Radical zinc-atom-transfer-based carbozincation of haloalkynes with dialkylzincs

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Abstract
The formation of alkylidenezinc carbenoids by 1,4-addition/carbozincation of dialkylzincs or alkyl iodides based on zinc atom radical transfer, in the presence of dimethylzinc with β-(propargyloxy)enoates having pendant iodo- and bromoalkynes, is disclosed. Formation of the carbenoid intermediate is fully stereoselective at −30 °C and arises from a formal anti-selective carbozincation reaction. Upon warming, the zinc carbenoid is stereochemically labile and isomerizes to its more stable form.

Introduction
The last few years have witnessed a gaining interest in the use of organozinc reagents as nontoxic radical precursors or mediators [1-3]. As part of this development, the so-called radical-polar reactions in which alkylzinc reagents are used as mediators in a radical transformation that affords a new zincated species, have emerged as valuable tools in synthesis. Pivotal to the processes disclosed so far using alkylzinc derivatives is zinc atom radical transfer [4]. In general terms, the reaction involves a radical chain process initiated by the formation of an alkyl radical from the organozinc derivative in the presence of oxygen [5-14]. The newly formed radical then undergoes one or more radical transformations before being reduced by the alkylzinc reagent through homolytic substitution at zinc, producing a new organozinc derivative along with an alkyl radical that sustains a radical chain. Overall, the in situ transformation of simple organozinc reagents into more elaborate ones is thus achieved, and subsequent reaction with electrophiles is possible [15-30].

More specifically, building on well-established addition reactions of carbon-centered radicals to carbon–carbon double and triple bonds, such reactivity has been advantageously employed in the context of carbozincation chemistry [31]. The intramolecular carbozincation of unactivated terminal alkenes following zinc atom transfer processes, including a 5-exo-trig cyclization step, has been reported. This is, for instance, the case in the for-
mation of (pyrrolidinylmethyl)zinc and (tetrahydrofuranyl-methyl)zinc derivatives by reaction of dialkyliczinc, organozinc and copper–zinc mixed reagents with (N-allyl)aminoenotes [32-34] and β-(allylloxy)enoates [35], in the formation of (pyrrolidinomethyl)zinc by condensation of dialkyliczincs with N,N-diallylpropionaldehyde [36], and also in the cyclization of alkenylzinc iodides to cyclopentylmethylzinc iodides, formerly believed to be anionic in nature [4]. Carbozincations of alkynes based on zinc atom transfer have also been disclosed. The reaction of dialkylzincs or of alkyl iodides in the presence of Me₂Zn/O₂ with β-(propargyloxy)enoates entails the intramolecular carbometallation of the pendant alkynes substituted by silyl, alkyl, aryl, alkenyl or amino groups by a 5-exo dig radical cyclization step [37,38]. Intermolecular carbozincation of terminal arylacetylenes [39] and of diethyl acetylenedicarboxylate [40] has been achieved by dialkylzinc-mediated radical additions. Worthy of note is that in some cases the zinc-atom-transfer-based carbozincation of alkynes can occur with anti selectivity [38,40], and thereby represents a complementary approach to transition-metal-mediated carbozincations, which are generally syn-selective [41-46].

To explore further the possibilities offered by zinc atom transfer processes we considered the possibility to prepare alkylidene zinc carbenoids by radical-based carbozincation of haloalkynes. Such carbenoids are multipurpose reagents [47] that are typically prepared from 1,1'-dihaloalkenes, either by lithium/halogen exchange followed by transmetalation with zinc salts or by direct zinc/halogen exchange [48-50]. Alternatively, they can also be prepared by selective monohalogenation of alkylidene gem-bismetallic intermediates [51].

To the best of our knowledge, the preparation of alkylidene zinc carbenoids by the direct carbozincation of haloalkynes has not been reported [52]. As a starting point to develop such an approach, we reasoned that the reaction of dialkyliczincs with β-(propargyloxy)enoates bearing pendant haloalkynes would be ideally suited (Scheme 1). On the one hand it would provide a means to control totally the regioselectivity of the radical addition to the haloalkyne, and on the other hand the envisioned zinc atom transfer to an α-halo vinylc radical should be favorable as a result of the presence of the ester moiety. Hereafter, we disclose our findings concerning this reaction.

