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Highly Regio- and Stereoselective Double Michael Addition–Cyclization of 2,3-Allenoates with Organozinc Compounds: Efficient Synthesis of 5-Benzylidenecyclohex-2-enones**

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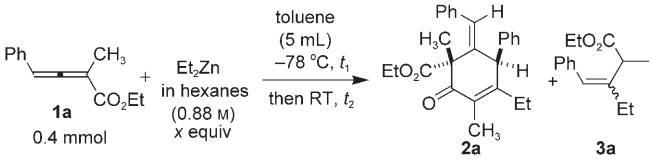
Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday

Highly substituted α,β-unsaturated cyclohexenones, which are found in a wide range of natural products, have caught the attention of many synthetic organic and medicinal chemists.[1] For example, (+)-guttiferone, hyperforin, and aristoforin are inhibitors of the human sirtuins SIRT1 and SIRT2;[1a] bisorbicillinol exhibits antioxidant activity; bisvertinolone is an antifungal agent;[1b,c] and garsubellin A has potent neurotrophic activity.[1d] α,β-Unsaturated cyclohexenones have also been used as intermediates to synthesize other natural products, such as carvone.[2] Herein, we report a highly regio- and stereoselective double addition–cyclization reaction of two molecules of a 2,3-allenoate with organozinc compounds providing an efficient route to highly substituted 5-benzylidenecyclohex-2-enone derivatives.

Recently, we reported an iron-catalyzed conjugate addition reaction of 2,3-allenoates with Grignard reagents to afford β,γ-unsaturated alkenoates with high regio- and stereoselectivity.[3] When we attempted the reaction of ethyl 2-methyl-4-phenyl-2,3-butadienoate (**1a**) with diethylzinc (3 equiv) under the catalysis of $Fe(acac)_3$ by treatment at −78 °C for 1.5 h followed by warming to room temperature for 6 h, the conjugate addition product ethyl 3-ethyl-2-methyl-4-phenyl-3-butenoate (**3a**) was formed in low yield along with an unknown side product (Table 1, entry 1). Through spectroscopic analysis (^1H and ^{13}C NMR, MS) and X-ray diffraction analysis,[4] we identified that the side product contained a cyclohexenone unit with an *exo Z* carbon–carbon double bond, and that the reaction showed excellent diastereoselectivity with respect to the two stereogenic centers at the 4- and 6-positions (Figure 1). A control experiment showed that the reaction even proceeds in the absence of $Fe(acac)_3$ to afford **2a** in 61% yield (Table 1, entry 2). The yield of **2a** decreased when less diethylzinc was used (Table 1, entries 3–5). Furthermore, we found that when a solution of diethylzinc in hexanes was added dropwise to a solution of **1a** in toluene at room temperature, the reaction also afforded **2a** in 76% yield together with **3a** in 10% yield (Table 2, entry 1). The solvents THF, Et_2O, Bu_2O, CH_2Cl_2, benzene, and ethylbenzene failed to give better results (Table 2, entries 2–7). Therefore, for

Table 1: Effects of reaction time and the amount of diethylzinc on the addition–cyclization of 2,3-allenoate **1a** with diethylzinc.



Entry	*x*	t_1 [min]	t_2 [h]	Yield of **2a** [%][a]	Yield of **3a** [%][a]
1[b]	3	90	6	47	14
2	3	90	9	61	14
3	3	15	10	69	5
4	2	15	10	60	14
5	1.5	15	10	58	16

[a] The yield was determined by NMR spectroscopy using CH_2Br_2 as the internal standard. [b] $Fe(acac)_3$ (5 mol%) was added as a catalyst. acac = acetylacetonate.

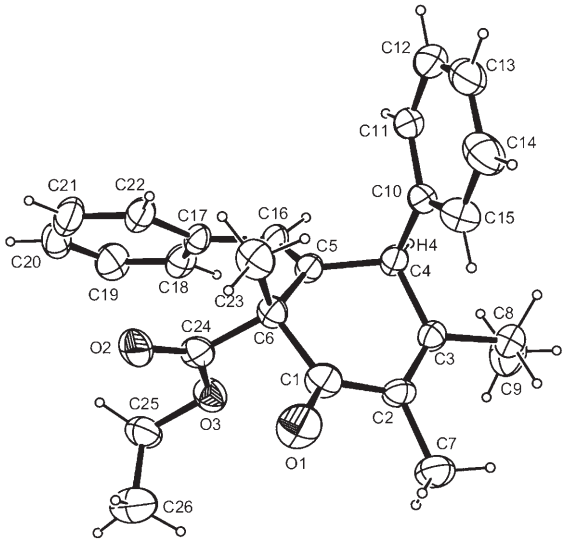


Figure 1. ORTEP representation of **2a**.

