Radical Zinc-Atom Transfer Based Multicomponent Approaches to 3-Alkylidene-Substituted Tetrahydrofurans

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Abstract: A domino 1,4-addition/alkyne carbozincation sequence based on a radical zinc-atom transfer process is disclosed. Two efficient multicomponent approaches to 3-alkylidenetetrahydrofurans from β-(propargyloxy)enoates bearing pendant alkynes (including ynamides) have been established: one involving the direct addition of dialkylzincs, and the second involving the dimethylzinc-mediated addition of alkyl iodides. Both sequences utilize the stereoselective formation of intermediate alkylidenezincs well suited for in situ functionalization with electrophiles.

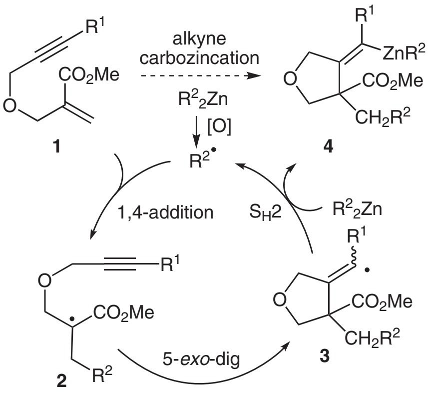
Key words: zinc, radicals, tandem reaction, alkynes, metalation

1 Introduction

The use of organozinc reagents as nontoxic radical precursors or mediators is a field of growing interest.[1] The fast reaction of alkylzincs with oxygen has been known since their discovery[2] and even though its exact mechanism is still under investigation,[3–6] the fact that this oxidation leads to the formation of alkyl radicals has been documented since the late 1960s.[7]

While diethyl- and dimethylzinc are established reagents that initiate or mediate in the presence of oxygen a range of radical reactions,[1,8] radical zinc-atom transfer reactions[9] wherein an alkylzinc is transformed into a more elaborated one via a radical chain transfer mechanism allowing for a so-called radical-polar process are far more rare. Most strategies have been based on the reduction of enoxy radicals by diethyl- or dimethylzinc via homolytic substitution at zinc (S_H2). The zinc enolates produced following radical 1,4-additions[10–13] or from α-iodo esters[14] have then been engaged in situ in 1,2-additions to aldehydes, ketones, imines, or esters or in allylation reactions. Some examples where the resulting species is an alkylzinc that can be further elaborated have also been disclosed.[15] They involve the formation of a primary alkylzinc species by S_H2 reaction of primary radicals with dialkylzincs,[16–19] primary[16b] and secondary[9] organozinc halides, and copper–zinc mixed reagents.[16b,c] Conversely, radical-polar reactions involving the formation of a vinylzinc species are barely known.[20–23]

In this context, some time ago, we reported preliminary results wherein we showed that dialkylzinc derivatives reacted with β-(propargyloxy)enoates to afford the corresponding zincated alkylidenetetrahydrofuran adducts that could then undergo a subsequent in situ reaction.[24] A mechanism based on a radical zinc-atom transfer process was proposed (Scheme 1). In an initiation step, oxidation of the dialkylzinc by traces of oxygen produces a radical that undergoes 1,4-addition onto the α,β-unsaturated ester **1** to afford an enoxy radical **2**. Following 5-*exo*-dig cyclization on the alkyne moiety, a vinyl radical **3** is formed and it reacts subsequently with the dialkylzinc via homolytic substitution to give an alkenylzinc species **4** with concomitant formation of a radical that propagates the chain.



Scheme 1

The 1,4-addition/cyclization radical-polar crossover reaction of zinc reagents with enoates bearing pendant alkynes provides a potential multicomponent approach to polyfunctional five-membered cyclic molecules. In addition to its potential synthetic value, we felt that it could also rep-

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Biographical Sketches

Prof. Fabrice Chemla was born in Paris, France, in 1963. After his diploma degree from the Ecole Supérieure de Physique et Chimie Industrielles de Paris in 1987, he received his Ph.D. in 1990 from the Ecole Normale Supérieure under the supervision of Prof. M. Julia. After a one-year postdoctoral fellowship with Prof. R. W. Hoffmann (Marburg, Germany), he joined Prof. J. F. Normant's group (Paris) as an assistant professor in 1992. He was appointed as a full professor in Université Pierre et Marie Curie (Paris) in 2001. His research interests are focused on the design and the development of new functionalized carbenoids, as well as on carbometalation reactions and the design of new metal-mediated reactions for the total synthesis of biologically useful compounds.

Florian Dulong was born in Bernay, France, in 1986. He studied chemistry at the Ecole Normale Supérieure of Cachan (France) from 2006 to 2010. In 2010, he carried out his M.Sc. thesis at Université Pierre et Marie Curie under the guidance of Prof. F. Chemla and Dr A. Pérez-Luna. He then joined Dr M. Ephritikhine's group at the Laboratoire de Chimie de Coordination des Eléments f, in the Commissariat aux Energies Atomiques et aux Energies Alternatives, France, where he is currently undertaking his Ph.D. studies working on CO and CO_2 activation supported by new redox structures for lanthanides.

Dr Franck Ferreira was born in France in 1968. He obtained an engineer diploma from the Ecole Nationale Supérieure de Chimie de Paris in 1992 and received his Ph.D. from the Université Pierre et Marie Curie Paris VI under the supervision of Prof. J.-P. Genêt in 1996. After a postdoctoral stay with Prof. J.-Y. Lallemand at the Ecole Polytechnique (Palaiseau, France), he was appointed assistant professor in J. F. Normant's group (Université Pierre et Marie Curie, Paris VI) in 1998. He joined Prof. F. Chemla's group in 2001. His current work is focused on the use of 3-hetero-substituted propargylmetals for the asymmetric synthesis of acetylenic aziridines, 1,2-amino alcohols, and biologically interesting compounds.

Max Peter Nüllen was born in Düsseldorf, Germany, in 1981. He studied chemistry at the Westfälische Wilhelms-Universität of Münster (Germany) from 2000 to 2005 and received his diploma thesis in 2005 under the guidance of Prof. B. Witulski. In 2007 he joined the group of Prof. R. Göttlich at the Justus Liebig-Universität in Gieβen, Germany where he is currently carrying out his Ph.D. studies working on the synthesis of sterically hindered biaryls by means of a palladium-catalyzed Ullmann–Ziegler cross-coupling reaction. In 2009 he was a visiting student for six months in Prof. F. Chemla's group at Université Pierre et Marie Curie.

Dr Alejandro Pérez-Luna was born in London, United Kingdom, in 1977. He studied at the Ecole Nationale Supérieure de Chimie de Paris, where he obtained an engineer diploma in 2000. He obtained his Ph.D. in the laboratory of Prof. H.-P. Husson (Paris Descartes University, Paris V) under the guidance of Dr L. Micouin in 2003. After a postdoctoral stay at the University of Geneva (Switzerland) as a Lavoisier Fellow in Prof. E. P. Kündig's group, he obtained a permanent position in CNRS in 2004 and returned to Paris (Université Pierre et Marie Curie, Paris VI) as Chargé de Recherche in Prof. F. Chemla's group. His scientific interests include the fields of metal-mediated synthesis, organozinc chemistry, and asymmetric synthesis.

resent a good working tool that would advance the establishment of a new general entry to the carbozincation of alkynes based on radical zinc-atom transfer. From this twofold perspective, we have investigated the scope and limitations of the reaction, including substrate and nucleophile variations. We disclose hereafter a full account of our work combining our recent advances and, when necessary for the sake of clarity, a reminder of the most significant initial results.

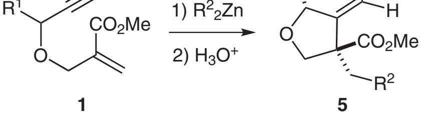
2 1,4-Addition/Cyclization of Dialkylzincs on β-(Propargyloxy)enoates

β-(Propargyloxy)enoates are readily available compounds that are efficiently prepared by reaction of the parent propargylic alcohol and methyl 2-(bromomethyl)acrylate.[24]

2.1 β-(Propargyloxy)enoates with a Pendant Terminal Alkyne

We initiated our studies by considering substrates having a pendant terminal alkyne (Table 1). We were glad to find that dibutyl- and diethylzinc reacted smoothly in diethyl ether at room temperature with enoate **1a** to afford, after acidic workup, the corresponding 1,4-addition/cyclization products **5aa** and **5ab** in 54% and 55% yields (entries 1 and 2). Optimal conditions involved the use of three equivalents dialkylzinc; the use of an equimolar quantity of dialkylzinc generally resulted in lower yields.

Table 1 Reaction of Dialkylzinc Reagents with β-(Propargyloxy)enoates **1a**–**c** with Pendant Terminal Alkynes[a]



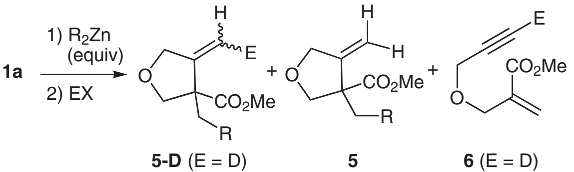
Entry	Enoate	R^1	R^2	Product	Yield[b] (%) [dr][c]
1[d]	**1a**	H	Bu	**5aa**	54 [–]
2[d]	**1a**	H	Et	**5ab**	55 [–]
3[e]	**1b**	pentyl	Bu	**5ba**	60 [75:25]
4	**1c**	Ph	Bu	**5ca**	59 [70:30]

[a] Reaction conditions*:* (1) R^2_2Zn (3 equiv), Et_2O, r.t., 20 h; (2) aq 1 M HCl.
[b] Combined isolated yield after chromatography.
[c] Determined by ^1H NMR analysis of the crude material. Relative configuration as indicated.
[d] Ref. 24.
[e] Bu_2Zn (2 equiv) was used.

Substrates **1b** and **1c** substituted at the propargylic position by a pentyl and a phenyl group respectively, also reacted with dibutylzinc under the same conditions and provided exomethylene-substituted tetrahydrofurans **5ba** (from **1b**) and **5ca** (from **1c**) in good chemical yields (60% and 59%, respectively), albeit as a mixture of diastereomers (dr 75:25 and 70:30, respectively) (entries 3 and 4). The modest level of diastereoselectivity obtained was in line with that observed for the related 1,4-addition/cyclization reactions of β-(allyloxy)enoates.[16d] As a consequence, the relative configuration between the propargylic substituent and the CO_2Me group of the major isomers was assumed to be the same as for β-(allyloxy)enoates.