Results and Discussion

β-(Propargyloxy)enoates 3a and 3b having a pendant bromoalkyne and an iodoalkyne moiety, respectively, were prepared by condensation of propargylic alcohols 1 with methyl 2-(bromomethyl)acrylate 2 (Scheme 2). Enoate 3a was readily obtained by direct reaction of 3-bromopropargyl alcohol (1a).

By contrast, the reaction of the iodo analogue 1b with 2 proved troublesome as it led to inseparable mixtures of the desired enoate 3b and non-iodinated enoate 3c. Thus, 3b was best prepared by iodinating (AgNO₃/NIS) the terminal alkyne of enoate 3c prepared from propargyl alcohol (1c) and acrylate 2.

According to our previously optimized conditions for the 1,4-addition/carbozincation reaction of dialkyliczincs with β-(propargyloxy)enoates [37,38], bromoalkyne 3a was treated with Et₂Zn at room temperature in Et₂O under an argon atmosphere (Table 1, entry 1). To our delight, following acidic work-up, the expected methylenetetrahydrofuranyl bromide 4aa was obtained in 43% isolated yield as a mixture of diastereoisomers in a 77:23 Z/E ratio [53]. Hydrolysis with D₂O evidenced the intermediate formation of an alkylidene zinc carbenoid as deuterated 4aa-D was produced (Table 1, entry 2). As previously noted in the case of similar 1,4-addition/carbozincation sequences [37,38], deuterium incorporation was nearly quantitative for the Z isomer, and much lower for the E one. More
Table 1: 1,4-addition/carbozincation of dialkylzincs with β-(propargyloxy)enoates 3 having pendant haloalkynes in the presence of traces of air.\textsuperscript{a}

\begin{tabular}{c|cccccc}

| Entry | Enolate | X & Solvent & R & Products (Yield\textsuperscript{b} (\%)) & [dr\textsuperscript{c} (Z/E)] |
|-------|----------|-----|-----|-----|---------------------------------|----------------|
| 1     | 3a       | Br  | Et\textsubscript{2}O | Et  | 4aa (43 [77:23]; 5a (40 [79:21]) |
| 2     | 3a       | Br  | Et\textsubscript{2}O | Et  | 4aa-D\textsuperscript{d} (44 [81(90\% D):19(10\% D)]; 5a-D\textsuperscript{d} (35 [84(85\% D):16(40\% D)]) |
| 3     | 3b       | I   | Et\textsubscript{2}O | Et  | 4ba (40 [98:2]); 5a (21 [82:18]) |
| 4     | 3a       | Br  | Et\textsubscript{2}O | n-Bu| 4ab (76 [70:30]); 5b (7 [nd\textsuperscript{f}]) |
| 5     | 3b       | I   | Et\textsubscript{2}O | n-Bu| 4bb (58 [98:2]) |
| 6     | 3a       | Br  | CH\textsubscript{2}Cl\textsubscript{2} | Et  | 4aa (39\textsuperscript{e} [78:22]; 5a (17\textsuperscript{d} [91:9]) |
| 7     | 3a       | Br  | CH\textsubscript{2}Cl\textsubscript{2} | n-Bu| 4ab (37 [76:24]; 5b (12 [nd\textsuperscript{f}]) |

\textsuperscript{a}Reaction conditions: R\textsubscript{2}Zn (3 equiv), rt, 24 h under Ar atmosphere (see Experimental section).
\textsuperscript{b}Combined yield of diastereomers after chromatography unless otherwise noted.
\textsuperscript{c}Determined by \textsuperscript{1}H NMR analysis of the crude material.
\textsuperscript{d}The reaction mixture was quenched with D\textsubscript{2}O. The percentage of deuterium incorporation is given in parenthesis for each compound.
\textsuperscript{f}Not determined.

unexpectedly, however, 40\% of alkylidenetetrahydrofuran 5a, wherein the bromine atom had been substituted by an ethyl group, was also isolated as a 79:21 Z/E mixture. Deuterium labeled 5a-D\textsuperscript{d} was produced following hydrolysis with D\textsubscript{2}O (Table 1, entry 2), thereby showing that an alkylidenezinc intermediate was being formed in the generation of this side-product under these reaction conditions.

