

Domino Reactions

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

Zhan Lu, Guobi Chai, and Shengming Ma*

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-butenate (**3a**) was formed in low yield along with an unknown side product (Table 1, entry 1). Through spectroscopic analysis (¹H and ¹³C 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

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

Entry	<i>x</i>	<i>t</i> ₁ [min]	<i>t</i> 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 CH₂Br₂ as the internal standard. [b] Fe(acac)₃ (5 mol %) was added as a catalyst. acac = acetylacetonate.

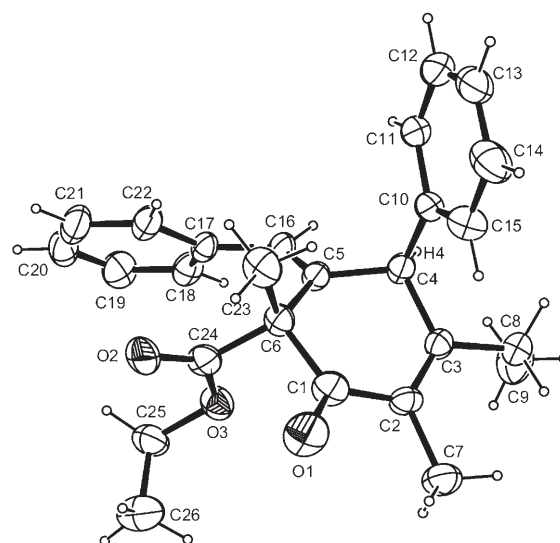


Figure 1. ORTEP representation of **2a**.

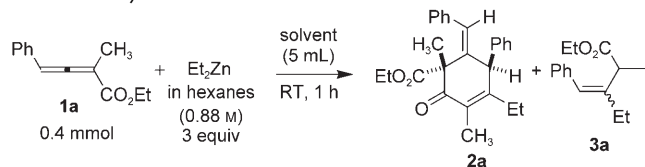
when less diethylzinc was used (Table 1, entries 3–5). Furthermore, we found that when a solution of diethylzinc in hexanes was added dropwise to a solution of **1a** in toluene at room temperature, the reaction also afforded **2a** in 76 % yield together with **3a** in 10 % yield (Table 2, entry 1). The solvents THF, Et₂O, Bu₂O, CH₂Cl₂, benzene, and ethylbenzene failed to give better results (Table 2, entries 2–7). Therefore, for

[*] Z. Lu, G. Chai, Prof. Dr. S. Ma
Laboratory of Molecular Recognition and Synthesis
Department of Chemistry, Zhejiang University
Hangzhou 310027, Zhejiang (China)
Fax: (+86) 21-6416-7510
E-mail: masm@mail.sioc.ac.cn

[**] Financial support was received from the National Natural Science Foundation of China (20732005) and the Major State Basic Research Development Program (2006CB806105). Shengming Ma is a Qiu Shi Adjunct Professor at Zhejiang University. We thank Guangke He in this research group for reproducing the results presented in entries 2, 4, 5, and 9 of Table 3.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200801497>.

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



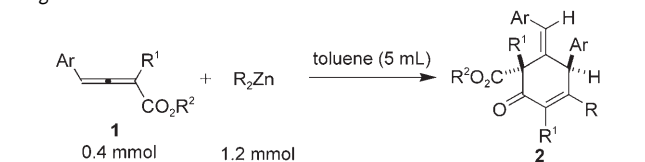
Entry	Solvent	Yield of 2a [%] ^[a]	Yield of 3a [%] ^[a]	Recovery of 1a [%] ^[a]
1	toluene	76	10	–
2	THF	trace	13	68
3	Et ₂ O	46	20	10
4	Bu ₂ O	50	16	–
5	CH ₂ Cl ₂	57	17	8
6	benzene	59	8	–
7	ethylbenzene	72	10	–

[a] The yield was determined by NMR spectroscopy using CH₂Br₂ 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). ¹H 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 stereo-selectivities. Aryl groups with electron-withdrawing or electron-donating substituents are tolerated, and the reaction proceeds when R¹ and R² are alkyl groups. When diethyl- or dibutylzinc were used, the reaction proceeded at room temperature (Table 3, entries 1–7 and 12). However, when