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Table 2: Effect of the solvent on the addition–cyclization of 2,3-allenoate **1a** with diethylzinc.

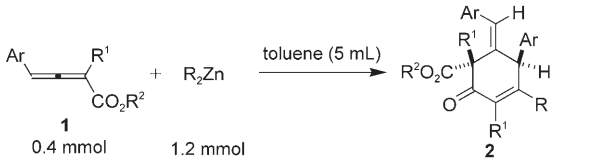
Entry	Solvent	Yield of **2a** [%][a]	Yield of **3a** [%][a]	Recovery of **1a** [%][a]
1	toluene	76	10	–
2	THF	trace	13	68
3	Et_2O	46	20	10
4	Bu_2O	50	16	–
5	CH_2Cl_2	57	17	8
6	benzene	59	8	–
7	ethylbenzene	72	10	–

[a] The yield was determined by NMR spectroscopy using CH_2Br_2 as the internal standard.

further study, we defined the standard reaction conditions to be the addition of a dialkyl zinc reagent (3 equiv) to a solution of the 2,3-alkadienoate in toluene at room temperature (Table 2, entry 1). ^{1}H NMR spectroscopic analysis of the crude product showed that only one diastereoisomer was formed.

The scope of the reaction was investigated under these standard conditions (Table 3). The reaction of a variety of substituted 2,3-allenoates with dialkyl zinc reagents afforded the cyclohex-2-enone derivatives with high regio- and stereoselectivities. Aryl groups with electron-withdrawing or electron-donating substituents are tolerated, and the reaction proceeds when R^1 and R^2 are alkyl groups. When diethyl- or dibutylzinc were used, the reaction proceeded at room temperature (Table 3, entries 1–7 and 12). However, when dimethylzinc was used, the product was not formed at room temperature (Table 3, entry 8); at 100 °C, the corresponding products were formed in 52–64 % yield (Table 3, entries 9–11).

Table 3: Addition–cyclization of 2,3-allenoates **1** with dialkyl zinc reagents.[a]

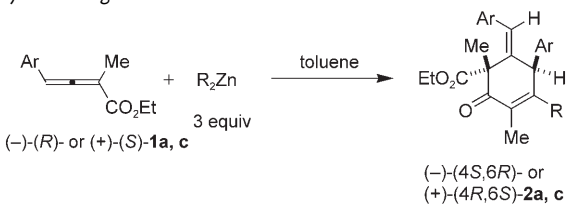


Entry	Ar	R^1	R^2	R	*T* [°C]	*t* [h]	Yield [%][b]
1	Ph	Me	Et (**1a**)	Et	RT	1	65 (**2a**)
2	Ph	Me	Me (**1b**)	Et	RT	23	79 (**2b**)
3	*p*-BrC_6H_4	Me	Et (**1c**)	Et	RT	3	63 (**2c**)
4	*p*-ClC_6H_4	Me	Et (**1d**)	Et	RT	3	69 (**2d**)
5	*p*-FC_6H_4	Me	Et (**1e**)	Et	RT	8	65 (**2e**)
6	*p*-$MeOC_6H_4$	Me	Et (**1f**)	Et	RT	2	57 (**2f**)
7	Ph	Et	Et (**1g**)	Et	RT	3	47 (**2g**)
8	Ph	Me	Et (**1a**)	Me	RT	13	–[c]
9	Ph	Me	Et (**1a**)	Me	100	18	52 (**2h**)
10	Ph	Me	Me (**1b**)	Me	100	24	64 (**2i**)
11	*p*-ClC_6H_4	Me	Et (**1d**)	Me	100	12	60 (**2j**)
12	Ph	Me	Et (**1a**)	*n*Bu	RT	3	82 (**2k**)

[a] The reaction was conducted with Et_2Zn in hexanes (0.88 M), Me_2Zn in toluene (1.2 M), or nBu_2Zn in heptane (1.0 M). [b] Yield of the isolated product. [c] The substrate **1a** was recovered in 60% yield.