When iodoalkyne 3b was used, a similar 40\% yield of vinyl iodide 4ba was obtained, but in a lower 21\% yield and similar diastereoselectivity (82:18 Z/E ratio). Significantly lower levels of side-product formation arising from halogen substitution were observed when n-Bu\textsubscript{2}Zn was used, thus leading to improved results (Table 1, entries 4 and 5). The reaction with bromoalkyne 3a provided vinyl bromide 4ab in 76\% yield and 70:30 Z/E ratio and only 7\% of 5b. Better, the reaction with iodoalkyne 3b afforded exclusively iodide 4bb in 58\% yield and complete diastereoselectivity in favor of the (Z) isomer. Formation of substitution side-products was also diminished when CH\textsubscript{2}Cl\textsubscript{2} was used as the solvent instead of Et\textsubscript{2}O, even though this had little impact on the efficiency and diastereoselectivity of vinyl halide formation (Table 1, entries 6 and 7). Reaction of Et\textsubscript{2}Zn with 3a provided vinyl bromide 4aa in 39\% yield (78:22 Z/E ratio) and 5a in 17\% yield, while reaction of n-Bu\textsubscript{2}Zn gave 4ab in 37\% yield (76:24 Z/E ratio) and 5b in 12\% yield. It is worthy of note that no difference was observed between the different dialkylzincs in this case.

The formation of alkylidenezinc derivatives 7 leading to compounds 5 is intriguing (Scheme 3). A first possible mechanistic route could involve the reaction of zinc carbenoid 6 and the
excess of dialkylzinc reagent via the intermediate formation of a zincate [48-51] (Scheme 3, path a). The stereoselectivity of such rearrangements is often dependent on the substrate structure, so the diastereopurity of 5 is not necessarily informative about that of 6 [48-51]. An alternative possibility to account for the formation of 7 could be the reaction of the dialkylzinc reagent with enoate 8 arising from a prior substitution of bromoalkyne 3a with the dialkylzinc reagent (Scheme 3, path b). Both the diastereoselectivity and the levels of deuterium incorporation are very close to those obtained for the reaction of diethylzinc with pure 8 [37], which argues in favor of this mechanistic scenario.

To try to discriminate between these possibilities we conducted some additional test experiments (Scheme 4). In agreement with the general consideration that dialkylzinc reagents do not undergo uncatalyzed cross-coupling reactions with bromoalkynes, no reaction was observed between Et2Zn and 1-bromo-hexyne (9) [54]. By contrast, bromoalkyne 11 having a silyloxy group at the propargylic position reacted smoothly to afford ethyl-substituted alkyne 10 along with alkene 12, which had incorporated two ethyl groups. 12 was isolated as a mixture of diastereoisomers in 70:30 dr. The fact that no reaction takes place between pure 10 and Et2Zn indicates that 12 is not formed by carbozincation. Hence, most likely it is formed by the reaction of Et2Zn and carbenoid 13 arising from the carbozincation of 11 (Scheme 4). Moreover, if 13 is indeed formed, it would also lead to alkyne 10 following Fritsch–Buttenberg–Wieschell (FBW) rearrangement [55-57]. Since the presence of the oxygen atom in the propargylic position should facilitate the carbometallation reaction [58], this mechanistic pathway provides a plausible explanation for the fact that bromine substitution occurs from α-oxygenated bromoalkyne 11 and not from 9.

Regarding our 1,4 addition/carbocyclization sequence, these test experiments provide two important pieces of evidence for the behavior of 3a in the presence of a dialkylzinc. First, β-alkoxy bromoalkynes undergo direct substitution with Et2Zn to some extent. Second, alkylidenezinc carbenoids react with dialkylzincs to afford the bromine substitution product. Thus, formation of alkylidenezinc compound 7 (and thereby 5) most probably arises from both depicted mechanistic pathways (paths a and b, Scheme 3). In such a situation, we reasoned that in both possibilities, reducing the reaction time would limit the production of the unwanted side-products by limiting the contact time between the dialkylzinc reagent and either the starting bromoalkyne or the generated zinc carbenoid. Thus, we considered adding air to the reaction media in order to accelerate the oxidation of the dialkylzinc species and therefore radical production (Table 2).

