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Dialkylzinc-Mediated Atom Transfer Sequential Radical Addition Cyclization

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Alkylative cycloisomerization of *N*,*N*-diallylpropiolamide into α-alkylidene-γ-lactams was mediated by dialkylzinc reagents in aerobic medium. In the presence of an alkyl iodide, final oxidation by iodine-atom transfer predominates over reductive zincation. The dialkylzinc-mediated radical process tolerates the presence of the acidic terminal alkyne.
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Introduction

Atom transfer radical addition (ATRA) and cyclization (ATRC) are widespread free-radical methodologies that have expanded their scope regarding both organic synthesis[1] and polymer chemistry.[2] The pioneering work of Curran on iodine-atom transfer[3] has stimulated numerous developments.[4]

Iodine-atom-transfer methodologies were initially carried out under irradiation with a sun lamp in the presence of hexaalkyldistannanes in order to trap any free iodine formed in the reaction medium.[3,4] Tin-free methodologies using triethylborane or DIBAL-H have been developed.[5] Iodine-atom transfer using dilauroyl peroxide at reflux in benzene has also been proposed by Renaud.[6]

The use of dialkylzinc reagents as mediators in radical reactions is a field of current interest in our group[7,8] and others.[7,9–12] We evaluated the potential of dialkylzinc reagents as mediators for iodine-atom transfer sequential radical addition/cyclization processes (I-ATRAC). The results obtained with *N*,*N*-diallylpropiolamide (**1**) and allyl propynoate (**11**) are reported herein. The alkylative cycloisomerization of these 1,6-enynes constitutes a potential route to α-alkylidene-γ-lactams and lactones. Such transformations have mainly been promoted with transition metals.[13–15]

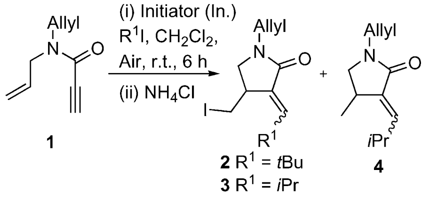
To the best of our knowledge, two examples of α-alkylidene–lactone syntheses by radical methodologies from propiolic esters, using tributyltin hydride or perfluoroalkyl iodides, have been reported.[16] One example of formation of α-alkylidene-γ-lactams through the second methodology has been described.[16b]

Beside their interest as synthetic methodology, the reactions reported herein address the question of the dual behaviour of dialkylzinc reagents (depending on the nature of the alkyl group and on the reaction conditions) that was pointed out by our group and others.[7,8,10,17,18]

Results and Discussion

As mentioned in Table 1, very high yields of iodide **2** (obtained roughly as 9:1 mixture of *E*/*Z* isomers[19]) were isolated when amide **1** was treated with either diethyl or dimethylzinc in the presence of *t*BuI and oxygen at room temperature. The cascade involving iodine-atom transfer from the tertiary iodide to ethyl or methyl radical, *tert*-butyl radical addition to the activated triple bond, 5-*exo* cyclization of the intermediate vinyl radical **A** leading to **B**, or iodine-atom transfer leading to **C** was the only observed pathway (Scheme 1). No competitive reduction leading to

Table 1. Reaction of dialkylzincs with amide **1** in the presence of an alkyl iodide.



Entry	In. (equiv.)	R^1I (equiv.)	Product, Yield [%] (*E*/*Z*)
1	Et_2Zn (1.5)	*t*BuI (10)	**2**, 98 (92:8)
2	Et_2Zn (0.6)	*t*BuI (10)	**2**, 82 (88:12)
3	Me_2Zn (1.5)	*t*BuI (10)	**2**, 95 (88:12)
4	Et_2Zn (0.9)[a]	*i*PrI (10)	**3**, 69 (80:20) **4**, 22 (78:22)
5	Et_2Zn (0.9)[a]	*i*PrI (20)	**3**, 84 (80:20) **4**, 5 (78:22)
6	Me_2Zn (1.5)	*i*PrI (10)	**3**, 66[b] (80:20)
7	Et_3B (2)	*i*PrI (10)	**3**, 74 (80:20)

[a] $ZnEt_2$ was added by portion: first 0.6 equiv. and then, after 1 h, 0.3 equiv. more. [b] Trace amount of **1** was detected in the ^{1}H NMR spectrum of the crude mixture.