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



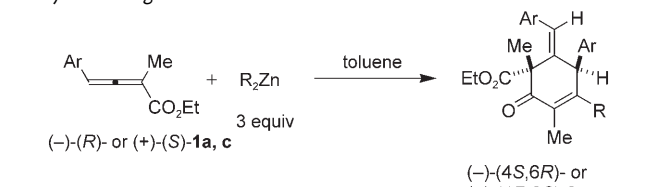
Entry	Ar	R ¹	R ²	R	T [°C]	t [h]	Yield [%] ^[b]
1	Ph	Me	Et (1a)	Et	RT	1	65 (2a)
2	Ph	Me	Me (1b)	Et	RT	23	79 (2b)
3	<i>p</i> -BrC ₆ H ₄	Me	Et (1c)	Et	RT	3	63 (2c)
4	<i>p</i> -ClC ₆ H ₄	Me	Et (1d)	Et	RT	3	69 (2d)
5	<i>p</i> -FC ₆ H ₄	Me	Et (1e)	Et	RT	8	65 (2e)
6	<i>p</i> -MeOC ₆ H ₄	Me	Et (1f)	Et	RT	2	57 (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	<i>p</i> -ClC ₆ H ₄	Me	Et (1d)	Me	100	12	60 (2j)
12	Ph	Me	Et (1a)	<i>n</i> Bu	RT	3	82 (2k)

[a] The reaction was conducted with Et₂Zn in hexanes (0.88 M), Me₂Zn in toluene (1.2 M), or *n*Bu₂Zn in heptane (1.0 M). [b] Yield of the isolated product. [c] The substrate **1a** was recovered in 60% yield.

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).

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

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



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

[a] The reaction was conducted with Et₂Zn in hexanes (0.88 M), Me₂Zn in toluene (1.2 M), or *n*Bu₂Zn 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.

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 (+)-

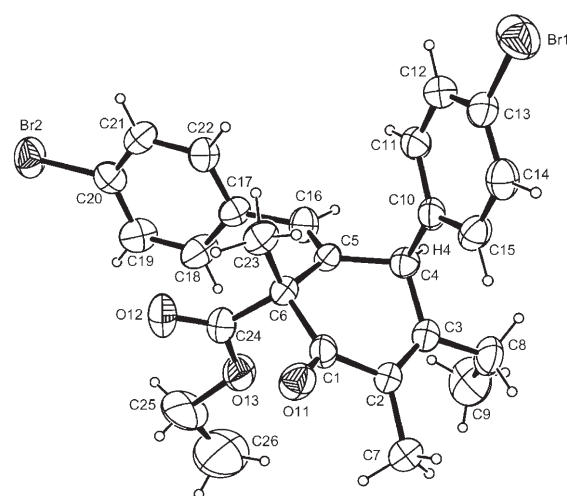
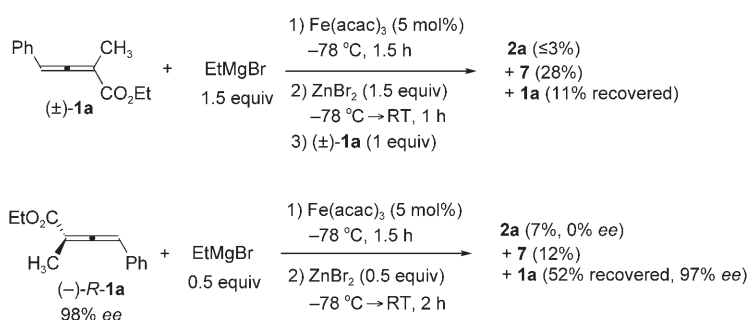