A reduced amount of side-product 5 was indeed observed in the reaction of enoate 3a with Et2Zn in CH2Cl2 at room temperature in the presence of added dry air (Table 2, entry 1). A mixture of vinyl bromide 4aa and alkene 5a in a 84:16 ratio and in 69% overall yield was obtained. However the diastereoselectivity of the formation of 4aa dropped significantly. Lowering the reaction temperature had a highly beneficial impact on the reaction outcome. At 0°C, the formation of 5a was totally suppressed, and 4aa was obtained with a much better diastereoselectivity, though remarkably in favor of the E isomer (Table 2, entry 2). At −30°C, the exclusive and totally diastereoselective formation of (E)-4aa in excellent 89% isolated yield was obtained (Table 2, entry 3). Hydrolysis with D2O led to (E)-4aa-D with 83% deuterium incorporation when either CH2Cl2 or DCE were used as solvent (entries 4 and 5), therefore evidencing the intermediate stereoselective formation of an alkylidene zinc carbenoid. Similar results were obtained by using n-Bu2Zn, indicating that the process is quite general (Table 2, entry 6).

The diastereoselectivity of the formation of 4aa seemed to be dependent not only on the reaction temperature, but also on the total reaction time (compare Table 1, entry 6 and Table 2, entry 1). Suspecting a possible Z/E isomerization of the alkylidene carbenoid intermediate, we conducted an experiment wherein air was added to a mixture of enoate 3a and Et2Zn in CH2Cl2 at −30°C, and the reaction was first kept for 1 h at this temperature and then for 23 h at room temperature (Table 2, entry 10).
14-cyclisation of enoxy radical

exo-dig of radical R to the starting enoate and the subsequent (Scheme 1) and can be rationalized according to the following with our anticipated zinc atom radical transfer mechanism.

The different results obtained for the 1,4-addition/carbozincation of dialkylzincs on 3a in the presence of added air.

Table 2: 1,4-Addition/carbozincation of dialkylzincs on 3a in the presence of added air.

| Entry | R   | Reaction conditions | Products [ratio] | Yield (E/Z) | dr of product 4 (E/Z) |
|-------|-----|---------------------|------------------|-------------|----------------------|
| 1     | Et  | rt, 1 h             | 4aa/(Z)-5a [84:16] | 69%         | 54:46                |
| 2     | Et  | 0 °C, 1 h           | 4aa              | 93%         | 87:13                |
| 3     | Et  | −30 °C, 1 h         | 4aa              | 89%         | >98:2                |
| 4     | Et  | −30 °C, 1 h         | 4aa-D<sup>8</sup> | 96%         | >98(83% D):2         |
| 5     | Et  | −30 °C, 1 h, DCE<sup>f</sup> | 4aa-D<sup>8</sup> | 89%         | >98(83% D):2         |
| 6     | Bu  | −30 °C, 1 h         | 4ab              | 93%         | >98:2                |
| 7     | Et  | −30 °C, 1 h then rt, 24 h | 4aa/(Z)-5a [78:22] | 78%         | 44:56                |
| 8     | Et  | −30 °C, 1 h then rt, 24 h | 4aa-D<sup>8</sup>/(Z)-5a-D<sup>8</sup> [78:22] | 78%         | 44(10% D):56(10% D) |

<sup>a</sup>Reaction conditions: R<sub>2</sub>Zn (3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, dry air was bubbled at once into the reaction mixture, which was then kept under Ar atmosphere (see Experimental section).

<sup>b</sup>Combined yield of products after chromatography unless otherwise noted.

<sup>c</sup>Determined by <sup>1</sup>H NMR analysis of the crude material.

<sup>d</sup>Determined by <sup>1</sup>H NMR spectroscopy based on analysis of the crude mixture with biphenyl as the internal standard.

<sup>e</sup>The reaction mixture was quenched with D<sub>2</sub>O. The percentage of deuterium incorporation is given in parenthesis for each isomer.

<sup>f</sup>DCE = 1,2-dichloroethane was used as solvent instead of CH<sub>2</sub>Cl<sub>2</sub>.