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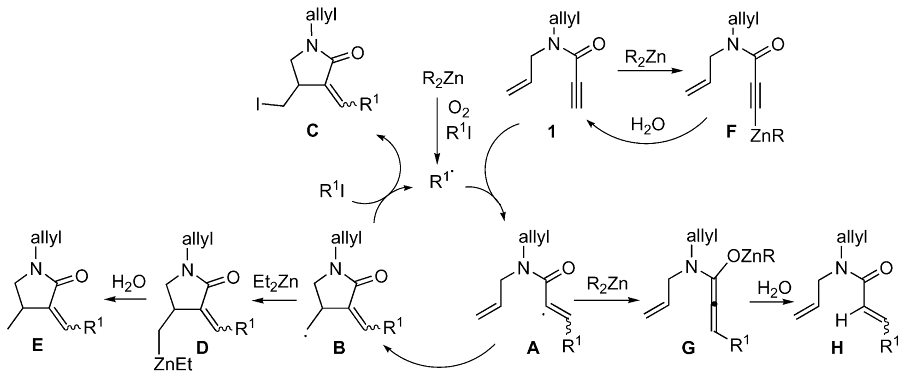


Scheme 1. General mechanism.

D was detected. According to this mechanism, a catalytic amount of dialkylzinc should be sufficient for the reaction to proceed to completion.

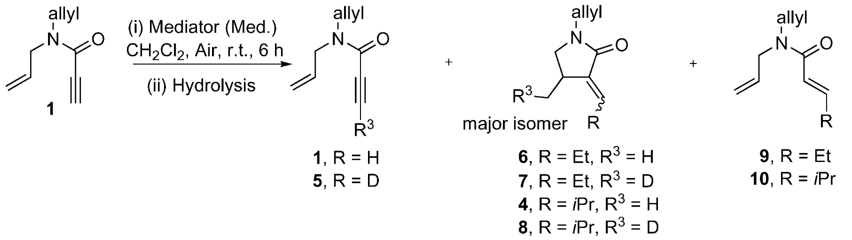
In fact, owing to the fast consumption of diethylzinc by oxidation, and conversely, to the lower efficacy of dimethylzinc oxidation in producing methyl radicals,[20] the amount of dialkylzinc could not be lowered to less than 0.6 equiv. in the case of diethylzinc and 1.5 equiv. in the case of dimethylzinc (Table 1, entries 1–3).

In the presence of *i*PrI, the reaction led to iodide **3** as the only product under dimethylzinc mediation (Table 1, entry 6). In this respect, similar results could be obtained by using triethylborane as the mediator (Table 1, entry 7). In the case of diethylzinc, besides iodide **3**, the reduction product **4** was also isolated (Table 1, entry 4). The amount of **4** was lowered in the presence of a large excess of isopropyl iodide (Table 1, entry 5). This observation can be interpreted according to Scheme 1 by the competition between iodine-atom transfer leading to **C** and S_H2 at diethylzinc leading to primary alkylzinc **D**.[21] The latter is protonated upon workup to give **E**.[22] Homolytic displacement at zinc with a primary alkyl radical should become easier as the C–Zn bond becomes weaker.[23]

It is noteworthy that iodine-atom transfer was the only observed pathway in the presence of *t*BuI. The data obtained in the presence of an alkyl iodide are rather puzzling, as in all cases, no unreacted starting material, which might be recovered from the protonation of the metallated substrate (**F**), was detected.[24] This suggests that the presence of the alkyl iodide could modify the polarity of the C–Zn bonds. Comparative data obtained with dialkylzinc reagents in the absence of alkyl iodide are reported in Table 2.

Whatever the experimental conditions (degassed medium, nondegassed medium, or nondegassed medium with

Table 2. Reaction of dialkylzinc reagents with amide **1** in the absence of alkyl iodide.



Entry	Med. (equiv.)	Air	Hydrolysis	Products (ratio)[a]	Product, isolated yield [%]
1	Me_2Zn (2)	degassed	D_2O	**1** (4)/**5** (96)	quantitative
2	Me_2Zn (2)	20 mL/1 h	D_2O	**1** (13)/**5** (87)	quantitative
3	Et_2Zn (2)	degassed	D_2O	**5** (95)[b]/**7** (4)/**9** (1)	
4	Et_2Zn (2)	nondegassed	D_2O	**5** (81)[b]/**7** (16)/**9** (2)	
5	Et_2Zn (2)	20 mL/1 h	H_2O	**1** (53)/**6** (41)/**9** (6)	
6	Et_2Zn (2)[c]	10 mL/15 min	H_2O	**1** (35)/**6** (65)/**9** (traces)	**1**, 19; **6**, 37
7	*i*Pr_2Zn (2)	20 mL/1 h	H_2O	**1** (63)/**4** (26)/**10** (11)	
8	*i*Pr_2Zn (1)	20 mL/1 h	D_2O	**5** (38)[b]/**8** (54)[b]/**10** (8)	**5**, 23;[b] **8**, 33[b]
9	*i*Pr_2Zn (1)[d]	10 mL/15 min	H_2O	**1** (30)/**4** (68)/**10** (2)	**1**, 18; **4**, 41
10	Et_3B (2)	20 mL/1 h	H_2O	**1**[e]	**1**, 48