In order to check for the possibility to functionalize the expected vinylzinc species arising from the tandem sequence, we conducted deuterium labeling experiments (Table 2). Much to our surprise, when the intermediate obtained from dibutylzinc and enoate **1a** was quenched with deuterium oxide (entry 1), even if **5aa-D** was obtained in 33% yield as a mixture of diastereomers in a ratio *E*/*Z* 51:49, reduced **5aa** was also produced in 33% yield. In addition, product **6**, wherein the terminal hydrogen atom of the alkyne had been exchanged by deuterium, was also recovered in 10% yield. A similar trend was observed with other electrophiles (entries 2 and 3). In particular, treatment with iodine led to the formation of vinyl iodide **5aa-I** (ratio *E*/*Z* 55:45) in 24% yield, but also reduced **5aa** was obtained in 37% yield and iodinated starting material **7** in 9% yield. Increasing the number of equivalents of dibutylzinc had a limited (if not negative) impact since similar amounts of deuterium incorporation were obtained (entry 4). Conversely, using diethylzinc, the ratio of zincation versus reduction was increased, but non-metalated **5ab** was still produced in 23% yield. Worthy of note, the *E*/*Z* ratio of the deuterated compounds varied

Table 2 In Situ Functionalization of Vinylzinc Reaction Product of Dialkylzincs with Enoate **1a**[a]

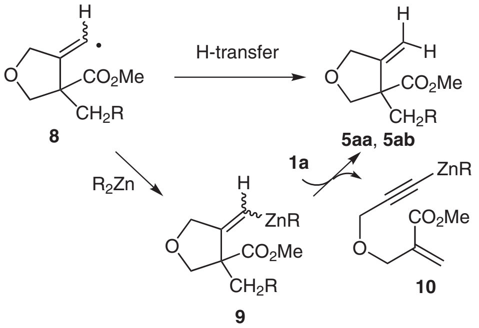


Entry	R	Equiv	E	Products [yield[b] (%) (ratio)]
1[c]	Bu	3	D[d]	**5aa-D** [33 (*E*/*Z*[e] 51:49)], **5aa** [33], **6** [10]
2[c]	Bu	3	D[f]	**5aa-D** [32 (*E*/*Z*[e] 51:49)], **5aa** [35], **6** [7]
3	Bu	3	I[g]	**5aa-I** [24 (*E*/*Z*[e] 55:45)], **5aa** [37], **7** [9]
4	Bu	6	D[d]	**5aa-D** [26 (*E*/*Z*[e] 65:35)], **5aa** [32], –
5	Et	6	D[d]	**5ab-D** [39 (*E*/*Z*[e] 38:62)], **5ab** [23], –

[a] Reaction conditions*:* (1) R_2Zn, Et_2O, r.t., 20 h; (2) D_2O, DCl, or I_2, THF.
[b] Determined by ^1H NMR spectroscopy based on analysis of the crude mixture with biphenyl as internal standard.
[c] Ref. 24.
[d] EX = D_2O.
[e] Determined by ^1H NMR analysis of the crude material. Assignment was based on NOE experiments on **5ag** (R = *t*-Bu).
[f] EX = DCl.
[g] EX = I_2 in THF.

both with the amount and the nature of the dialkylzinc used, even though low diastereoselectivities were recorded in all cases.

The formation of non-deuterated **5aa** and **5ab** was unforeseen. On the basis of the presence of products **6** and **7** that provided evidence for the formation of an alkynyl anion **10** in the reaction medium, we first considered deprotonation of the starting terminal alkyne **1a** by the formed vinyl species **9** as a possible reaction pathway (Scheme 2).[25] However, to be consistent with the observed yields higher than 50%, this possibility implies the formation of a *gem*-Zn,Zn-bimetalated species but this was not detected after either deuterium or iodine quench.[26] In fact, recovery of **6** and **7** rather seems to indicate that **10** does not undergo the 1,4-addition/cyclization sequence readily. Therefore, it seems reasonable to consider that, while in situ protonation of **9** to some extent cannot be ruled out,[27] compounds **5aa** and **5ab** arise mainly from reduction of the intermediate vinyl radical **8** by hydrogen-atom abstraction. The possibility of an intramolecular hydrogen shift can be eliminated based on the fact that no deuterium incorporation has been detected by ^{2}H NMR elsewhere in the molecule.[26] H-Abstraction must, consequently, occur intermolecularly. Even though they remain unidentified, possible hydrogen-atom donors might include molecules leading to α-alkoxyalkyl radicals[1b] (i.e., the solvent, the starting propargylic ethers or the final tetrahydrofurans) but also alkylzinc or alkoxyzinc species.[17] Consistent with this picture, it can be argued that the higher metalation ratio obtained with diethylzinc over dibutylzinc is related to an easier zinc-atom transfer as a result of a weaker C–Zn bond.[6] Finally, concerning the diastereoselectivity of vinylzinc formation, no clear-cut conclusion can be advanced (besides the fact that it is low in all cases), as we have no means to estimate the possible consumption of **9** by protonation that might be stereoselective and substrate dependent.

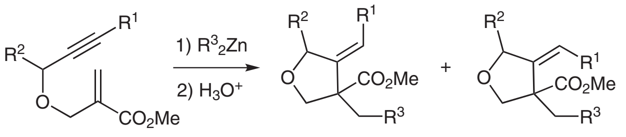


Scheme 2

2.1 β-(Propargyloxy)enoates with a Pendant Substituted Alkyne

Substrates possessing ethyl- or trimethylsilyl-substituted alkynes were next examined (Table 3). Reaction of dibutylzinc with ethyl-substituted enoate **1d** afforded, after hydrolysis, alkylidenefuran **5da** in 64% yield as a 64:36 *Z*/*E* mixture (entry 1). In contrast, and to our pleasure, in the case of TMS-substituted enoate **1e**, reaction with dibutyl- and diethylzinc provided the corresponding vinylsilanes (*Z*)-**5ea** and (*Z*)-**5eb** in good to excellent yields (67% and 91%, respectively) and in diastereomerically pure form (entries 2 and 3). Similarly, the addition of dibutylzinc onto **1f** led to the formation of two diastereomeric (*Z*)-**5fa** vinylsilanes in 61% combined yield in a 71:29 ratio (entry 4). Thus, in spite of the fact that, as previously, the levels of diastereocontrol of the propargylic center on the newly created stereogenic center were only moderate, the presence of a substituent in the propargylic position was well tolerated and had no influence on the *Z*/*E* selectivity.

Table 3 Reaction of Dialkylzincs with β-(Propargyloxy)enoates Having Ethyl- and TMS-Substituted Alkynes[a]



Entry	Enoate	R^1	R^2	R^3	Product	Yield[b] (%)	Ratio[c] (*Z*/*E*)
1[d]	**1d**	Et	H	Bu	**5da**	64	64:36
2[d]	**1e**	TMS	H	Bu	**5ea**	67	>95:5
3[d]	**1e**	TMS	H	Et	**5eb**	91	>95:5
4	**1f**	TMS	Ph	Bu	**5fa**[e]	61[f]	>95:5
5[d]	**1e**	TMS	H	*i*-Pr[g]	**5ec**	49[h]	>95:5

[a] Reaction conditions: (1) $R^3{}_2Zn$ (3 equiv), Et_2O, r.t., 20 h; (2) aq 1 M HCl.

[b] Isolated yield after chromatography.

[c] Determined by ^{1}H NMR analysis of the crude material; *Z*/*E* assignment was on the basis of NOE experiments, see ref. 24 and Supporting Information.

[d] Ref. 24.

[e] A 71:29 mixture of two diastereomeric (*Z*)-vinylsilanes was obtained.

[f] Determined on the crude ^{1}H NMR with biphenyl as internal standard.

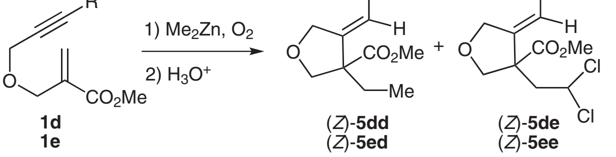
[g] Prepared salt-free from *i*-PrMgCl.[28]

[h] 40% of 3-(trimethylsilyl)prop-2-yn-1-ol was isolated.

As illustrated by the reaction of diisopropylzinc with **1e**, the use of secondary dialkylzinc reagents was also possible (entry 5). Diastereomerically pure (*Z*)-**5ec** was obtained in 49% yield. However, 3-(trimethylsilyl)prop-2-yn-1-ol was also recovered in 40% yield. While it seems likely that the propargylic alcohol arises from a competitive process involving the β-fragmentation of a zinc enolate,[16d] it is not clear why enolate formation occurs with secondary dialkylzincs and not with primary ones. One might put forward that since homolytic substitution at zinc is easier in the case of diisopropylzinc (the C–Zn bond is weaker[29] and a secondary *i*-Pr radical is produced) reduction to a zinc enolate of the intermediate enoxy radical arising from radical 1,4-addition might occur.

Prompted by a report on the formation of alkenylzinc intermediates by reaction of tetrahydrofuran with phenylacetylenes in the presence of dimethylzinc/oxygen,[20] we also became interested in the possibility of using dimethylzinc for our 1,4-addition/cyclization process. Not surprisingly, owing to the fact that the oxidation of dimethylzinc is slower than that of other dialkylzincs,[6,30] no reaction occurred between dimethylzinc and **1e** under our previously optimized conditions involving the use of diethyl ether as solvent under an argon atmosphere containing only traces of oxygen. We, thus, examined the conditions reported for radical 1,4-additions of dimethylzinc wherein dichloromethane is used as the solvent and air is bubbled into the reaction medium.[10e] After some experimentation, we found that **1e** reacted with dimethylzinc (5 equiv) completely within two hours at 0 °C in dichloromethane under bubbling air (Table 4, entry 1). Following acidic hydrolysis, vinylsilane (*Z*)-**5ed** was obtained in 73% yield and in diastereomerically pure form. Furthermore, ethyl-substituted enoate **1d** also reacted smoothly and afforded vinylsilane (*Z*)-**5dd** in a somewhat lower 44% yield (entry 2), but interestingly as a single isomer, in sharp contrast with the addition of dibutylzinc (Table 3). Both (*Z*)-**5ed** and (*Z*)-**5dd** were, however, contaminated with around 10% of (*Z*)-**5ee** and (*Z*)-**5de**, respectively, arising from the addition of the dichloromethyl radical to **1d**. 1,2-Dichloroethane was thus used as the solvent and (*Z*)-**5ed** and (*Z*)-**5dd** were obtained pure in 76% and 56% yields, respectively. In 1,2-dichloroethane, however, six equivalents dimethylzinc were required to reach full conversion of the starting acceptors.