<sup>g</sup>30% deuterium incorporation was observed for product 5a-D.<n

entry 7). Following acidic quench, very similar results to those noted for the same reaction carried out at room temperature (Table 2, entry 1) were observed. 4aa was recovered in 61% yield as a 56:44 mixture of isomers along with alkene (Z)-5a in 22% yield. It is worthy to note that very low levels of deuterium incorporation were observed in this case.

These results have a three-fold consequence. First, they indicate that Z/E isomerization of the alkylidenezinc carbened occurs between −30 °C and room temperature. Second, it demonstrates that alkene 5a can be formed by the reaction between the zinc carbened and Et<sub>2</sub>Zn (Scheme 3, path a), and that in such a case the transformation is stereoselective. Third, when oxygen is introduced into the reaction media, the alkylidenezinc carbened is eventually demetallated upon standing at room temperature.

The different results obtained for the 1,4-addition/carbozincation of enoates having pendant bromoalkynes are consistent with our anticipated zinc atom radical transfer mechanism (Scheme 1) and can be rationalized according to the following scenario (Scheme 5). The process involves the initial 1,4-addition of radical R to the starting enoate and the subsequent 5-exo-dig cyclisation of enoxy radical 14 to provide α-bromovinyl radical 15 of E geometry. Substitution by electron-withdrawing groups slows down E to Z isomerization of vinyl radicals, and therefore, due to the presence of the bromine atom, interconversion of (E)-15 into (Z)-15 should not be fast. Thus, (E)-15 reacts by Zn atom transfer prior to its equilibration to provide stereoselectively carbened (Z)-6 [59] and to some extent by H-atom transfer to give reduced bromoalkene (E)-4 [60]. Upon warming, (Z)-6 isomerizes to its more stable isomer (E)-6 wherein the zinc atom is coordinated intramolecularly to the adjacent ester. To a minor extent, reaction with the excess dialkylzinc present in the reaction media provides alkylidenezinc (E)-7 stereoselectively. Note, however, that in the case where reactions are conducted at room temperature, E/Z equilibration of the intermediate radical 15 should be faster and zinc atom transfer from (Z)-15 may also contribute to the formation of (E)-6.

Two situations are next to be distinguished. Under the conditions involving excess air, carbened 6 is protonated in the reaction media (even though we have not identified the proton source). It is possible that protonation occurs prior to full E to Z isomerization and vinyl bromide 4 is obtained in low diastereoselectivity. Under the conditions involving only a trace of air, after 24 h at room temperature, carbened 6 is still present and
Scheme 5: Mechanistic rationale for the reaction of dialkylzincs with β-(propargyloxy)enoate 3a.

total Z to E isomerization has occurred. The reason why vinyl bromide 4 is only isolated with moderate diastereoselectivity following hydrolysis, is that (E)-4, formed from (E)-15 by H-abstraction, is present from the start.

We finally considered the prospect to carry out the carbozincation of bromoalkynes using a combination of an alkyl iodide and dimethylzinc (Table 3). Towards this end, we first treated enoate 3a with Me₂Zn, following our previously reported optimized conditions for the 1,4-addition/carbozincation of β-(propargyloxy)enoates with Me₂Zn [38], which proceeds in CH₂Cl₂ at 0 °C and under continuous introduction of dry air over a period of 1 h (Table 3, entry 1). After acidic quench, vinylic bromide (E)-4ac [61] was isolated in 77% yield as a single diastereoisomer. The stereoselective formation of an alkylidenezinc carbenoid intermediate was this time evidenced by treating the reaction mixture with iodine (Table 3, entry 2). Vinylic dihalide 16 was isolated in 64% yield, again as a single Z diastereoisomer. Thus, Me₂Zn showed a similar reactivity to its higher homologues Et₂Zn and n-Bu₂Zn, with the additional advantage that no direct formation of vinyl bromide (E)-4ac by hydrogen abstraction was observed.

In the presence of 5 equiv iPrI, a mixture of two (diastereomerically pure) compounds 4ad and 4ac in 87:13 ratio was observed. Incorporation of the iPr moiety was therefore the major reaction pathway. The competitive addition of a Me group could be reduced by increasing the amount of iPrI to 10 equiv (Table 3, entries 3 and 4). However, in this case, significant amounts of vinylic dihalide 17 were also isolated. Thus, if large amounts of iodide are used, radical iodine atom transfer between iPrI and the a-bromovinyl radical 15 resulting from the cyclization step (Scheme 5) becomes competitive with the desired zinc atom transfer and hampers the carbozincation process.