[a] Determined by ^1H NMR spectroscopic analysis of the crude mixture. [b] Deuteration of **5** was ≈95%, deuteration of **8** was ≈70%. [c] Et_2Zn was added in portions (10 × 0.2 equiv.), and each addition was immediately followed by injection of air (10 mL over 15 min). [d] *i*Pr_2Zn was added in portions (7 × 0.14 equiv.), and each addition was immediately followed by injection of air (10 mL over 15 min). [e] ^1H NMR spectrum of the crude reaction mixture showed the presence of the starting material mixed together with small amounts of unidentified product.

addition of air by a syringe pump), the only reaction observed with dimethylzinc was the deprotonation of the triple bond to form the corresponding metallated derivative. This was well confirmed by the deuteration of the terminal alkyne upon the quenching of the reaction with D_2O (Table 2, entries 1 and 2). This behaviour is in agreement with the low oxidation rate of Me_2Zn[20] and the poor reactivity of methyl radical regarding conjugate addition.[25]

According to the already cited theoretical calculations,[23] for dialkylzinc reagents, the negative charge at the carbon atom decreases in the order Me > Et > *i*Pr. Diethylzinc and diisopropylzinc oxidation rates were fast enough to compete with proton transfer and cyclized products **4** and **6**–**8** were isolated. The formation of **4** and **6**–**8** implies that oxidized species like ROOZnR or RZnOR formed during the oxidation process are less basic than R_2Zn species.[26]

Alkyne metallation was the main pathway observed with diethylzinc in degassed medium (Table 2, entry 3). However, in the presence of oxygen, the amount of lactam **6** (or its deuterated analogue **7**) resulting from the addition of ethyl radical to the triple bond increased (Table 2, entries 3–5). Under these conditions, the conjugate radical addition became competitive with respect to alkyne metallation. Owing to this competition, the highest yield in cyclized product was obtained when diethylzinc and air were added by portions to the substrate in solution (Table 2, entry 6). After workup, the starting material was recovered from alkynylzinc **F**. A trace amount of adduct **9** was also detected. Product **9** (**H** in Scheme 1) is likely to originate from attack of vinyl radical **A** at R_2Zn followed by protonation of the resulting zinc allenoate **G** upon workup. However, hydrogen abstraction from any potential hydrogen-atom donor present in the reaction medium cannot be excluded.

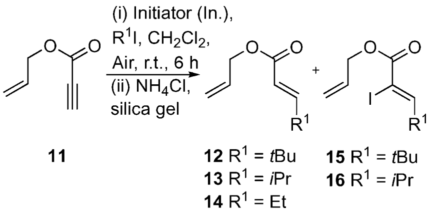
The behaviour of diisopropylzinc was very close to that of diethylzinc (Table 2, entries 7–9). When 1 equiv. was added in portions, amide **4** accounted for 68% of the mixture (41% isolated yield). A small amount of **10** resulting from conjugate radical addition was also detected.

In the presence of Et_3B, only partial degradation was observed. This result, together with the deuteration of compound **8** (almost equal to 70%, see: Table 2, entry 8, footnote b) argue in favour of the formation of **E** from **B** via **D** in the case of the Et_2Zn- and iPr_2Zn-mediated reactions (Scheme 1). Competitive direct hydrogen abstraction should be involved, as **8** was not fully deuterated.

When applied to ester **11**, the methodology led exclusively to noncyclized products **12**–**14** and **15** and **16** depending on the reagents (Table 3).The formation of both types of product can be rationalized according to a radical pathway (Scheme 2).

