Radical-Polar Crossover Domino Reaction Involving Alkynes: A Stereoselective Zinc Atom Radical Transfer

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Intramolecular radical cyclization has become over the years one of the most powerful strategies to synthesize carbocyclic and heterocyclic compounds.[1] In this context, cyclization of 5-hexynyl radicals has found widespread application for the preparation of *exo*-alkylidene derivatives. The most common protocols involve the use of metal hydrides (generally tin) as radical mediators and thus termination affords directly an alkene, which results in a loss of functionality. Halide atom transfer cyclization conditions leading to vinyl halides provide an elegant solution to retain functionality,[2] but further elaboration requires an additional synthetic step. Alternatively, processes where the intermediate vinyl radical is captured by reaction with a metallic reagent to generate a new carbon–metal bond, have also been disclosed.[3] In principle such a strategy is highly attractive since subsequent ionic reactions should offer multibond-forming events, however examples where the vinyl metal is retained and reacted further are scarce.[3c,e,f]

The use of organozinc reagents as non-toxic radical precursors or mediators is a field of growing interest.[4–6] Of particular interest are zinc atom transfer reactions which enable the transformation of simple readily available organozinc reagents into more elaborated ones via a radical chain transfer mechanism. This approach has already been applied for the preparation of zinc enolates[7,8] and alkylzinc reagents,[9–11] but to our knowledge never for vinyl zinc derivatives.

As part of our ongoing interest in carbometallation of zinc enolates,[12] we have recently disclosed a new access to (pyrrolidylmethyl) zinc and (tetrahydrofuranylmethyl) zinc derivatives by reaction of dialkylzinc, organozinc and copper-zinc mixed reagents with (*N*-allyl)aminoenoates[9a–c] and β-(allyloxy)enoates[9e] through a zinc atom transfer involving a domino 1,4-addition/carbocyclization sequence. We reasoned that addition on β-(propargyloxy)enoates, readily prepared by reaction of the corresponding propargylic alcohol with methyl 2-(bromomethyl)acrylate, might lead to (*exo*-methylene tetrahydrofuranyl) zinc[13,14] derivatives which can be functionalized further in-situ by reaction with an electrophile and afford polysubstituted alkenyl tetrahydrofurans (Scheme 1).
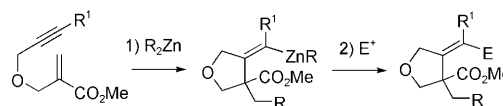
Scheme 1. New multicomponent approach to polysubstituted alkylidene tetrahydrofurans.

We have found that reaction of primary dialkylzincs proceeds smoothly in diethyl ether at room temperature with a number of β-(propargyloxy)enoates bearing diversely substituted alkynes to afford the corresponding *exo*-alkylidene tetrahydrofurans after acidic quench (Table 1).

Addition of Bu₂Zn (or Et₂Zn) on enoate **1a** bearing a terminal alkyne leads to *exo*-methylene tetrahydrofuran **2** (or **3**) in 54% (or 55%) yield (entries 1–2). Starting from TMS-substituted β-(propargyloxy)enoate **1b**, diastereomerically pure vinylsilanes (*Z*)-**4** and (*Z*)-**5** are obtained in good to excellent yields (entries 3–4). The sequence is also highly effective and stereoselective with substrates bearing conjugated alkynes. Reaction of Bu₂Zn and Et₂Zn with **1c** yields styrenes **7** and **8** in 81 and 79% yield, respectively, in a 90:10 *Z/E* ratio (entries 6–7), whereas enyne **1d** leads to diastereomerically pure diene (*Z*)-**9** in 59% yield (entry 8). Ste-

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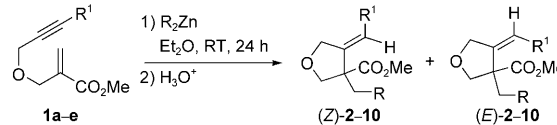75005 Paris (France)
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Table 1. Reaction of dialkylzincs on β-(propargyloxy)enoates **1a–e**.