Table 4 Reaction of Dimethylzinc with β-(Propargyloxy)enoates Having Ethyl- and TMS-Substituted Alkynes[a]

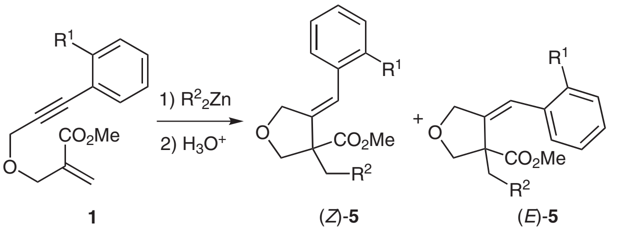


Entry	Enoate	R	Me_2Zn (equiv)	Solvent	Product (s)	Yield[b] (%) [ratio][c]
1	**1e**	TMS	5	CH_2Cl_2	**5ed/5ee**	73 [90:10]
2	**1d**	Et	5	CH_2Cl_2	**5dd/5de**	44 [89:11]
3	**1e**	TMS	5	DCE	**5ed**	53
4	**1e**	TMS	6	DCE	**5ed**	76
5	**1d**	Et	6	DCE	**5dd**	56

[a] Reaction conditions: (1) Me_2Zn, solvent, dry air (20 mL) bubbled through at 0 °C for 1 h, then 0 °C, 1 h; (2) aq 1 M HCl.
[b] Combined isolated yield after chromatography.
[c] Determined by ^1H NMR analysis of the crude material.

Enoates with aryl-substituted pendant alkynes also underwent the addition/cyclization process smoothly (Table 5). Reaction of dibutyl- or diethylzinc with **1g** and **1h** in diethyl ether afforded the corresponding styrenes **5** in good yields (71–81%). However, the diastereoselectivity varied with the aryl substitution. While a 90:10 *Z*/*E* ratio was obtained with acceptor **1g** having no substituent on the aryl moiety (entries 1 and 2), barely any selectivity was observed with **1h** having an *ortho* methoxycarbonyl substituent (entries 4 and 5). This drop in selectivity occurred regardless of the solvent used (Et_2O or CH_2Cl_2[31]). In contrast, dimethylzinc was found to react both with **1g** and **1h** to afford the corresponding styrenes **5gd** and **5hd** with excellent diastereoselectivity (>95:5 *Z*/*E* ratio), albeit in somewhat lower yields (entries 3 and 6).

Table 5 Reaction of Dialkylzincs with β-(Propargyloxy)enoates Having Aryl-Substituted Alkynes[a,b]

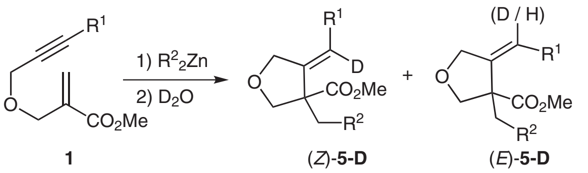


Entry	R¹	Enoate	R^2_2Zn (equiv)	Solvent	Product	Yield[c] (%) [ratio *Z*/*E*][d]
1[e]	H	**1g**	Bu_2Zn[a] (5)	Et_2O	**5ga**	81 [88:12]
2[e]	H	**1g**	Et_2Zn[a] (3)	Et_2O	**5gb**	79 [90:10]
3	H	**1g**	Me_2Zn[b] (5)	CH_2Cl_2	**5gd**	57 [>95:5]
4	CO_2Me	**1h**	Bu_2Zn[a] (3)	Et_2O	**5ha**	71 [59:41]
5	CO_2Me	**1h**	Bu_2Zn[a] (3)	CH_2Cl_2	**5ha**	71 [40:60]
6	CO_2Me	**1h**	Me_2Zn[b] (5)	CH_2Cl_2	**5hd**	27[f] [>95:5]

[a] Reaction conditions: (1) R^2_2Zn, solvent, r.t., 20 h; (2) aq 1 M HCl.
[b] Reaction conditions: (1) Me_2Zn, CH_2Cl_2, dry air (20 mL) bubbled through at 0 °C for 1 h, then 0 °C, 1 h (2) aq 1 M HCl.
[c] Isolated yield after chromatography.
[d] Determined by ^1H NMR analysis of the crude material. *Z*/*E* assignment was on the basis of NOE experiments, see ref. 24 and supporting information.
[e] Ref. 24.
[f] The product was contaminated with ~10% of product resulting from the addition of the dichloromethyl radical ($R^2 = CHCl_2$; *Z*/*E* >95:5).

In order to determine if the 1,4-addition/cyclization reaction leads to the formation of an alkylidenezinc species in the case of substrates having substituted alkynes, deuterium labeling experiments were carried out (Table 6). In the preliminary account of this work, we had shown that fully metalated adducts were obtained from reactions involving TMS- or phenyl-substituted enoates **1e** and **1g** that were highly *Z* selective (see, for instance, entry 1). The intermediate alkenylzinc adducts could thus be reacted with various electrophiles in a second in situ reaction. Conversely, for adduct **5da** arising from ethyl-substituted enoate **1d** as a mixture of diastereomers, whereas complete deuterium labeling was observed for the (*Z*)-**5da-D** isomer, only partial labeling was observed for the (*E*)-**5da-D** isomer (entry 2). This trend was further confirmed with the reaction of dibutylzinc with acceptor **1g** (entry 3). Even though the pendant alkyne was substituted by an aryl group, full deuterium incorporation was observed for the (*Z*)-**5ga-D** isomer, but only 17% for the (*E*)-**5ga-D** isomer.

Table 6 Deuterium Labeling of Vinylzinc Reaction Product of Dialkylzincs with Enoates Having Substituted Pendant Alkynes[a,b]



Entry	Enoate	R^1	R^2	Product	Yield[c] (%) [ratio *Z*/*E*][d]
1[e]	**1e**	TMS	Bu[a]	**5ea-D**	83 [>95:5][f]
2[e]	**1d**	Et	Bu[a]	**5da-D**	78 [66:34][g]
3	**1g**	$2\text{-}MeO_2CC_6H_4$	Bu[a]	**5ga-D**	78 [59:41][h]
4	**1e**	TMS	Me[d]	**5ed-D**	73[i] [>95:5][j]

[a] Reaction conditions: (1) Bu_2Zn (3 equiv), Et_2O, r.t., 20 h; (2) D_2O.

[b] Reaction conditions: (1) Me_2Zn (5 equiv), CH_2Cl_2, dry air (20 mL) bubbled through at 0 °C for 1 h, then 0 °C, 1 h; (2) D_2O.

[c] Combined isolated yield after chromatography.

[d] Determined by ^1H NMR analysis of the crude material.

[e] Ref. 24.

[f] *Z*-Isomer 99% D.

[g] *Z*-Isomer 92% D, *E*-isomer 47% D.

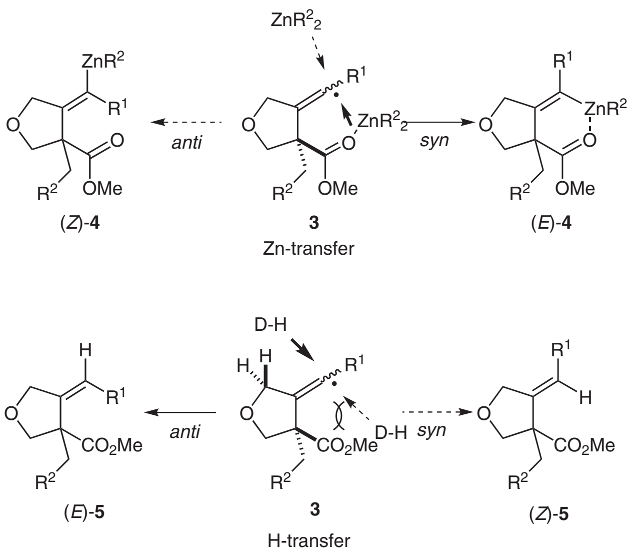
[h] *Z*-Isomer 99% D, *E*-isomer 17% D.

[i] The product was contaminated with 8% of the product arising from the addition of the dichloromethyl radical ($R^2 = CHCl_2$; *Z*/*E* >95:5 *Z*-isomer 98% D).

[j] *Z*-Isomer 98% D.

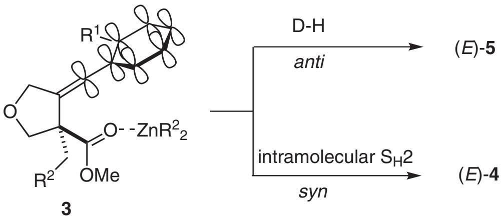
It was also important to check vinylzinc formation in the case of reactions involving dimethylzinc as this dialkylzinc is less prone to homolytic substitution at zinc (the C–Zn bond is stronger[29] and it leads to the production of a high energy methyl radical). Gratifyingly, 98% D-incorporation was obtained for the (*Z*)-**5ed-D** adduct resulting from dimethylzinc and **1e** (entry 4), indicating that H-abstraction did not interfere with the S_H2 step.

The diastereoselectivity of the 1,4-addition/cyclization process arises from the stereoselectivity of the zinc-atom radical transfer, since vinylzincs are configurationally stable.[32] To rationalize it, we propose an interpretation based on a kinetically controlled S_H2 step depending both on a directing effect brought about by the methoxycarbonyl group and on the structure (linear or bent)[33,34] of the vinyl radical being reduced. As a result of pre-coordination to the ester group of the dialkylzinc undergoing homolytic substitution, zinc-atom transfer occurs preferentially from the *syn* side (Scheme 3). Conversely, competitive intermolecular H-atom transfer takes place only from the *anti* side, less sterically hindered (Scheme 3).