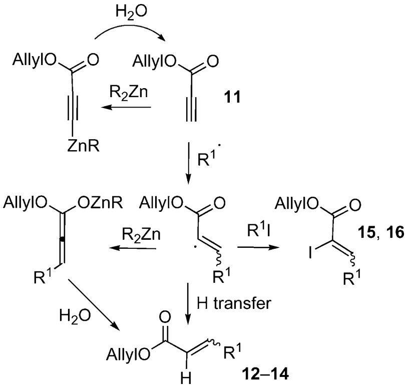
The vinyl radical resulting from addition of R^1 to the triple bond does not undergo 5-*exo* ring closure. It is known that the conversion of the more-stable *Z* rotamer into the *E* rotamer is essential for the 5-*exo* cyclization of α-alkoxycarbonyl and α-amide radicals to proceed.[27] Whereas α-amide radicals can reach the appropriate conformation, provided the substituent at the nitrogen atom is adequately selected, heating is needed to promote the cyclization of α-alkoxycarbonyl radicals[27a] at least in nonpolar medium.[5c,5d] The same argument should apply to their vinylic analogues [Equation (1)].

Table 3. Reaction of dialkylzinc reagents and R^1I (10 equiv.) with **11**.

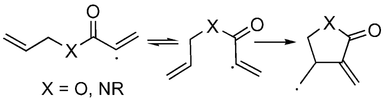


Entry	In. (equiv.)	R^1I	Yield[a] [%]	Products (ratio)
1	Et_2Zn (1.5)	*t*BuI	89	**12**[b]/**15**[c] (98:2)
2	Et_2Zn (0.4)[d]	*t*BuI	73	**12**[b]/**15**[c] (27:73)
3	Et_2Zn (0.2)[d]	*t*BuI	79	**12**[b]/**15**[c] (13:87)
4	Et_2Zn (1.5)	*i*PrI	87	**13**[e]/**16**[f] (83:17)
5	Et_2Zn (0.4)[d]	*i*PrI	78	**13**[e]/**16**[f] (28:72)
6	Et_2Zn (0.2)[d]	*i*PrI	70	**13**[e]/**16**[f] (14:86)
7	Et_2Zn (1.5)	none	60[g]	**14**[e]
8	Me_2Zn (2)	*i*PrI	34[g]	**13**[e]/**16**[h] (51:49)
9	Et_3B (2)	*i*PrI	94	**16**[f]

[a] Sum of individual isolated yields. [b] Only the *trans* double bond was observed in the ^1H NMR spectra of the crude mixture. [c] Only one isomer was detected. [d] Initiator was added in two portions. [e] A 90:10 mixture of *E*/*Z* isomers. [f] A 65:35 mixture of *Z*/*E* isomers. [g] Starting material was partially recovered, and it could not be accurately quantified owing to its low boiling point. [h] A 60:40 mixture of *Z*/*E* isomers.



Scheme 2. Rationale for the formation of **12**–**16**.



(1)

Thereby, at room temperature, the intermediate vinyl radical can either abstract an iodine atom from the alkyl iodide or react through homolytic substitution at the dialkylzinc to give a zinc allenoate. Again, as compounds **13** and **14** were partially deuterated (50%) upon workup with D_2O or ND_4Cl/D_2O, competitive reduction through hydrogen-atom transfer from any hydrogen-atom donor (including alkylzinc and alkoxyzinc species) present in the reaction medium must be envisaged.

In agreement with the relative bond strength of C–Zn bonds,[23] homolytic substitution at zinc should be more favoured with diethylzinc than with dimethylzinc. A larger amount of **13** was formed with Et_2Zn (Table 3, entries 4 and 8). In the presence of 1.5 equiv. of diethylzinc, the rate of reductive zincation is faster than iodine-atom transfer, whatever the alkyl iodide (Table 3, entries 1 and 4).

The influence of dialkylzinc concentration explains the reversal in the chemoselectivity (Table 3, entries 1,3 and 4,6). In addition, competitive metallation of the alkyne occurred with dimethylzinc as witnessed by the recovery of starting material after workup (Table 3, entry 8). Iodine-atom transfer was the only observed pathway when triethylborane was used as the mediator (Table 3, entry 9).

Conclusions

Dialkylzinc reagents were used to mediate atom transfer tandem radical addition/cyclization sequences leading to α-alkylidene-γ-lactams in good yields. In the presence of air, alkylative cycloisomerization of propiolic derivatives could be carried out without interference of the deprotonation of the acidic terminal alkyne. Final oxidation by iodine-atom transfer predominates over reductive zincation, which enlarges the synthetic potential of dialkylzinc-mediated processes.