The reaction of the optically active 2,3-allenoates (*R*)- or (*S*)-**1a** and **1c**[5] with dialkyl zinc reagents afforded the corresponding optically active cyclohex-2-enones without racemization (Table 4). The absolute configuration of the products was established by X-ray diffraction analysis of (−)-(4*S*,6*R*)-**2c** by using the two bromine atoms as the reference (Figure 2).[4,6] The reactions of (−)-(*R*)-**1a** (97 % *ee*) and (+)-

Table 4: Addition–cyclization of optically active 2,3-allenoates **1** with dialkyl zinc reagents.[a]



Entry	**1**			R	*t* [h]	**2**		
		Ar	*ee* [%][b]				Yield [%][c]	*ee* [%][b]
1	(*R*)-**1a**	Ph	97	Et	1[d]	(4*S*,6*R*)-**2a**	61	97
2	(*S*)-**1a**	Ph	96	Et	3[d]	(4*R*,6*S*)-**2a**	76	96
3	(*R*)-**1a**	Ph	97	Me	12[e]	(4*S*,6*R*)-**2h**	51	95
4	(*S*)-**1a**	Ph	96	Me	12[e]	(4*R*,6*S*)-**2h**	52	95
5	(*R*)-**1a**	Ph	98	*n*Bu	5[f]	(4*S*,6*R*)-**2k**	69	97
6	(*S*)-**1a**	Ph	96	*n*Bu	4[g]	(4*R*,6*S*)-**2k**	73	96
7	(*R*)-**1c**	*p*-BrC_6H_4	92	Et	4.5[d]	(4*S*,6*R*)-**2c**	65	92
8	(*S*)-**1c**	*p*-BrC_6H_4	86	Et	3[d]	(4*R*,6*S*)-**2c**	69	85

[a] The reaction was conducted with Et_2Zn in hexanes (0.88 M), Me_2Zn in toluene (1.2 M), or nBu_2Zn in heptane (1.0 M). [b] Determined by HPLC on a chiral phase. [c] Yield of the isolated product. [d] The reaction was carried out at room temperature. [e] The reaction was carried out at 100 °C. [f] The reaction was carried out at room temperature for 3 h, then at 30 °C for 2 h. [g] The reaction was carried out at room temperature for 2 h, then at 50 °C for 2 h.

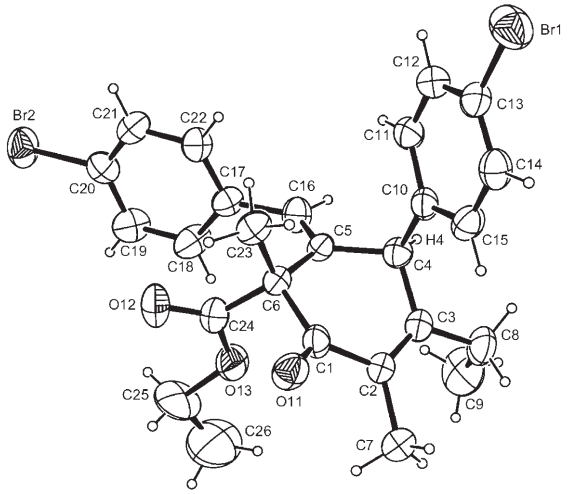
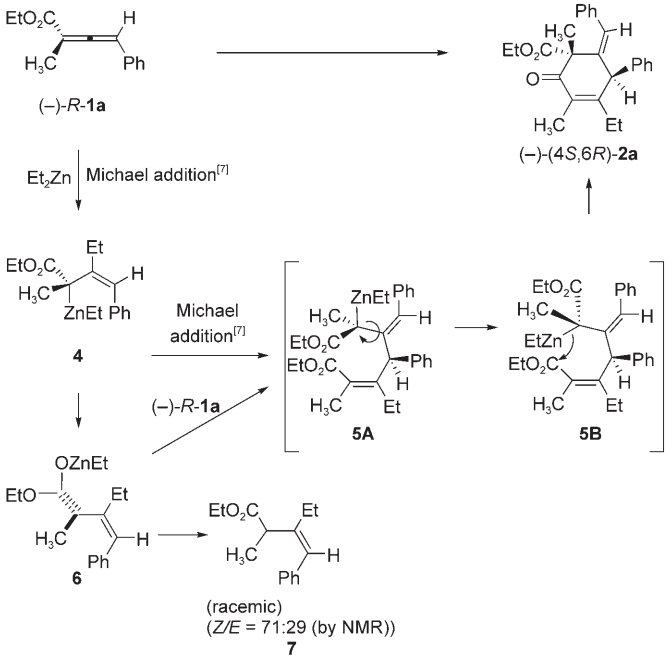


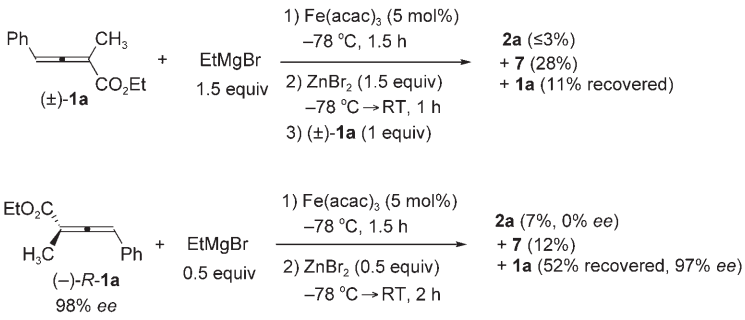
Figure 2. ORTEP representation of (−)-(4*S*,6*R*)-**2c**.