Scheme 3

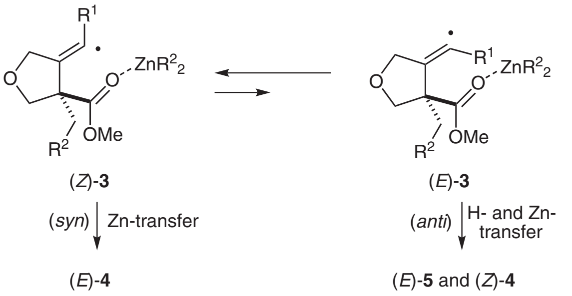
For linear sp hybridized radicals (**3**, R^1 = aryl), the competition between metalation and reduction reflects the relative transfer rate of zinc atom (mainly from the *syn* side) versus hydrogen atom (only from the *anti* side) (Scheme 4). Seemingly, the electronic nature of the styryl radical being reduced influences this relative rate. Whereas in the case of substrate **1g** leading to a phenyl-substituted styryl radical (**3**, R^1 = Ph), Zn-transfer (*syn*) overrides H-transfer (*anti*), in the case of substrate **1h** having an electron-withdrawing *ortho*-substituted phenyl ring (**3**, $R^1 = 2\text{-}MeO_2CC_6H_4$) H-abstraction competes with homolytic substitution. We cannot, however, provide a convincing explanation for this trend.



Scheme 4

Bent sp^2 hybridized radicals (R^1 = TMS, Et) are considered to exist in two diastereomeric forms and to invert with a very low barrier. Thus, the final reaction outcome depends both on the relative ease of each form to undergo zinc- or hydrogen-transfer and on the *Z*/*E* ratio (Scheme 5). With ‘big’ R^1 substituents (i.e., R^1 = TMS[35]), the *Z*/*E* equilibrium is largely in favor of the *Z* form that can only react from the *syn* side. Thus, solely zinc transfer is observed. With ‘smaller’ R^1 substituents (i.e., R^1 = Et), the concentration of (*E*)-**3** increases. Since it reacts exclusively from the *anti* side, H-transfer becomes competitive.

The outcome of the reactions where dimethylzinc is used can also be interpreted according to this model but they



Scheme 5

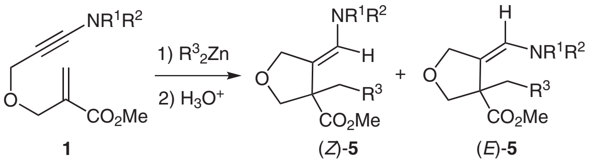
merit further comment. For all the substrates studied, the exclusive formation of (*E*)-alkylidenezincs (*E*)-**4** was observed. Thus, zinc transfer from the *anti* side did not occur, consistent with the fact that as dimethylzinc is less prone to homolytic substitution at zinc, activation by precoordination to the Lewis basic methyl ester was necessary. Worthy of note, in spite of a less favorable Zn-transfer, no competitive H-transfer took place.

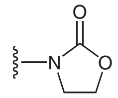
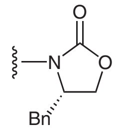
2.3 β-(Propargyloxy)enoate with a Pendant Ynamide

Seeking to produce even more functionalized alkenylzinc derivatives, we next became interested in the use of pendant ynamides since ynamides stabilized by an electron-withdrawing group on nitrogen have been recently shown to be excellent substrates for regioselective carbometalation.[36–38] Furthermore, as ynamides are electron-rich radical acceptors[39–41] we felt that they would be well suited to our radical-polar crossover sequence involving the addition of an electron-deficient enoxy radical.

The required enoates were readily prepared by reaction of methyl 2-(bromomethyl)acrylate and propargylic alcohols containing ynamide functionalities.[42] With them in hand, we investigated the 1,4-addition/cyclization process (Table 7). Acyclic *N*-tosyl ynamide **1i** reacted with diethylzinc to afford, after acidic hydrolysis, enamide **5ib** in a reasonable 47% yield, but with very poor diastereoselectivity. Pleasingly, a much better *E*/*Z* ratio was obtained for enamides **5jb** (*E*/*Z* 82:18) and **5ja** (*E*/*Z* 90:10) arising from the reaction between diethyl- and dibutylzinc and cyclic oxazolidin-2-one-derived ynamide-containing enoate **1j** (the *E* configuration of **5ja** and **5jb** was assigned by NOE experiments[42]). However, product purification proved problematic as a consequence of their low solubility, and only low isolated yields were obtained in these two cases. Finally, in an attempt to prepare non-racemic enamides, we investigated the reaction of diethylzinc with ynamide **1k** derived from an enantiopure oxazolidin-2-one. Disappointingly, though not unsurprisingly, in spite of a good 51% chemical yield, a 55:45 mixture of two diastereomeric (*E*)-enamides was obtained. Thus, the selectivity of the alkenylzinc formation was high, but barely any induction was obtained from the chiral inductor.

Table 7 Reaction of Dialkylzincs with β-(Propargyloxy)enoates Having Pendant Ynamides[a]



Entry	Enoate	NR^1R^2	R^3	Product	Yield[b] (%)	dr (*Z*/*E*)[c]
1	**1i**	NTsBn	Et	**5ib**	47	54:46
2	**1j**		Et	**5jb**	28	18:82
3	**1j**		Bu	**5ja**	27	10:90
4	**1k**		Et	**5kb**	52	2:98 (55:45)[d]

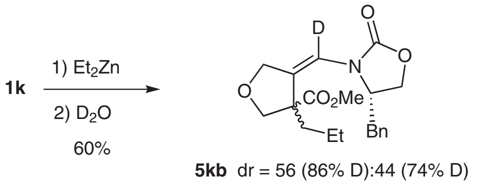
[a] Reaction conditions: (1) R^3_2Zn (3 equiv), Et_2O, r.t., 20 h; (2) aq 1 M HCl.

[b] Combined isolated yield after chromatography.

[c] Determined by ^1H NMR analysis of the crude material.

[d] A 55:45 mixture of two diastereomeric (*E*)-enamides was obtained.

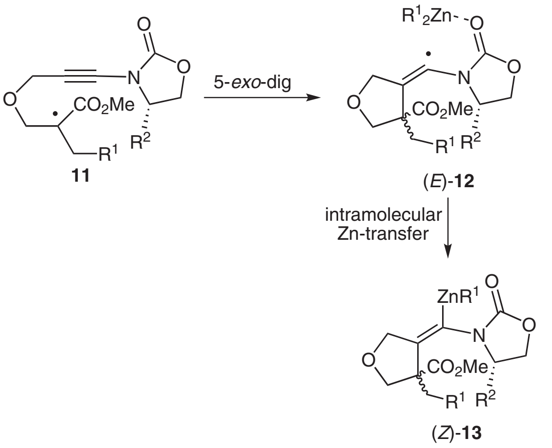
Deuteration of the product mixture arising from the reaction between diethylzinc and **1k** was investigated (Scheme 6). High levels of deuterium incorporation (86% and 74%) were obtained for both diastereomers of (*E*)-enamide **5kb**, indicating that, unlike for other substituted alkynes, even though zincation of the intermediate vinylic radical by homolytic substitution at zinc occurred from the side opposite to the methoxycarbonyl group, competitive H-transfer was only a minor side reaction. As a consequence, this reaction corresponds to an *anti* carbometalation process of the ynamide. This is of significant interest since previously reported anionic carbometalation of ynamides were found to be *syn*.[36–38]



Scheme 6

Following our above-described model, the results obtained with oxazolidinone-derived ynamides can be rationalized as following (Scheme 7). According to previous reports on radical additions to ynamides stabilized by electron-withdrawing groups on nitrogen, 5-*exo-dig* cyclization of enoxy radical **11** resulting from the 1,4-addition step should lead to a vinyl radical **12** of *E* geometry (two in the case of substituted oxazolidinone **1k** since no chiral induction is observed). As a consequence of the electronegative nitrogen, interconversion of (*E*)-**12** into

(*Z*)-**12** (not represented in the scheme) should not be fast.[40] Complexation to the carbonyl group of the oxazolidinone moiety activates the dialkylzinc towards homolytic substitution and thus directs the zinc-atom transfer to produce stereoselectively vinylzinc (*Z*)-**13**.



Scheme 7

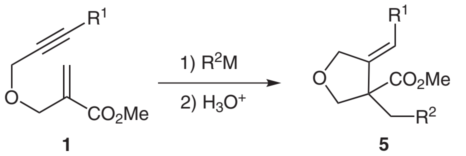
3 1,4-Addition/Cyclization of Alkylzinc Halides on β-(Propargyloxy)enoates

Seeking an additional synthetic value for our 1,4-addition/cyclization protocol, we envisaged using organozinc halides (RZnX) as nucleophiles.[43] These species show a high functional group tolerance, are more readily available than dialkylzincs, and are suitable for zinc-atom transfer based processes.[16b]

Gratifyingly, two equivalents of butylzinc bromide–lithium bromide obtained by transmetalation of butyllithium with zinc bromide reacted in diethyl ether with enoate **1a** having a pendant terminal alkyne to afford, after hydrolysis, methylenefuran **5aa** in 46% yield (Table 8, entry 1). Unfortunately, this yield could not be significantly improved by modification of the reaction conditions. While no difference was observed when zinc chloride was used instead of zinc bromide to prepare the organozinc reagent (entry 2), a decrease in conversion (with the same yield based on recovered starting material though) was noted when zinc iodide was used (entry 3). Copper–zinc mixed reagent Bu(CuCN)ZnBr·LiBr also afforded **5aa**, but again in a comparable 40% yield (entry 6). Finally, the only slight progress was achieved by increasing the amount of organozinc reagent. Using six equivalents of butylzinc bromide–lithium bromide, **1a** yielded 53% of **5aa** (entry 5). Interestingly however, the procedure was also well suited to secondary and tertiary organozinc halides (entries 7 and 8). Indeed, addition of *sec*-butyl- and *tert*-butylzinc bromide–lithium bromide (2 equiv) led in 41% yield to **5af** and **5ag**, respectively.

Disappointingly, attempts to functionalize a putative vinylzinc intermediate were unsuccessful. Following reaction of butylzinc bromide–lithium bromide with **1a** and subsequent treatment with deuterium oxide or iodine, only the reduced compound **5aa** was isolated in 48% and 51% yields, respectively. Thus, in the case of organozinc halides, hydrogen-atom transfer seems to override homolytic substitution (but still enables propagation of a radical chain) (Scheme 8).