Entry	Substrate	R^1	R$_2$Zn (equiv)	Product	Yield [%][a]	dr[b] Z/E
1	**1a**	H	Bu$_2$Zn (3)	**2**	54	–
2	**1a**	H	Et$_2$Zn (3)	**3**	55	–
3	**1b**	TMS	Bu$_2$Zn (5)	**4**	67	>95:05
4	**1b**	TMS	Et$_2$Zn (3)	**5**	91	>95:05
5	**1b**	TMS	iPr$_2$Zn (3)	**6**	49[c]	>95:05
6	**1c**	Ph	Bu$_2$Zn (5)	**7**	81	88:12
7	**1c**	Ph	Et$_2$Zn (3)	**8**	79	90:10
8	**1d**	1-Cx[d]	Bu$_2$Zn (3)	**9**	59	>95:05
9	**1e**	Et	Bu$_2$Zn (3)	**10**	64	64:36

[a] Combined yield of isolated diastereomers. [b] Determined by NMR analysis of the crude material. [c] 40% of 3-(trimethylsilyl)prop-2-yn-1-ol was isolated. [d] 1-Cx/ 1-cyclohexenyl.

reochemical assignment for products **4** and **8** arouse from NOE experiments (Scheme 2).[15]
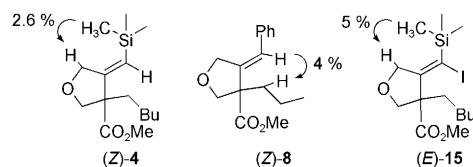
Scheme 2. Selected NOE signals for products (Z)-**4**, (Z)-**8** and (E)-**15**.

Reaction with alkyl substituted alkynes is also possible as evidenced by the addition of Bu$_2$Zn on **1e** (entry 9). However, in this case, a significant drop in diastereoselectivity is observed as a mixture of alkylidene furans **10** is obtained in a 64:36 Z/E ratio.

The domino sequence is not limited to primary dialkylzincs. For example, salt free iPr$_2$Zn prepared from iPrMgCl[16] reacts with **1b** to afford diastereomerically pure vinylsilane (Z)-**6** in 49% yield (Table 1, entry 5). Nevertheless, as evidenced by the recovery of 40% of 3-TMS-propargyl alcohol, a competitive addition/β-elimination process hampers the overall efficiency in this case.

In order to develop a three-component approach, we next investigated the subsequent functionalization of the vinylzinc resulting from the 1,4 addition/cyclization sequence (Table 2). Much to our surprise, deuteration of the intermediate obtained from Bu$_2$Zn and enoate **1a** afforded **11** as a mixture of two diastereomers in a 51:49 E/Z ratio but also 50% of non-deuterated methylene–tetrahydrofuran **2** (entries 1–2). On the contrary, complete deuterium labeling was observed starting with TMS-substituted enoate **1b** and (Z)-**14** was isolated (entry 5). The case of substrate **1e** bearing an ethyl substituted internal alkyne lies between the two previous cases. As expected, a mixture of diastereomers is obtained, but whereas complete deuterium labeling is observed for the Z isomers, only partial labeling is observed

for the E isomers, as for the non-substituted case (entries 3–4).