(*S*)-**1a** (96% *ee*) proceeded even with Me_2Zn at 100°C to give the products (−)-(4*S*,6*R*)-**2h** and (+)-(4*R*,6*S*)-**2h** with 95% *ee* (Table 4, entries 3 and 4).

A model to predict the stereochemical outcome of this reaction is shown in Scheme 1. In the first step, the regio- and stereoselective Michael addition[7] of Et_2Zn to (−)-(*R*)-**1a** affords the optically active α-zincated 2-alkenoate **4**.[8] A second Michael addition[7] of the γ-carbon atom of intermediate **4** to the center carbon atom of the allene moiety in (−)-(*R*)-**1a** affords **5A** with high stereoselectivity. Its conformer **5B** then undergoes an intramolecular 1,2-addition reaction to form the six-membered ring. Owing to the steric interaction between the Ar group (in this case phenyl) of the 2,3-allenoate and the approaching allylic group in **4**, the *Z* stereoselectivity for the *exo* C=C bond is high.[3] Of course, **4** may be further converted into the optically active atropisomeric zinc 1,3-dienolate **6**,[9] which would be transformed into racemic **7** or **5A** upon reaction with H^+ or (−)-(*R*)-**1a**, respectively. However, the fact that the zinc 1,3-dienolate formed by transmetalation with $ZnBr_2$ of the magnesium 1,3-dienolate (prepared by the iron-catalyzed conjugate addition of a Grignard reagent to (±)-**1a**)[3] reacted with 2,3-allenoate (±)-**1a** to afford (±)-**2a** in less than 3% yield (as determined by NMR spectroscopy) indicated the low reactivity of the zinc dienolate intermediate **6** towards **1a**[10] (Scheme 2). In a further test reaction, a magnesium 1,3-dienolate was formed by the $Fe(acac)_3$-catalyzed Michael addition reaction of (−)-(*R*)-**1a** with EtMgBr (0.5 equiv) at −78°C and subsequently converted into a zinc 1,3-dienolate of type **6** by transmetalation with $ZnBr_2$ (0.5 equiv) at −78°C. The reaction of this zinc 1,3-dienolate with the remaining 0.5 equivalents of (−)-(*R*)-**1a** afforded the cyclic product **2a** in 7% yield with 0% *ee* (Scheme 2). This result ruled out the possibility that the racemic[11] zinc 1,3-dienolate reacts with (−)-(*R*)-**1a** to afford the optically active cyclic product **2**.[9] Further study is required to determine the true mechanistic nature of this transformation.[12]



Scheme 1. Model for the prediction of the stereochemical outcome of the reaction.



Scheme 2. Mechanistic study. Yields and recoveries were determined by NMR spectroscopy using CH_2Br_2 as the internal standard.

In summary, we have developed a highly regio- and stereoselective double Michael addition–cyclization of two molecules of a 2,3-allenoate with organozinc compounds. The (*Z*)-5-benzylidenecyclohex-2-enones were produced with high diastereoselectivity with respect to the two stereogenic centers at the 4- and 6-positions. The aromatic group at the 4-position may increase the reactivity of 2,3-allenoates towards organozinc compounds. When optically active 2,3-allenoates were employed, optically active (*Z*)-5-benzylidenecyclohex-2-enones were produced without racemization. Owing to the relatively low reactivity of dialkyl zinc reagents in terms of conjugate addition to C=C bonds,[7a] this study should stimulate new research in the chemistry of organozinc compounds. We are conducting further studies in this area.