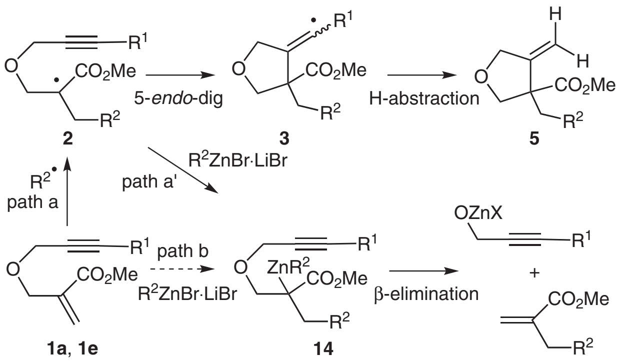
Table 8 Reaction of Alkylzinc Reagents with β-(Propargyloxy)enoates **1a** and **1e**[a]



Entry	Enoate	R^1	R^2M (equiv)[a]	Product	Yield (%)
1	**1a**	H	BuZnBr·LiBr (2)[b]	**5aa**	46[c]
2	**1a**	H	BuZnCl·LiCl (2)[b]	**5aa**	42[d]
3	**1a**	H	BuZnI·LiI (2)[b]	**5aa**	28[d,e]
4	**1a**	H	BuZnBr·LiBr (3)[b]	**5aa**	46[d]
5	**1a**	H	BuZnBr·LiBr (6)[b]	**5aa**	53[d]
6	**1a**	H	BuZn(CuCN)Br·LiBr (2)[f]	**5aa**	40[d]
7	**1a**	H	*s*-BuZnBr·LiBr (2)[b]	**5af**	41[c]
8	**1a**	H	*t*-BuZnBr·LiBr (2)[b]	**5ag**	41[c]
9	**1e**	TMS	BuZnBr·LiBr (3)[b]	**5ea**	24[c]
10	**1e**	TMS	BuZnBr (5) + $ZnBr_2$ (2.5)	**5ea**	76[d]
11	**1e**	TMS	Bu_2Zn·2 LiBr (3)[b]	**5ea**	22[c,g]

[a] Reaction conditions: (1) BuM, Et_2O, r.t., 20 h; (2) aq 1 M HCl.
[b] Prepared from salt-free R^2Li and ZnX_2.
[c] Isolated yield after chromatography.
[d] Yield determined by ^1H NMR spectroscopy based on analysis of the crude mixture with biphenyl as internal standard.
[e] 41% yield was obtained based on recovered starting material.
[f] Prepared from salt-free BuLi, CuCN, and $ZnBr_2$.
[g] 70% of 3-(trimethylsilyl)prop-2-yn-1-ol was isolated.

Moreover, the 1,4-addition/cyclization process with organozinc halides could not be generalized to other substrates. Reaction between TMS-substituted enoate **1e** only yielded **5ea** in a very poor 24% yield (entry 9). Suspecting



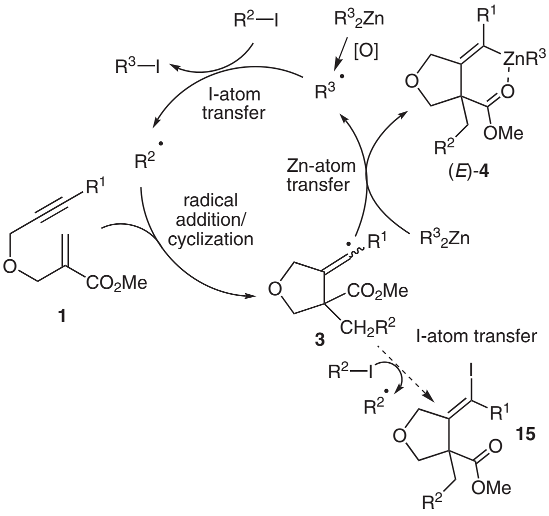
Scheme 8

a deleterious influence of the lithium bromide present in the reaction mixture, we conducted two control experiments (entries 10 and 11). In the first one (entry 10), butylzinc bromide was prepared via the equilibration between dibutylzinc and zinc bromide via the Schlenk equilibrium.[44] Even in the presence of excess zinc bromide, **5ea** was produced in 76% yield, a similar result to that of the reaction with dibutylzinc (see Table 3, entry 2). In the second one, non-salt-free dibutylzinc prepared by mixing butyllithium (2 equiv) and zinc bromide (1 equiv) was reacted with **1e**. In sharp contrast with the results obtained using salt-free dibutylzinc, **5ea** was produced in only 22% yield and 3-(trimethylsilyl)prop-2-yn-1-ol was isolated in 70% yield.

The formation of the latter is indicative of the role played by lithium halides as it most likely implies the intermediate formation of a zinc enolate and its subsequent anionic β-elimination (Scheme 8). A similar observation had been made in our previous studies regarding additions on β-(allyloxy)enoates.[16d] At the time, we suggested that preferential formation of zinc enolate **14** in the presence of lithium bromide could be related to the formation of an ate complex such as ($BuZnBr_2^-$, Li^+) that could either make possible an initial polar conjugate addition or undergo SH2 with radical **2** more readily than butylzinc bromide. In light of both these new results and our previous observations involving cyclization on alkenes, it seems that the extent of 'anionic' β-fragmentation increases when the rate of the radical cyclization decreases (it is known that hex-5-ynyl radical undergoes 5-*exo*-cyclization with a slower rate than hex-5-enyl radical).[45] While we cannot put forward a definitive answer, this trend is rather consistent with an enhanced reduction rate of α-alkoxycarbonyl radical **2** by S_H2 in the presence of lithium halides, that can thus eventually compete with radical cyclization depending on the ease of cyclization of the radical.

4 Dialkylzinc-Mediated 1,4-Addition/Cyclization of Alkyl Iodides on β-(Propargyloxy)enoates

Given the modest results obtained for the addition of organozinc halides, to try to broaden the synthetic scope of our domino sequence, we next considered an alternative approach depicted in Scheme 9. Building on the established dialkylzinc-mediated radical additions of alkyl iodides,[10,17,46–48] we reasoned that an iodine-atom transfer step could be advantageously combined with the zinc-atom radical transfer to provide a new radical-polar process. The radical arising from the oxidation of the dialkylzinc could react with an alkyl iodide to give a new radical that would then undergo the 1,4-addition/cyclization sequence. Reduction of the resulting radical by the dialkylzinc reagent would then produce a vinylzinc and a radical to propagate the radical chain. Thus, in the end, the zinc reagent would ensure the metalation step and could, thus, be simple and readily (commercially) available, while the 'nucleophilic' fragment being added would come from easy-to-access alkyl iodides.



Scheme 9

Success of such an approach relies upon two significant features. First, iodine-atom transfer between radical R^3 arising from the dialkylzinc and the alkyl iodide has to override competitive 1,4-addition on the Michael acceptor. Second, vinyl radical **3** resulting from the 1,4-addition/cyclization has to undergo the S_H2 reaction faster than competitive iodine-atom transfer with the alkyl iodide.

Looking for a proof of concept, we first investigated the addition of isopropyl iodide to several substrates in the presence of dimethylzinc. This reagent was chosen, first because in this case the chain would be propagated by a poorly nucleophilic methyl radical[49] (ensuring low 1,4-addition rates) and second, because complete diastereoselective metalation had been observed for all the acceptors.

Using our previously established reaction conditions, TMS-substituted enoate **1e** was treated in dichloromethane at 0 °C with five equivalents of isopropyl iodide in the presence of three equivalents of dimethylzinc (Table 9, entry 1). Following acidic quench, the formation in a good 60% yield of only two (diastereomerically pure) compounds **5ec** and **5ed** in 87:13 ratio was observed. This ratio could be increased to 93:7 (in 68% overall yield) when ten equivalents of isopropyl iodide were used (entry 3). These results indicated first that, in spite of some competitive addition of a methyl group, addition of the isopropyl moiety was the major reaction pathway and second, that vinyl iodide formation was not taking place. Furthermore, deuterium-labeling studies indicated full deuterium incorporation in **5ec**-**D** and **5ed**-**D** (entry 2). In consequence and as anticipated, an iodine-atom transfer could be efficiently included into our radical 1,4-addition/cyclization zinc-atom transfer process. Interestingly, the use of dichloromethane was not a problem for these reactions since only traces of products resulting from the addition of the dichloromethyl radical were observed.

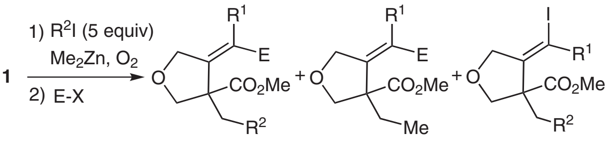
A similar reaction outcome was obtained with aryl-substituted acceptors (entries 4–7). In the presence of five equivalents of isopropyl iodide, enoate **1g** or **1h** led to a mixture of **5gc** and **5gd** or **5hc** and **5hd** in 85:15 or 84:16 and 58% or 50% overall yield, respectively. Again, providing evidence for the intermediate formation of a vinylzinc species, full deuterium incorporation was observed for adducts **5gc-D**, **5gd-D**, **5hc-D**, and **5hd-D** when the reactions were quenched with deuterium oxide.

In contrast, following reaction under the same conditions, enoate **1d** having a pendant ethyl-substituted alkyne led to the formation not only of alkylidenetetrahydrofurans **5dc** and **5dd**, but also of vinyl iodide (*Z*)-**15dc** [**5dc**/**5dd**/(*Z*)-**15dc** 71:15:14] (entry 8). Quenching with deuterium oxide afforded **5dc-D** and **5dd-D**, thereby proving the intermediate formation of two parent (*E*)-vinylzinc (entry 9).

The possibility to use other alkyl iodides was surveyed. The reaction between **1e** and another secondary iodide, cyclohexyl iodide, proceeded well and afforded adducts **5eh** and **5ed** in 56% yield but only in a 76:24 ratio (entry 10), somewhat lower than in the case of isopropyl iodide. As a result of a slower iodine-atom transfer between the methyl radical and ethyl iodide, a large excess was required to override methyl addition to enoate **1e** and reach reasonable levels of ethyl incorporation (entries 11 and 12). Using 10 equivalents, a mixture of **5eb** and **5ed** in a 55:45 ratio was obtained, and 20 equivalents were required to attain 77% ethyl transfer.