Functionalization of the intermediate vinylzinc species was thus considered with substrates affording high degrees of Z selectivity. The intermediate *gem* Si/Zn bimetallated alkene resulting from the addition of Bu$_2$Zn or Et$_2$Zn on **1b** was trapped with iodine to afford iodo vinylsilane (E)-**15** in 72% as a single diastereomer or allylated with allyl bromide following transmetallation with CuCN·2LiCl to give trisubstituted vinylsilane (Z)-**16** (entries 6–7). As confirmed by NOE experiments on **15** (Scheme 2), full retention of configuration was observed.[15] Likewise, electrophilic trapping of the intermediate vinyl zinc was also possible starting from enoate **1c** bearing a phenylacetylene moiety (Table 2, entries 8–9). Reaction with Bu$_2$Zn followed by iodolysis afforded **17** in 79% yield in a 93:07 E/Z ratio, whereas reaction with Et$_2$Zn followed by transmetallation and trapping with allyl bromide gave tetrasubstituted alkene **18** in 42% as a single Z diastereomer. Here again, as evidenced by the slight increase in diastereoselectivity with respect to simple acidic quench (Table 1, entries 6–7) the alkenyl intermediate leading to the Z product seems to be fully metallated but not the one leading to the E product.
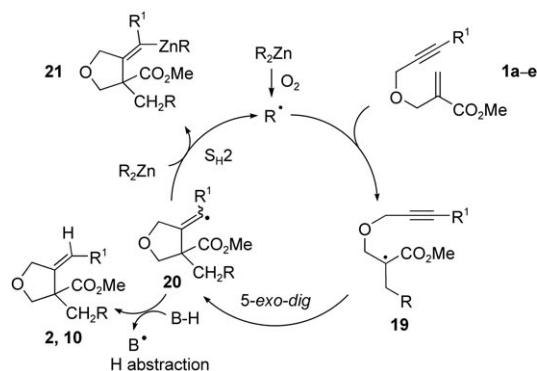
The observed transformations are believed to follow a radical-polar crossover mechanism similar to the one we evidenced for the related reactions involving (N-allyl)amino-enoates and β-(allyloxy)enoates (Scheme 3).[9a,b,e] Initial oxidation of the organometallic species by traces of oxygen produces a radical that undergoes 1,4-addition onto the Michael acceptor **1a–e** to afford an enoxy radical **19**.[17] Subsequent 5-*exo-dig* cyclization on the alkyne moiety and reduction of the resulting vinyl radical **20** by the organometallic species gives the (tetrahydrofuranylalkenyl)zinc intermediate **21** and a new radical that propagates the chain. The formation of the non-metallated compounds **2** and (E)-**10** is unexpected. In the case of **1a** (R^1=H), we initially considered a possible deprotonation of the starting terminal alkyne by the formed vinylzinc **21**.[18] To be consistent with the observed yields higher than 50%, this possibility would imply the formation of a *gem*-Zn,Zn bimetallated species which was not detected after a deuterium quench.[19] Moreover, such a possibility would not account for the formation of the reduced product even with internal alkynes. It therefore seems reasonable to consider that non-metallated compounds **2** and (E)-**10** arise from reduction of the intermediate vinyl radicals by hydrogen abstraction. Since a possible intramolecular hydrogen shift was ruled out by the fact that no deuterium incorporation was detected by ^{2}H-NMR elsewhere in the molecule,[19] H abstraction must in consequence occur intermolecularly, though the hydrogen donor still remains unidentified.[20]

Vinyl zinc derivatives being known to be configurationally stable,[21] the diastereoselectivity of the process arises from the stereoselectivity of the kinetically controlled S$_H$2 step.[22] Building on models reported for reductive cyclization of hexynyl radicals[23] and iodine atom transfer cyclization of hex-5-ynyl iodides,[2b] we propose an interpretation of the

Table 2. In situ functionalization of vinyl zinc reaction products of dialkylzincs with β-(propargyloxy) enoates.

Entry	Substrate	R₂Zn	E-X	Product		Yield[a] [%]	dr[b]
1	1a	Bu₂Zn	D₂O		11	66	51 ([D] 51%[c]):49 ([D] 49%[c])
2	1a	Bu₂Zn	DCl		11	67	51 ([D] 49%[c]):49 ([D] 47%[c])
3	1e	Bu₂Zn	D₂O		12	78	66 ([D] 92%[c]):34 ([D] 47%[c])
4	1e	Et₂Zn	D₂O		13	64	62 ([D] 94%[c]):38 ([D] 60%[c])
5	1b	Bu₂Zn	D₂O		14	83	>95 ([D] 94%[c]):05
6	1b	Bu₂Zn	I₂, THF		15	72	>95:05
7	1b	Et₂Zn	allylBr,[c] THF		16	51	>95:05
8	1c	Bu₂Zn	I₂, THF		17	79	93:07
9	1c	Et₂Zn	allylBr,[c] THF		18	42	>95:05