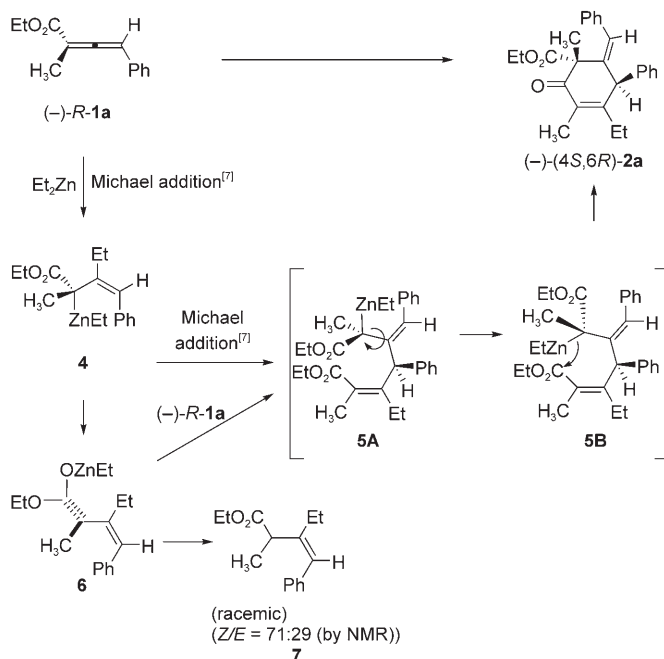
Figure 2. ORTEP representation of (–)-(4*S*,6*R*)-**2c**.

(*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 stereo-



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



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

selectivity. 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 $\text{Fe}(\text{acac})_3$ -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]

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.: $125\text{--}126^\circ\text{C}$ (hexane); IR (neat): $\tilde{\nu} = 2975, 2939, 1744, 1667, 1641, 1599, 1492, 1449, 1366, 1223, 1193, 1098\text{ cm}^{-1}$; ^1H NMR (300 MHz, CDCl_3): $\delta = 7.35\text{--}7.17$ (m, 8H), $7.17\text{--}7.09$ (m, 2H), 6.86 (s, 1H), 4.47 (s, 1H), $3.60\text{--}3.47$ (m, 1H), $3.30\text{--}3.15$ (m, 1H), $2.70\text{--}2.50$ (m, 1H), $2.22\text{--}2.10$ (m, 1H), 2.00 (s, 3H), $1.20\text{--}1.10$ (m, 6H), 0.90 ppm (t, $J = 7.1\text{ Hz}$, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 197.3, 170.4, 157.7, 141.5, 141.4, 136.0, 131.4, 129.0, 128.63, 128.58, 127.9, 127.6, 127.2, 127.1, 60.9, 58.6, 54.3, 27.4, 24.2, 13.4, 11.9, 11.6$ 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; $[\alpha]_D^{20} = +285.3 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ ($c = 0.82 \text{ g dL}^{-1}$, 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, $n = 230 \text{ nm}$, $t_R(\text{minor}) = 7.8 \text{ min}$, $t_R(\text{major}) = 8.7 \text{ min}$). $[\alpha]_D^{20} = +74.6 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ ($c = 1.49 \text{ g dL}^{-1}$, CHCl_3). The analytical and spectroscopic data of (+)-(4*R*,6*S*)-(Z)-**2a** were identical to those of racemic (Z)-**2a**.

Received: March 30, 2008

Revised: April 30, 2008

Published online: July 9, 2008

Keywords: allenes · cyclization · esters · Michael addition · organozinc reagents