Conclusion

In conclusion, we have shown that β-(propargyloxy)enoates having pendant iodo- and bromoalkynes undergo a 1,4-addition/carbozincation sequence by reaction with dialkylzincs or with alkyl iodides in the presence of dimethylzinc. The sequence involves a radical chain mechanism initiated by air and provides the proof of concept that alkylidenezinc carbenoids can be prepared by carbozincation based on zinc atom transfer. In the disclosed process, we have demonstrated that the formation of a bromocarbenoid intermediate is fully stereoselective at −30 °C and arises from a formal anti-selective carbozincation reaction. Upon warming, the zinc carbenoid is stereochemically labile and isomerizes to its more stable form. In the absence of added air, no decomposition of the carbenoid intermediate is observed at room temperature for at least 24 h. Deuterium labeling and iodolysis experiments evidence that the zinc carbenoids
Table 3: Me$_2$Zn-mediated 1,4-addition/carbozincation of alkyl iodides with 3a in the presence of added air.$^a$

![Diagram](image_url)

| Entry | iPrI (equiv) | E-X | Yield$^b$ (%) | Products [ratio] |
|-------|-------------|-----|---------------|-----------------|
| 1     | 0           | H$_2$O | 77            | 4ac             |
| 2     | 0           | I$_2$  | 64            | 16              |
| 3$^d$ | 5           | H$_2$O | 59            | 4ad/4ac [87:13] |
| 4$^d$ | 10          | H$_2$O | 87            | 4ad/4ac/17 [75:6:19] |
| 5$^d$ | 10          | D$_2$O | 75            | 4ad-D/4ac-D/17 [75 (95% D):6 (95% D):19] |

$^a$Reaction conditions: Me$_2$Zn (5 equiv), iPrI (equiv), CH$_2$Cl$_2$, 0 °C, 20 mL dry air was bubbled during 1 h into the reaction mixture via a syringe pump.

$^b$Combined yield of isolated products after chromatography unless otherwise noted.

$^c$The product was contaminated with ~10% of product resulting from the addition of the dichloromethyl radical (4ae, R = CHCl$_2$).

$^d$3 equiv Me$_2$Zn were used.

Prepared under such reactions can act as typical nucleophiles and should, thus, be well-suited for subsequent functionalization [47-51]. Furthermore, as indicated with the formation of some side-products observed during this work, they should also react readily as electrophiles toward organometallic nucleophiles and undergo intramolecular nucleophilic substitution reactions [47-51].

**Experimental**

Experiments involving organometallic compounds were carried out in dried glassware under a positive pressure of dry Ar. All solvents were distilled to remove stabilizers and dried with a MBRAUN Solvent Purification System SPS-800. n-Bu$_2$Zn (Fluka, ~1 N in heptane), Et$_2$Zn (Aldrich, 1.0 M in hexanes), Me$_2$Zn (Aldrich, 1.0 M in heptane) and all other reagents were of commercial quality and were used without purification. $^1$H NMR, $^{13}$C NMR spectra were recorded with a Bruker AVANCE 400 spectrometer fitted with BBFO probe with Z gradient. Chemical shifts are reported in $\delta$ relative to an internal standard of residual chloroform ($\delta$ 7.27 for $^1$H NMR and 77.16 for $^{13}$C NMR). IR spectra were recorded with an ATR diamond spectrophotometer. High-resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95.

**General Procedure 1. Reaction of n-Bu$_2$Zn and Et$_2$Zn with β-(propargyloxy)enoates 3a and 3b having pendant haloalkynes in the presence of a trace amount of air (Table 1):** Under argon, to a stirred solution of β-(propargyloxy)enoate (0.2 mmol) in Et$_2$O (1 mL) at room temperature was added R$_2$Zn (0.6 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was hydrolyzed with an aqueous solution of HCl (1 M, 10 mL). The layers were separated, the aqueous one being extracted with Et$_2$O (2 × 15 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure, and the residue was purified by flash chromatography (pentane/ether).