By contrast, no methyl addition was observed when enoates **1e** and **1g** were reacted with five equivalents of *tert*-butyl iodide in the presence of dimethylzinc (entries 13 and 14). However, this time, in addition to alkylidenes

Table 9 Dimethylzinc-Mediated 1,4-Addition/Cyclization of Alkyl Iodides on β-(Propargyloxy)enoates[a]



5dc **5dd** (*Z*)-**15dc**
5eb, 5ec, 5eh, 5eg **5ed** (Z)-**15eg**
5hc **5hd**
5gc, 5gg **5gd** (Z)-**15gg**

Entry	Enoate	R^1	R^2	E	Products	Yield[b] (%) [ratio][c]
1	**1e**	TMS	*i*-Pr	H	**5ec/5ed**	60 [87:13]
2	**1e**	TMS	*i*-Pr	D	**5ec-D/5ed-D**	64 [87:13][d]
3	**1e**	TMS	*i*-Pr[e]	H	**5ec/5ed**	68 [93:7]
4	**1g**	Ph	*i*-Pr	H	**5gc/5gd**	58 [85:15]
5	**1g**	Ph	*i*-Pr	D	**5gc-D/5gd-D**	54 [85:15][f]
6	**1h**	2-MeO$_2$CC$_6$H$_4$	*i*-Pr	H	**5hc/5hd**	50 [84:16]
7	**1h**	2-MeO$_2$CC$_6$H$_4$	*i*-Pr	D	**5hc-D/5hd-D**	65 [84:16][g]
8	**1d**	Et	*i*-Pr	H	**5dc/5dd/15dc**	72 [71:15:14]
9	**1d**	Et	*i*-Pr	D	**5dc-D/5dd-D/15dc**	75 [71:15:14][h]
10	**1e**	TMS	Cy	H	**5eh/5ed**	56 [76:24]
11	**1e**	TMS	Et[e]	H	**5eb/5ed**	66 [55:45]
12	**1e**	TMS	Et[i]	H	**5eb/5ed**	61 [77:23]
13	**1e**	TMS	*t*-Bu	H	**5eg/5ed/15eg**	77 [91:0:9]
14	**1g**	Ph	*t*-Bu	H	**5gg/5gd/15gg**	80 [81:0:19]

[a] Reaction conditions: (1) Me$_2$Zn (3 equiv), R^{2}I, CH$_2$Cl$_2$, dry air (20 mL) bubbled through at 0 °C for 1 h, then 0 °C, 1 h; (2) EX = HCl (aq 1 M), or D$_2$O.

[b] Combined isolated yield after chromatography.

[c] Determined by ^{1}H NMR analysis of the crude material.

[d] **5ec-D** 95% D, **5ed-D** 95% D.

[e] 10 equiv R^{2}I were used.

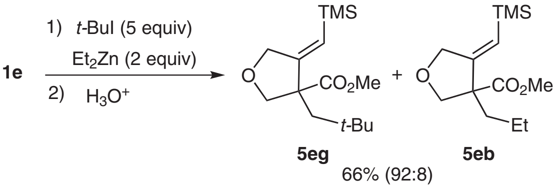
[f] **5gc-D** 95% D, **5gd-D** 95% D.

[g] **5hc-D** 95% D, **5hd-D** 95% D.

[h] **5dc-D** 95% D, **5dd-D** 95% D.

[i] 20 equiv EtI were used.

5eg and **5gg**, formation of vinyl iodides (*Z*)-**15eg** and (*Z*)-**15gg** was observed as a result of a more favorable iodine-atom transfer between the tertiary iodide and the intermediate vinyl radical arising from the cyclization step. The ratio of alkylidene versus iodide was dependent on the substrate considered and varied from 91:9 for TMS-substituted **1e** to 81:19 for phenyl-substituted **1g**. In agreement with this picture, starting from **1e**, vinyl iodide formation could be suppressed using diethylzinc as mediator, since the zinc-atom transfer step was accelerated (Scheme 10). However, this was done to the expense of a diminished ratio of *tert*-butyl incorporation related to a less favorable atom transfer between the ethyl radical and *tert*-butyl iodide. As a consequence, a mixture of **5eg** and **5eb** in a 92:8 ratio was isolated in 66% yield (Scheme 10).



5eg **5eb**

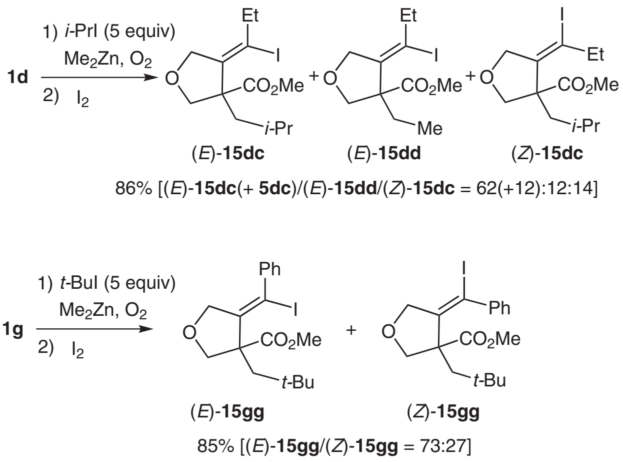
66% (92:8)

Scheme 10

Worthy of note, vinyl iodides **15** arising from iodine-atom transfer were found to be of *Z*-configuration, thus evidencing a stereoselective process. This conclusion was reached by carrying out iodine quench experiments (Scheme 11). Following reaction between **1d** and isopropyl iodide, iodine quench led to the formation of three vinyl iodides (*E*)-**15dc**, (*E*)-**15dd**, and (*Z*)-**15dc** in a 62:12:14 ratio (12% of **5dc** were also present), (*E*)-**15dc** and (*Z*)-**15dc** having incorporated an isopropyl group [the ratio of isopropyl to methyl incorporation was the same as for other substrates (88:12)]. Since (*E*)-**15dc** was formed by iodination of the intermediate vinylzinc, it should be of *E* configuration, thus implying the *Z* configuration of (*Z*)-**15dc**. Similarly, treatment with iodine of the reaction mixture resulting from the addition of *tert*-butyl iodide to **1g** afforded a mixture of diastereomeric iodides (*E*)-**15gg** and (*Z*)-**15gg** in a 73:27 ratio (Scheme 11). The first one arising from the parent vinyl zinc it should be of *E* configuration, hence the *Z*-configuration of the second one.

The model proposed above to account for the selectivity of Zn- versus H-atom transfer in the case of direct addition of dialkylzincs also provides an adequate explanation for the results of the alkyl iodide additions. As previously stated, both for linear and bent radicals, zinc-atom transfer from dimethylzinc only occurs from the *syn* side. Conversely, as evidenced by the observed *Z*-configurations of the vinyl iodides formed, iodine-atom transfer only takes place from the *anti* side, less sterically hindered.[50]

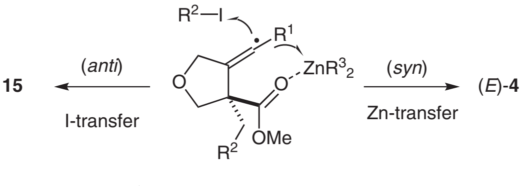
In the case of linear radicals (Scheme 12), the competition between metalation and iodination reflects the relative ease of the latter to undergo zinc-atom transfer versus iodine-atom transfer. As illustrated in the case of phenyl-substituted enoate **1g**, S_H2 on the complexed dimethylzinc overrides iodine transfer from the alkyl iodide, and even in the case of *tert*-butyl iodide only minor amounts of vinyl iodide are formed.



86% [(*E*)-**15dc**(+ **5dc**)/(*E*)-**15dd**/(*Z*)-**15dc** = 62(+12):12:14]

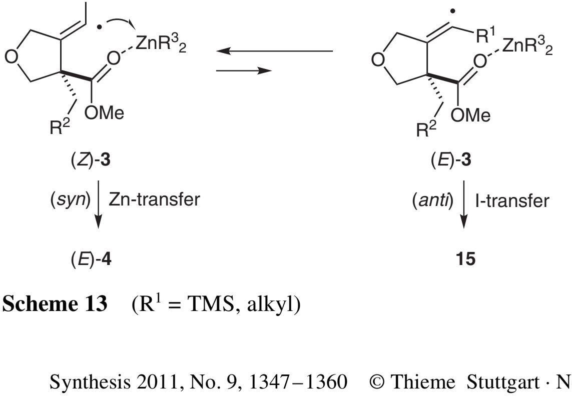
85% [(*E*)-**15gg**/(*Z*)-**15gg** = 73:27]

Scheme 11



Scheme 12 (R^1 = aryl)

In the case of rapidly interconverting bent radicals (Scheme 13), while the radical of *Z*-configuration undergoes exclusive zinc-atom transfer, the radical of *E* configuration only reacts with the alkyl iodide. The final metalation versus iodination depends again on the relative rate of this elementary steps (i.e., from TMS-substituted **1e**, iodide formation is observed from *tert*-butyl iodide but not with isopropyl iodide, and it is observed using dimethylzinc but not with diethylzinc), but also on the *Z*/*E* ratio of the reacting vinylic radical [i.e. for the same alkyl iodide (*i*-PrI), vinyl iodide formation is observed from ethyl-substituted radical **3** (R^1 = Et, R^2 = *i*-Pr), but not from TMS-substituted radical **3** (R^1 = TMS, R^2 = *i*-Pr) for which the amount of *Z*/*E* ratio should be higher]. Generally however, as for linear radicals, zinc-atom transfer predominates over iodine-atom transfer for bent radicals.

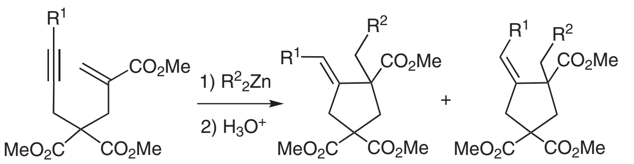


Scheme 13 (R^1 = TMS, alkyl)

5 Conclusion; Current and Future Work

In conclusion, we have disclosed a new stereoselective domino 1,4-addition/alkyne carbozincation sequence based on a radical zinc-atom transfer reaction. In terms of synthetic value, two efficient multicomponent approaches to polysubstituted alkylidene tetrahydrofurans from β-(propargyloxy)enoates have been established: one involving the direct addition of dialkylzincs, and the second involving the dimethylzinc-mediated addition of alkyl iodides. Both sequences involve the stereoselective formation of an alkylidenezinc intermediate that is well suited for subsequent functionalization by in situ reaction with electrophiles. Having shown that the processes tolerate well a range of alkyne substituents, future work in our group will be directed to extending the approach to the synthesis of other hetero- or carbocycles by using diversely linked 1,6-enynes. Preliminary studies involving the enoates with a malonate linkage have shown a behavior very similar to that of β-(propargyloxy)enoates (Table 10).