- [1] a) C. Gey, S. Kyrylenko, L. Hennig, L.-N. D. Nguyen, A. Büttner, H. D. Pham, A. Giannis, *Angew. Chem.* **2007**, *119*, 5311; *Angew. Chem. Int. Ed.* **2007**, *46*, 5219; b) K. C. Nicolaou, G. Vassilikogiannakis, K. B. Simonsen, P. S. Baran, Y.-L. Zhong, V. P. Vidali, E. N. Pitsinos, E. A. Couladouros, *J. Am. Chem. Soc.* **2000**, *122*, 3071; c) K. C. Nicolaou, K. B. Simonsen, G. Vassilikogiannakis, P. S. Baran, V. P. Vidali, E. N. Pitsinos, E. A. Couladouros, *Angew. Chem.* **1999**, *111*, 3762; *Angew. Chem. Int. Ed.* **1999**, *38*, 3555; d) A. Kuramochi, H. Usuda, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 14200; e) R. Alibés, P. Bayón, P. de March, M. Figueredo, J. Font, G. Marjanet, *Org. Lett.* **2006**, *8*, 1617; f) A. Nakazaki, T. Era, Y. Numada, S. Kobayashi, *Tetrahedron* **2006**, *62*, 6264; g) A. Srikrishna, V. H. Pardeshi, G. Satyanarayana, *Tetrahedron Lett.* **2007**, *48*, 4087; for the catalytic enantioselective alkylative aldol reaction of allenic esters and ketones with dialkyl zinc reagents towards the synthesis of functionalized δ -lactones, see: h) D. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 14440.
- [2] a) A. Srikrishna, D. H. Dethe, *Org. Lett.* **2004**, *6*, 165; b) A. Srikrishna, D. H. Dethe, P. R. Kumar, *Tetrahedron Lett.* **2004**, *45*, 2939; c) K. C. Nicolaou, D. Pappo, K. Y. Tsang, R. Gibe, D. Y.-K. Chen, *Angew. Chem.* **2008**, *120*, 958; *Angew. Chem. Int. Ed.* **2008**, *47*, 944.
- [3] Z. Lu, G. Chai, S. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 14546.
- [4] Crystal data for **2a**: $C_{26}H_{28}O_3$, $M_r = 388.51$, monoclinic, $P121/c1$, $\text{Mo}_{\text{K}\alpha}$, final R indices ($I > 2\sigma(I)$): $R1 = 0.0491$, $wR2 = 0.1028$, $a = 10.4687(8)$, $b = 14.8999(10)$, $c = 14.6133(10) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 103.0580(19)$, $\gamma = 90^\circ$, $V = 2220.5(3) \text{ \AA}^3$, $Z = 4$, number of reflections measured/unique: 5052/1585 ($R_{\text{int}} = 0.061$), 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.
- [5] S. Ma, S. Wu, *Chem. Commun.* **2001**, 441.
- [6] Crystal data for (-)-(4*S*,6*R*)-**2c**: $C_{26}H_{26}Br_2O_3$, $M_r = 546.30$, monoclinic, $P1211$, $\text{Mo}_{\text{K}\alpha}$, final R indices ($I > 2\sigma(I)$): $R1 = 0.0635$, $wR2 = 0.1966$, $a = 7.3758(4)$, $b = 24.7978(13)$, $c = 14.0258(7) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 90.2228(14)$, $\gamma = 90^\circ$, $V = 2565.4(2) \text{ \AA}^3$, $Z = 4$, number of reflections measured/unique: 5956/3461 ($R_{\text{int}} = 0.073$), number of observations: 5956 ($I > 2\sigma(I)$), 561 parameters.
- [7] For a monograph on carbozincation, see: a) E. Lorthiois, C. Meyer, *The Chemistry of Organozinc Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2006**, pp. 863–977; for the uncatalyzed Michael addition of *t*Bu₂Zn to conjugated alkynes, see: b) J. Auger, G. Courtois, L. Miginiac, *J. Organomet. Chem.* **1977**, *133*, 285; c) G. Courtois, L. Miginiac, *J. Organomet. Chem.* **1980**, *194*, 13; d) L. Miginiac, *J. Organomet. Chem.* **1982**, *238*, 235; for the *anti* addition of nucleophiles to allenates, see: e) Y. Naruse, S. Kakita, A. Tsunekawa, *Synlett* **1995**, 711.
- [8] In the reported crystal structure of the Reformatsky reagent ($\text{BrZnCH}_2\text{COO}i\text{Bu}\cdot\text{THF}$)₂, the C–Zn bond was clearly visible: a) J. Dekker, P. H. M. Budzelaar, J. Boersma, G. J. M. van der Kerk, A. L. Spek, *Organometallics* **1984**, *3*, 1403; see also: b) J. Dekker, A. Schouten, P. H. M. Budzelaar, J. Boersma, G. J. M. van der Kerk, A. L. Spek, A. J. M. Duisenberg, *J. Organomet. Chem.* **1987**, *320*, 1; for the configurational stability of organozinc reagents, see: S. Klein, I. Marek, J. F. Normant, *J. Org. Chem.* **1994**, *59*, 2925.
- [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-allenates.
- [11] The reaction of optically active (-)-(R)-**2a** with RMgBr provided the racemic products of conjugate addition.
- [12] For an uncatalyzed addition of a dialkyl zinc reagent to 2-alkenoates with a radical mechanism, see: F. Denes, S. Cutri, A. Perez-Luna, F. Chemla, *Chem. Eur. J.* **2006**, *12*, 6506.