**General Procedure 2. Reaction of n-Bu$_2$Zn and Et$_2$Zn with β-(propargyloxy)enoate 3a in the presence of added air (Table 2):** Under argon, to a stirred solution of β-(propargyloxy)enoate 3a (0.2 mmol) in CH$_2$Cl$_2$ (2 mL) at −30 °C was added R$_2$Zn (0.6 mmol). Air (2 mL) was bubbled at once into the solution via a syringe fitted with a CaCl$_2$ guard and the reaction mixture was stirred at −30 °C for 1 h. CH$_2$Cl$_2$ (20 mL) and an aqueous solution of HCl (1 M, 10 mL) were added to quench the reaction. The layers were separated, the aqueous one being extracted with Et$_2$O (2 × 15 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure to afford the crude product.

(Z)-Methyl 4-(bromomethylene)-3-propyltetrahydrofuran-3-carboxylate ((Z)-4aa): Prepared according to general procedure 1 from enoate 3a (50 mg, 0.2 mmol) and Et$_2$Zn (0.6 mL, 1.0 M in hexanes, 0.6 mmol). Purification by flash chromatography with pentane/ether (95:05) as eluent gave the title compound ((Z)-4aa) (19 mg, 33%) as a colorless oil. IR (neat):
(E)-Methyl 4-(bromomethylene)-3-ethyltetrahydrofuran-3-carboxylate ((E)-4aa): Prepared according to general procedure 2 from enoate 3a (47 mg, 0.2 mmol) and Et$_2$Zn (0.6 mL, 1.0 M in hexanes, 0.6 mmol). The title compound ((E)-4aa) was isolated pure (47 mg, 89%) as a colorless oil and did not require further purification. IR (neat): 2960, 2873, 1769, 1730, 1433, 1217, 1122, 1074, 968, 732 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.34 (t, $J = 2.7$ Hz, 1H), 4.42 (d(AB system), $J = 9.1$ Hz, 1H), 4.40 (d br, $J = 2.9$ Hz, 2H), 3.84 (d(AB system), $J = 9.1$ Hz, 1H), 3.74 (s, 3H), 1.90 (m, 1H), 1.68 (m, 1H), 1.24 (m, 2H), 0.91 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.3, 146.6, 100.4, 75.7, 72.8, 58.5, 52.6, 39.5, 18.8, 14.2; HRMS–ESI (m/z): [M + Na]$^+$ calecd for C$_{10}$H$_{15}$O$_2$BrNa: 285.00968; found: 285.00990.

(Z)-4-(iodomethylene)-3-pentyltetrahydrofuran-3-carboxylate ((Z)-4bb): Prepared according to general procedure 1 from enoate 3b (40 mg, 0.14 mmol) and Bu$_2$Zn (0.42 mL, ~1 N in heptane, 0.42 mmol). Purification by flash chromatography with pentane/ether (80:20) as eluent gave the title compound ((Z)-4bb) (28 mg, 58%) as a colorless oil. IR (neat): 2951, 2925, 2856, 1731, 1434, 1230, 1073, 939, 730 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.36 (t, $J = 2.6$ Hz, 1H), 4.49 (d(AB system), $J = 9.1$ Hz, 1H), 4.31 (d br, $J = 2.6$ Hz, 2H), 3.90 (d(AB system), $J = 9.1$ Hz, 1H), 3.74 (s, 3H), 1.90 (m, 1H), 1.66 (m, 1H), 1.40–1.20 (m, 6H), 0.91 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.2, 146.7, 98.5, 78.3, 73.8, 58.5, 52.7, 34.7, 17.9, 14.8; HRMS–ESI (m/z): [M + Na]$^+$ calecd for C$_{10}$H$_{15}$O$_2$BrNa: 285.0097; found: 285.0091.