Table 10 Reaction of Dialkylzinc Reagents with Malonate-Derived Enoates **16a** and **16b**[a,b]



16 (*Z*)-**17** (*E*)-**17**

Entry	Enoate	R^1	R^2	Product	Yield[c] (%)	dr[d] (*Z*/*E*)
1	**16a**	TMS	Et[a]	**17ab**	70	>95:5
2	**16a**	TMS	Me[b]	**17ad**	53[e]	>95:5
3	**16b**	Et	Et[a]	**17bb**	50[f]	70:30

[a] Reaction conditions: (1) Et_2Zn (3 equiv), Et_2O, r.t., 20 h; (2) aq 1 M HCl.

[b] Reaction conditions: (1) Me_2Zn (5 equiv), CH_2Cl_2, dry air (20 mL) bubbled through at 0 °C for 1 h, then 0 °C, 1 h; (2) aq 1 M HCl.

[c] Isolated yield after chromatography.

[d] Determined by ^{1}H NMR analysis of the crude material.

[e] The product was contaminated with 8% of the product resulting from the addition of the bichloromethyl radical ($R^2 = CHCl_2$).

[f] Determined by ^{1}H NMR spectroscopy based on analysis of the crude mixture with biphenyl as internal standard.

Diethylzinc addition on enoates **16a** and **16b** having respectively a TMS- and ethyl-substituted pendant alkyne led to the corresponding alkylidene cyclopentanes **17ab** and **17bb** in yields and selectivities similar to those of the analogous β-(propargyloxy)enoates. Dimethylzinc addition/cyclization on **16a** provided **17ad** in 53% yield (entry 2).

From a mechanistic perspective, the above described transformations are to be related to carbozincations of non-activated alkynes that are highly valuable transformations.[51] It is remarkable by the fact that an alkylzinc derivative is transformed into a vinylzinc in what represents one of a few examples of a radical zinc-atom transfer between a dialkylzinc and a vinyl radical. Moreover, this work has brought about valuable information concerning the key homolytic substitution at zinc (S_H2) step and we hope that our findings will foster future studies to generalize this new entry to alkyne carbozincation. Amongst other, it provides further evidence that adjacent Lewis basic functions such as esters or oxazolidinones, presumably by activating by coordination the dialkylzinc towards homolytic substitution,[3,14b,17] are able to direct efficiently the zinc transfer and thus ensure highly diastereoselective transformations. Significantly, in terms of reactivity, this activation by coordination provides zinc-atom transfer reactions so efficient that they can override processes as fast as iodine-atom transfer between a vinyl radical and *tert*-butyl iodide.

Experiments involving organometallic compounds were carried out in dried glassware under a positive pressure of dry argon. All solvents were distilled to remove stabilizers and dried with an Mbraun Solvent Purification System SPS-800. $ZnBr_2$ (98%) was melted under dry N_2 and, immediately after cooling to r.t., was dissolved in Et_2O. Bu_2Zn (Fluka, ~1 M in heptane), Et_2Zn (Aldrich, 1.0 M in hexanes), Me_2Zn (Aldrich, 1.0 M in heptane) and all other reagents were of commercial quality and were used without purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer fitted with BBFO probe with Z gradient with an internal standard of residual $CHCl_3$ (δ = 7.27 for ^{1}H NMR and 77.16 for ^{13}C NMR). IR spectra were recorded with an ATR diamond spectrophotometer. HRMS were obtained on a Finnigan MAT 95.

Methyl 4-Methylene-3-pentyltetrahydrofuran-3-carboxylate (5aa) by Reaction of Bu_2Zn or Et_2Zn with β-(Propargyloxy)enoates (Table 1, Entry 1);[24] Typical Procedure

Under argon, to a stirred soln of β-(propargyloxy)enoate **1a** (0.5 mmol) in Et_2O (5 mL) at r.t. was added ~1 M Bu_2Zn in heptane (0.6 mL, 0.6 mmol). The mixture was stirred at r.t. for 20 h. The reaction was hydrolyzed with aq 1 M HCl (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. Purification by flash chromatography (silica gel, pentane–Et_2O) afforded **5aa** (57 mg, 54%).

IR (neat): 2954, 2928, 2859, 1731, 1379 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3 H), 1.20–1.32 (m, 6 H), 1.61 (m, 1 H), 1.96 (m, 1 H), 3.73 (s, 3 H), 3.74 (d, *J* = 9.0 Hz, 1 H), 4.34 (dt, *J* = 13.1, 2.2 Hz, 1 H), 4.37–4.43 (m, 2 H), 5.07 (t, *J* = 2.1 Hz, 1 H), 5.22 (t, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 25.2, 32.0, 37.1, 52.3, 56.8, 71.7, 75.0, 106.2, 150.4, 173.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{20}O_3Na$: 235.13047; found: 235.13043.

Methyl (*Z*)-3-Ethyl-4-[(trimethylsilyl)methylene]tetrahydrofuran-3-carboxylate (5ed) by Reaction of Me_2Zn with β-(Propargyloxy)enoates (Table 4, Entry 4); Typical Procedure

Under argon, to a stirred soln of β-(propargyloxy)enoate **1e** (0.2 mmol) in DCE (1 mL) at 0 °C was added 1.0 M Me_2Zn in heptane (1.2 mL, 1.2 mmol). Air (20 mL) was slowly introduced over 1 h into the soln via a syringe pump using a syringe fitted with a $CaCl_2$ guard. The mixture was then stirred at 0 °C for 1 h. CH_2Cl_2 (5 mL) was then added and the reaction was hydrolyzed with aq 1 M HCl (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. Purification by flash chromatography (silica gel, pentane–Et_2O) afforded **5ed** (37 mg, 76%).

IR (neat): 2953, 2360, 1731, 1627, 837 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 9 H), 0.86 (t, *J* = 7.4 Hz, 3 H), 1.64 (m, 1 H), 1.98 (m, 1 H), 3.70 (s, 3 H), 3.74 (d, *J* = 7.2 Hz, 1 H), 4.32 (dd, *J* = 13.6, 2.3 Hz, 1 H), 4.38 (dd, *J* = 13.6, 2.3 Hz, 1 H), 4.38 (d, *J* = 7.2 Hz, 1 H), 5.67 (t, *J* = 2.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 158.0, 120.1, 73.8, 71.1, 60.0, 52.4, 30.2, 10.0, 0.7.

HRMS: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{22}O_3NaSi$: 265.12304; found: 265.12251.

Methyl 4-Methylene-3-pentyltetrahydrofuran-3-carboxylate (5aa) by Reaction of RZnBr·LiBr with β-(Propargyloxy)enoates (Table 8, Entry 1); Typical Procedure

Under argon, to stirred 1 M $ZnBr_2$ in Et_2O (1.0 mL, 1.0 mmol) was added dropwise 2.2 M BuLi in hexane (0.45 mL, 0.99 mmol) at –60 °C. After 5 min, the initial slurry gave a colorless soln. The mixture was further stirred at r.t. for 15 min before it was cooled again to –30 °C. Et_2O (2 mL), and a soln of β-(propargyloxy)enoate **1a** (0.5 mmol) in Et_2O (2 mL) were added. The mixture was stirred at r.t. for 20 h. The reaction was hydrolyzed with aq 1 M HCl (10 mL). The layers were separated, the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. Purification by flash chromatography (silica gel, pentane–Et_2O) afforded **5aa** (49 mg, 46%).

Methyl (*Z*)-3-Isobutyl-4-[(trimethylsilyl)methylene]tetrahydrofuran-3-carboxylate (5ec) by Me_2Zn-Mediated Reaction of Alkyl Iodides with β-(Propargyloxy)enoates having Pendant Alkynes (Table 9, Entry 3); Typical Procedure

Under argon, to a stirred soln of β-(propargyloxy)enoate **1e** (0.2 mmol) and *i*-PrI (2 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added 1.0 M Me_2Zn in heptane (0.6 mL, 0.6 mmol). Air (20 mL) was slowly introduced over 1 h into the soln via a syringe pump using a syringe fitted with a $CaCl_2$ guard. The mixture was then stirred at 0 °C for 1 h. CH_2Cl_2 (5 mL) was the added and the reaction was hydrolyzed with aq 1 M HCl (5 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. Purification by flash chromatography (silica gel, pentane–Et_2O) afforded **5ec** (36 mg, 68%).

IR (neat): 2954, 1731, 1626, 837 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 9 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 1.46 (dd, *J* = 13.9, 6.2 Hz, 1 H), 1.60 (m, 1 H), 2.02 (dd, *J* = 13.9, 7.1 Hz, 1 H), 3.66 (d, *J* = 9.0 Hz, 1 H), 3.69 (s, 3 H), 4.28 (dd, *J* = 13.6, 2.4 Hz, 1 H), 4.40 (dd, *J* = 13.6, 2.4 Hz, 1 H), 4.53 (d, *J* = 9.0 Hz, 1 H), 5.74 (t, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.3, 23.2, 24.4, 26.5, 46.4, 52.8, 58.4, 71.0, 74.5, 120.8, 158.7, 174.1.

HRMS *m/z* $[M + Na]^+$ calcd for $C_{14}H_{26}O_3NaSi$: 293.15434; found: 293.15470.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) Reviews: (a) Bazin, S.; Feray, L.; Bertrand, M. P. *Chimia* **2006**, *60*, 260. (b) Akindele, T.; Yamada, K.-i.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345.

(2) Historical account, see: Seyferth, D. *Organometallics* **2001**, *20*, 2940.

(3) (a) Lewinski, J.; Marciniac, W.; Lipkowski, J.; Justyniak, I. *J. Am. Chem. Soc.* **2003**, *125*, 12698. (b) Lewinski, J.; Sliwinski, W.; Dranka, M.; Justyniak, I.; Lipkowski, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 4826. (c) Lewinski, J.; Suwala, K.; Kubisiak, M.; Ochal, Z.; Justyniak, I.; Lipkowski, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7888. (d) Lewinski, J.; Bury, W.; Dutkiewicz, M.; Maurin, M.; Justyniak, I.; Lipkowski, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 573. (e) Lewinski, J.; Koscielski, M.; Suwala, K.; Justyniak, I. *Angew. Chem. Int. Ed.* **2009**, *48*, 7017. (f) Lewinski, J.; Suwala, K.; Kaczorowski, T.; Galezowski, M.; Gryko, D. T.; Justyniak, I.; Lipkowski, J. *Chem. Commun.* **2009**, 215.

