. Moreover, a terminal activating EtO moiety in the substrate with the use of HMPA could lead to 1,6-conjugate addition successfully. Overall, the scope of substrates can prove the efficient methodology for the regioselective formation of *C*−alkyl, *C*−aryl, *C*−alkenyl, and *C*−alkynyl bonds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01774.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(14) The alkyne moiety was found to be highly effective for relieving the steric constraints in alkyl addition to α-imino esters. See ref 8e.

(15) For synthetic reasons, the EtO group was selected. We examined ethyl addition to substrates with other groups, such as MeO, *i*-PrO, Me_3SiCH_2O, and *N*-pyrrolidinyl. However, due to the stability of these starting materials and/or the corresponding products, a complex mixture was obtained. See the SI.

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