(E)-Methyl 4-(bromomethylene)-3-isobutyltetrahydrofuran-3-carboxylate ((E)-4ad): Under argon, to a stirred solution of β-(propargyloxy)enoate 3a (47 mg, 0.2 mmol) and iPrI (0.2 mL, 2.0 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added Me$_2$Zn (0.6 mL, 1.0 M in heptane, 0.6 mmol). Air (20 mL) was slowly introduced into the mixture via a syringe pump by using a syringe fitted with a CaCl$_2$ guard. The reaction mixture was then stirred at 0 °C for 1 h. CH$_2$Cl$_2$ (5 mL) was then added, and the reaction was hydrolyzed with an aqueous solution of HCl (1 M, 5 mL). The layers were separated, the aqueous one being extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pentane/ether 80:20) afforded the title compound ((E)-4ad) (38 mg, 77%) as a colorless oil. IR (neat): 2953, 1767, 1731, 1638, 1229, 1138, 1034, 936, 786 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.17 (t, $J = 1.9$ Hz, 1H), 4.41 (dd(AB system), $J = 12.7$, 1.9 Hz, 1H), 4.33 (dd(AB system), $J = 12.7$, 1.9 Hz, 1H), 4.13 (d(AB system), $J = 8.9$ Hz, 1H), 3.98 (d(AB system), $J = 8.9$ Hz, 1H), 3.75 (s, 3H), 2.21 (m, 1H), 2.00 (m, 1H), 0.96 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.2, 146.4, 98.5, 77.9, 73.8, 58.5, 52.6, 25.2, 8.9; HRMS–ESI (m/z): [M + Na]$^+$ calecd for C$_{10}$H$_{15}$O$_2$BrNa: 270.99403; found: 270.99477.
3H), 0.95 (d, J = 8.4 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 173.1, 146.9, 98.6, 78.0, 73.6, 58.1, 52.5, 40.5, 24.9, 24.5, 24.4; HRMS–ESI (m/z): [M + Na]+ calcd for C11H12O3BrNa: 299.02533; found: 299.02606.

(Z)-Methyl 4-(bromiodomethylene)-3-ethyltetrahydrofuran-3-carboxylate (16) (Table 3, entry 2): Under argon, to a stirred solution of β-((propargyloxy)enoate 3a (45 mg, 0.2 mmol) in CH2Cl2 (1 mL) at 0 °C was added Me2Zn (1 mL, 1.0 M in heptane, 1.0 mmol). Air (20 mL) was slowly introduced over 1 h into the solution via a syringe pump by using a syringe fitted with a CaCl2 guard. The reaction mixture was then stirred at 0 °C for 1 h. A solution of I2 (330 mg, 1.3 mmol) in THF (1 mL) was then added at the same temperature, and the mixture was stirred for 1 h. CH2Cl2 (10 mL) followed by an aqueous solution of Na2S2O3 (10%) were added. The layers were separated, the aqueous one being extracted with CH2Cl2 (2 × 10 mL). The combined organic layers were washed with HCl (1 M) (10 mL) and brine (10 mL), dried over MgSO4, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pentane/ether 80:20) afforded the title compound 16 (46 mg, 64%) as a pale yellow oil. IR (neat): 2947, 2878, 1730, 1630, 1500, 1181, 725 cm−1; 1H NMR (400 MHz, CDCl3) δ 4.32 (d, J = 14.0 Hz, 1H), 4.27 (d, J = 14.0 Hz, 1H), 4.24 (d, J = 8.8 Hz, 1H), 4.15 (d, J = 8.8 Hz, 1H), 3.75 (s, 3H), 2.21 (m, 1H), 1.95 (m, 1H), 0.98 (t, J = 7.5 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 172.4, 152.4, 80.1, 79.5, 60.9, 52.8, 41.2, 25.5, 9.0; HRMS–ESI (m/z): [M + Na]+ calcd for C9H12O2BrNa: 396.89067; found: 396.89159.

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The stereochemical assignment was done on the basis of the comparison of the NMR data of 4ac and 4aa. Among others, the chemical shift (δ = 6.17 ppm) and coupling constant of the vinylic proton (J = 1.9 Hz) are indicative of the \( \text{\textit{E}} \)-configuration.

Even though the H-donor has not been identified, competitive H-atom transfer is a frequent side-reaction in the 1,4-addition/cyclization reaction of dialkylzincs with \( \beta \)-(propargyloxy)enoates, see references [37] and [38].

The stereochemical assignment was done on the basis of the comparison of the NMR data of 4ac and 4aa. Among others, the chemical shift (δ = 6.17 ppm) and coupling constant of the vinylic proton (J = 1.9 Hz) are indicative of the \( \text{\textit{E}} \)-configuration.

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