(4) Jana, S.; Berger, R. J. F.; Fröhlich, R.; Pape, T.; Mitzel, N. W. *Inorg. Chem.* **2007**, *46*, 4293.

(5) Mileo, E.; Benfatti, F.; Cozzi, P. G.; Lucarini, M. *Chem. Commun.* **2009**, 469.

(6) Maury, J.; Feray, L.; Bazin, S.; Clément, J.-L.; Marque, S. R. A.; Siri, D.; Bertrand, M. P. *Chem. Eur. J.* **2011**, *17*, 1586.

(7) Davies, A. G.; Roberts, B. P. *Acc. Chem. Res.* **1972**, 387; and references cited therein.

(8) For the first use of Et_2Zn as radical mediator in the presence of oxygen in the context of synthesis, see: Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335.

(9) Cohen, T.; Gibney, H.; Ivanov, R.; Yeh, E. A.-H.; Marek, I.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 15405.

(10) (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. (b) Bazin, S.; Feray, L.; Siri, D.; Naubron, J.-V.; Bertrand, M. P. *Chem. Commun.* **2002**, 2506. (c) Bazin, S.; Feray, L.; Vanthuyne, N.; Bertrand, M. P. *Tetrahedron* **2005**, *61*, 4261. (d) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D.; Bertrand, M. P. *Tetrahedron* **2007**, *63*, 77. (e) Maury, J.; Feray, L.; Perfetti, P.; Bertrand, M. P. *Org. Lett.* **2010**, *12*, 3590.

(11) Van der Deen, H.; Kellog, R. M.; Feringa, B. L. *Org. Lett.* **2000**, *2*, 1593.

(12) (a) Miyabe, H.; Asada, R.; Yoshida, K.; Takemoto, Y. *Synlett* **2004**, 540. (b) Miyabe, H.; Asada, R.; Takemoto, Y. *Tetrahedron* **2005**, *61*, 385.

(13) Yamada, K.-i.; Umeki, M.; Maekawa, M.; Yamamoto, Y.; Akindele, Y.; Nakano, M.; Tomioka, K. *Tetrahedron* **2008**, *64*, 7258.

(14) (a) Cozzi, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2951. (b) Cozzi, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2075. (c) Cozzi, P. G.; Mignogna, A.; Vicennati, P. *Adv. Synth. Catal.* **2008**, *350*, 975. (d) Fernández-Ibañez, M. A.; Maciá, B.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1317. (e) Cozzi, P. G.; Benfatti, F.; Guiteras Capdevila, M.; Mignogna, A. *Chem. Commun.* **2008**, 3317.

(15) Furthermore, it has been proposed that transition-metal-promoted zinc/iodine exchange involves a radical mechanism, Cu(I): (a) Rozema, M. J.; AchyuthaRao, S.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956. Pd(0): (b) Stadtmüller, H.; Vaupel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204. (c) Stadtmüller, H.; Lentz, R.; Tucker, C.; Stüdemann, T.; Dörner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027. Ni(0): (d) Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 8349. (e) Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743. Mn(II)/Cu(I): (f) Riguet, E.; Klement, I.; Kishan Reddy, Ch.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 5865.

(16) (a) Denes, F.; Chemla, F.; Normant, J.-F. *Angew. Chem. Int. Ed.* **2003**, *42*, 4043. (b) Denes, F.; Pérez-Luna, A.; Cutri, S.; Chemla, F. *Chem. Eur. J.* **2006**, *12*, 6506. (c) Denes, F.; Pérez-Luna, A.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 398. (d) Giboulot, S.; Pérez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Tetrahedron Lett.* **2008**, *49*, 3963.

(17) Feray, L.; Bertrand, M. P. *Eur. J. Org. Chem.* **2008**, 3164.

(18) For a related photoinduced reaction, see: Charette, A. B.; Beauchemin, A.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1998**, *120*, 5114.

(19) For important studies on radical formation by SET from dialkylzinc coordination complexes, see: (a) Wissing, E.; Rijnberg, E.; van der Schaaf, P. A.; van Gorp, K.; Boersma, J.; van Koten, G. *Organometallics* **1994**, *13*, 2609. (b) Wissing, E.; van der Linden, S.; Rijnberg, E.; Boersma, J.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Organometallics* **1994**, *13*, 2602; and references cited therein.

(20) Chen, Z.; Zhang, Y.-X.; An, Y.; Song, X.-L.; Wang, Y.-H.; Zhu, L.-L.; Guo, L. *Eur. J. Org. Chem.* **2009**, 5146.

(21) Reductive zincation of a vinyl radical has also been suggested to account for the formation of allenoates following zinc-mediated radical addition to propiolates, see ref. 17.

(22) Vinylcyclopentyl zinc has been prepared by reductive cyclization: Crandall, J. K.; Ayers, T. A. *Organometallics* **1992**, *11*, 473.

(23) Ni(II)-catalyzed intermolecular carbozincation, see: Stüdemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1997**, *36*, 93.

(24) Pérez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Chem. Eur. J.* **2008**, *14*, 8784.

(25) Selected examples: (a) Bertrand, M. T.; Courtois, G.; Migniniac, L. *Tetrahedron Lett.* **1974**, *15*, 3147. (b) Nakamura, M.; Fujimoto, T.; Endo, K.; Nakamura, E. *Org. Lett.* **2004**, *6*, 4837. (c) Cantagrel, F.; Pinet, S.; Gimbert, Y.; Chavant, P. Y. *Eur. J. Org. Chem.* **2005**, 2694.

(26) See the supporting information in ref. 24.

(27) Deprotonation of **1a** responsible for the formation of **10** could also be effected by Bu$_2$Zn, even though deprotonation of terminal alkynes by dialkylzincs in the absence of ligands is not a fast process, see: (a) Okhlobystin, O. Y.; Zakharkin, L. I. *J. Organomet. Chem.* **1965**, *3*, 257. (b) De Koning, A. J.; Van Rijn, P. E.; Boersma, J.; Van der Kerk, G. J. M. *J. Organomet. Chem.* **1979**, *174*, 129. (c) Pinet, S.; Pandya, S. U.; Chavant, P. Y.; Ayling, A.; Vallée, Y. *Org. Lett.* **2002**, *4*, 1463.

(28) Cote, A.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 2771.

(29) Haaland, A.; Green, J. C.; McGrady, G. S.; Downs, A. J.; Gullo, E.; Lyall, M. J.; Timberlake, J.; Tutukin, A. V.; Volden, H. V.; Ostby, K.-A. *Dalton Trans.* **2003**, 4356.

(30) Bamford, C. H.; Newitt, D. M. *J. Chem. Soc., Abstr.* **1946**, 688.

(31) When CH$_2$Cl$_2$ was used as solvent, the *Z*/*E* ratio of product **5ha** might not fully represent the diastereoselectivity of the zinc-atom transfer since in addition to these two diastereomers, a third tetrahydrofuran side product having incorporated a butyl residue was detected (~20% yield in the crude) but could not be fully identified. In any case the diastereoselectivity of the reaction between **1h** and Bu$_2$Zn in CH$_2$Cl$_2$ should at best be mediocre.

(32) Guijarro, A. In *The Chemistry of Organozinc Compounds*; Rappoport, Z.; Marek, I., Eds.; Wiley: Chichester, **2007**, 193–236.

(33) Journet, M.; Malacria, M. *J. Org. Chem.* **1992**, *57*, 3085.

(34) Curran, D. P.; Chen, M.-H.; Kim, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6265.

(35) Even though α-silyl stabilization of vinyl radicals leads to a tendency towards linearization: (a) Lalitha, S.; Chandrasekhar, J. *Proc.–Indian Acad. Sci., Chem. Sci.* **1994**, *106*, 259; they are better represented as very rapidly *Z*/*E* interconverting bent radicals:. (b) Rubin, H.; Fischer, H. *Helv. Chim. Acta* **1996**, *79*, 1670. (c) Bucher, G.; Mahajan, A. A.; Schmittel, M. *J. Org. Chem.* **2009**, *74*, 5850.

(36) (a) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098. (b) Prakash Das, J.; Chechik, H.; Marek, I. *Nature Chem.* **2009**, *1*, 128.

(37) (a) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802. (b) Gourdet, B.; Rudkin, M. E.; Watts, C. A.; Lam, H. W. *J. Org. Chem.* **2009**, *74*, 7849.

(38) (a) Yasui, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2007**, *36*, 32. (b) Yasui, H.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 373.

(39) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095.

(40) (a) Sato, A.; Yorimitsu, H.; Oshima, K. *Synlett* **2009**, 28. (b) Sato, A.; Yorimitsu, H.; Oshima, K. *Bull. Korean Chem. Soc.* **2010**, *31*, 570.

(41) Banerjee, B.; Litvinov, D. N.; Kang, J.; Bettale, J. D.; Castle, S. L. *Org. Lett.* **2010**, *12*, 2650.

(42) See the Supporting Information.

(43) (a) *The Chemistry of Organozinc Compounds*; Rappoport, Z.; Marek, I., Eds.; Wiley: Chichester, **2007**. (b) Knochel, P.; Millot, N.; Rodrigues, A. L. *Org. React.* **2001**, *58*, 417.

(44) Blake, A. J.; Shannon, J.; Stephens, J. C.; Woodward, S. *Chem. Eur. J.* **2007**, *13*, 2462.

(45) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(46) (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. (b) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951.

(47) (a) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (b) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443.

(48) (a) Yamada, K.-i.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. *Org. Lett.* **2006**, *8*, 87. (b) Yamada, K.-i.; Nakano, Y.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805.

(49) (a) Vleeschouwer, F. D.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. *Org. Lett.* **2007**, *9*, 2721. (b) Fischer, H.; Radom, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 1340.

(50) Similar stereoselectivities have been reported for other related iodine-atom transfer radical cascades, see for example: Miyabe, H.; Asada, R.; Toyoda, A.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 5863.

(51) See, (a) Chinkov, N.; Tene, D.; Marek, I. In *Metal-Catalyzed Cross Coupling Reactions*, 2nd ed.; Diederich, D.; de Meijere, A., Eds.; Wiley-VCH: New York, **2004**, 395. (b) Denès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366.