[a] Combined yield of isolated diastereomers after chromatography. [b] Determined by NMR analysis of the crude material. [c] Percentage of deuteration determined by NMR analysis. [d] Transmetallation with CuCN·2 LiCl (1.1 equivalent) was performed.

sidered to be sp² hybridized and to invert with a very low barrier. The Z/E ratio depending on the size of R¹, with "small" substituents, the concentration of (E)-**20** increases and its reduction, not only by non pre-complexed dialkylzinc but also by intermolecular H-transfer, becomes more important, thus leading to a selectivity drop and partial loss of the metal. Interestingly, for H-substituted vinyl radical **20**, H-transfer seems to compete both with *syn* and *anti* substitution to the same extent, perhaps as a consequence of a higher reactivity of the unsubstituted radical (Scheme 5).

In summary, we have disclosed a new efficient stereoselective multicomponent approach to polysubstituted alkylidene tetrahydrofurans from dialkylzincs and β-(propargyloxy)enoates, by means of a radical-polar domino 1,4-addition/carbocyclization sequence. From a mechanistic point of view, the transformation is related to carbozincations of non-activated alkynes by zinc
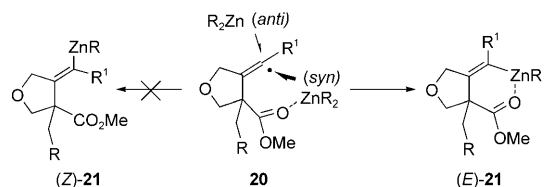
Scheme 3. Mechanism of the radical-polar crossover domino reaction.

stereoselectivity based on the structure of the vinyl radical (linear or bent).

Both for linear (R¹ = Ph, 1-cyclohexenyl) (Scheme 4) and bent (R¹ = TMS, Et) radicals (Scheme 5), reduction occurs selectively from the more sterically hindered *syn* side, presumably as a result of pre-coordination to the ester group of the dialkylzinc involved in the S_H2.[24] *anti* Reduction is nevertheless obtained to a significant extent for ethyl-substituted and unsubstituted vinyl radicals. These radicals are con-

Scheme 4. Origin of diastereoselectivity in the case of "linear" vinyl radicals (R¹ = Ph, 1-cyclohexene).
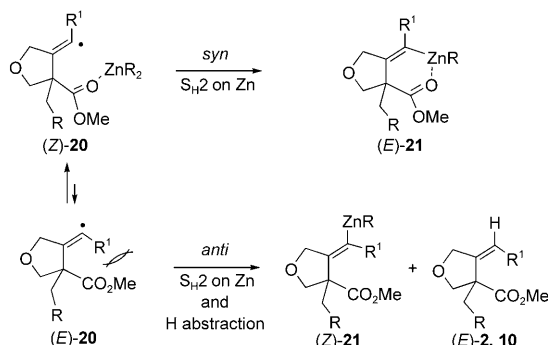
Scheme 5. Origin of diastereoselectivity in the case of "bent" vinyl radicals (R¹ = TMS, Et).

enolates which are rare.[18,25] It is remarkable by the fact that an alkylzinc derivative is transformed into a more basic vinylzinc in what represents, to our knowledge, the first example of a zinc atom radical transfer involving the formation of a vinylzinc species.[26] Synthetically, a new possibility to retain functionality following 5-*exo*-*dig* radical cyclizations is offered, and in our particular case, subsequent in situ transformation of the intermediate organozinc compound results in an overall process where up to three C−C bonds can be formed in one single step.

Experimental Section

General procedure for the radical-polar crossover domino reaction (Table 1): Under argon, to a stirred solution of β-(propargyloxy)enoate (0.2 mmol) in Et_2O (5 mL) was added dialkylzinc reagent R_2Zn (0.6 mL, ~1 N in heptane or hexane, 0.6 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. The reaction was hydrolyzed with an aqueous solution of HCl (1 M). The layers were separated, the aqueous one being extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents evaporated under reduced pressure. The product was purified by flash chromatography on silica gel.

For detailed experimental procedures and characterization data for compounds **1a–e**, **2–10**, and **15–18** see Supporting Information.).

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