Experimental Section

Synthesis of (±)-**2a**: Allene **1a** (83.6 mg, 0.4 mmol) and toluene (5 mL) were added sequentially to a dried Schlenk tube under a nitrogen atmosphere at room temperature. A solution of Et_2Zn in hexanes (1.36 mL, 1.2 mmol, 3 equiv) was then added to the reaction mixture with a syringe over 3–5 min at room temperature. When the reaction was complete (as monitored by TLC), it was quenched by the dropwise addition of saturated NH_4Cl (1 mL) and then water (5 mL) at room temperature. The mixture was extracted with diethyl ether (3 × 30 mL), and the organic layer was washed with dilute aqueous HCl (1%), a saturated aqueous solution of $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20:1) afforded (*Z*)-**2a** (0.0520 g, 65%) as a solid. M.p.: 125–126°C (hexane); IR (neat): $\tilde{\nu}$ = 2975, 2939, 1744, 1667, 1641, 1599, 1492, 1449, 1366, 1223, 1193, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 8H), 7.17–7.09 (m, 2H), 6.86 (s, 1H), 4.47 (s, 1H), 3.60–3.47 (m, 1H), 3.30–3.15 (m, 1H), 2.70–2.50 (m, 1H), 2.22–2.10 (m, 1H), 2.00 (s, 3H), 1.20–1.10 (m, 6H), 0.90 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 197.3, 170.4, 157.7, 141.5, 141.4, 136.0, 131.4, 129.0, 128.63, 128.58, 127.9, 127.6, 127.2, 127.1, 60.9, 58.6, 54.3, 27.4, 24.2, 13.4, 11.9, 11.6 ppm; MS: *m*/*z* (%): 388 (M^+, 61), 315

(100); elemental analysis: calcd (%) for $C_{26}H_{28}O_3$: C 80.38, H 7.26; found: C 80.45, H 7.10.

Synthesis of (+)-(4*R*,6*S*)-(*Z*)-**2a**: The treatment of (+)-(*S*)-**1a** (0.0404 g, 0.2 mmol, 96% *ee*; $[\alpha]_D^{20} = +285.3\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.82\ g\,dL^{-1}$, $CHCl_3$))[1d] in toluene (2.5 mL) with a solution of Et_2Zn in hexanes (0.88 M, 0.70 mL, 0.6 mmol, 3 equiv) afforded (+)-(4*R*,6*S*)-(*Z*)-**2a** (0.0297 g, 76%, 96% ee). The *ee* value was determined by HPLC (chiralcel AD-H, *n*-hexane/*i*PrOH = 95:5, 0.7 mL min^{-1}, $n =$ 230 nm, t_R(minor) = 7.8 min, t_R(major) = 8.7 min). $[\alpha]_D^{20} = +74.6\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.49\ g\,dL^{-1}$, $CHCl_3$). The analytical and spectroscopic data of (+)-(4*R*,6*S*)-(*Z*)-**2a** were identical to those of racemic (*Z*)-**2a**.

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[4] Crystal data for **2a**: $C_{26}H_{28}O_3$, $M_r = 388.51$, monoclinic, *P*121/*c*1, $Mo_{K\alpha}$, final R indices ($I > 2\sigma(I)$): $R1 = 0.0491$, $wR2 = 0.1028$, $a =$ 10.4687(8), $b = 14.8999(10)$, $c = 14.6133(10)$ Å, $\alpha = 90$, $\beta =$ 103.0580(19), $\gamma = 90°$, $V = 2220.5(3)$ Å^3, $Z = 4$, number of reflections measured/unique: 5052/1585 ($R_{int} = 0.061$), number of observations: 5051 ($I > 2\sigma(I)$), 291 parameters. CCDC 672093 (**2a**) and CCDC 672094 ((−)-(4*S*,6*R*)-**2c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[6] Crystal data for (−)-(4*S*,6*R*)-**2c**: $C_{26}H_{26}Br_2O_3$, $M_r = 546.30$, monoclinic, *P*1211, $Mo_{K\alpha}$, final *R* indices ($I > 2\sigma(I)$): $R1 =$ 0.0635, $wR2 = 0.1966$, $a = 7.3758(4)$, $b = 24.7978(13)$, $c =$ 14.0258(7) Å, $\alpha = 90$, $\beta = 90.2228(14)$, $\gamma = 90°$, $V =$ 2565.4(2) Å^3, $Z = 4$, number of reflections measured/unique: 5956/3461 ($R_{int} = 0.073$), number of observations: 5956 ($I >$ $2\sigma(I)$), 561 parameters.

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[9] We thank one of the referees for suggesting this mechanistic possibility.

[10] The fact that we did not observe the formation of the six-membered product **2** during the studies described in ref. [3] indicates the lower reactivity of magnesium 1,3-dienolates towards 2,3-allenoates.

[11] The reaction of optically active (−)-(*R*)-**2a** with RMgBr provided the racemic products of conjugate addition.

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