Experimental Section

General Procedure for the ATRAC Reaction: Alkyl iodide was added under an atmosphere of argon at room temperature to a 0.2-M solution of substrate **1** in dichloromethane. The mediator (R_2Zn or Et_3B) was then introduced, and the reaction was stirred at the same temperature whilst air (20 mL) was injected through a needle into the solution for 1 h. After stirring for 6 h, the reaction was quenched by adding aqueous NH_4Cl. The reaction mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (FC) on silica gel (see Table 1).

***N,N*-Diallylpropiolamide (1):** A solution of propiolic acid (1 mL, 16.2 mmol) in CH_2Cl_2 (35 mL) was cooled to –20 °C. Dicyclohexylcarbodiimide (3.34 g, 16.2 mmol) and diallylamine (2 mL, 16.2 mmol) were added, and the reaction was warmed up to room temperature. After one night at room temperature, the solution was filtered through a short pad of silica gel, which was washed with CH_2Cl_2. After concentration in vacuo, the resulting oil was purified by FC (10% AcOEt/pentane) to give **1** (1.49 g, 9.99 mmol, 62%). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.10 (s, 1 H), 4.00 (br. d, J = 6.0 Hz, 2 H), 4.16 (br. d, J = 5.7 Hz, 2 H), 5.11–5.27 (m, 4 H), 5.65–5.85 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.7 (CH_2), 50.9 (CH_2), 76.1 (CH), 79.0 (C), 118.6 (CH_2), 118.7 (CH_2), 132.2 (CH), 132.8 (CH), 153.6 (C=O) ppm. HRMS: calcd. for $C_9H_{11}NO$ $[M + H]^+$ 150.0913; found 150.0913.

1-Allyl-4-iodomethyl-3-(2,2-dimethylpropylidene)pyrrolidin-2-one (2): Treatment of **1** (100 mg, 0.67 mmol) according to the above general procedure in the presence of *tert*-butyl iodide (800 µL, 6.7 mmol, 10 equiv.) and diethylzinc (1 mL, 1 mmol, 1.5 equiv.) led to **2** (219 mg, 0.657 mmol, 98%, *E*/*Z* = 92:8) after FC (10% AcOEt/pentane). Treatment of **1** (100 mg, 0.67 mmol) according to the general procedure in the presence of *tert*-butyl iodide (800 µL, 6.7 mmol, 10 equiv.) and diethylzinc (0.4 mL, 0.4 mmol, 0.6 equiv.) led to **2** (184 mg, 0.554 mmol, 82%, *E*/*Z* = 88:12) after FC (10% AcOEt/pentane). Treatment of **1** (100 mg, 0.67 mmol) according to the general procedure in the presence of *tert*-butyl iodide (800 µL, 6.7 mmol, 10 equiv.) and dimethylzinc (0.5 mL, 1 mmol, 1.5 equiv.) led to **2** (213 mg, 0.64 mmol, 95%, *E*/*Z* = 88:12) after FC (10% AcOEt/pentane). Data for the (*E*) major isomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 3.04 (pseudo t, J = 10.2 Hz, 1 H), 3.24 (d, J = 10.0 Hz, 1 H), 3.29 (ddd, J = 10.0, 2.6, 1.2 Hz, 1 H), 3.45 (ddd, J = 10.2, 6.8, 1.2 Hz, 1 H), 3.49–3.57 (m, 1 H), 3.94 (ddt, J = 14.9, 6.2, 1.1 Hz, 1 H), 4.03 (ddt, J = 14.9, 6.2, 1.1 Hz, 1 H), 5.18–5.27 (m, 2 H), 5.75 (ddt, J = 17.4, 9.8, 6.2 Hz, 1 H), 6.59 (d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2 (CH_2), 30.2 (CH_3), 34.5 (C), 37.9 (CH), 46.1 (CH_2), 51.0 (CH_2), 118.2 (CH_2), 130.8 (C), 132.5 (CH), 146.0 (CH), 168.6 (C=O) ppm. HRMS: calcd. for $C_{13}H_{20}INO$ $[M + H]^+$ 334.0662; found 334.0664. Data for the (*Z*) minor isomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 9 H), 3.94–3.03 (m, 1 H), 3.10 (dd, J = 9.8, 3.4 Hz, 1 H), 3.12 (superimposed pseudo t, J = 10.2 Hz, 1 H), 3.26–3.34 (m, 2 H), 3.50 (dd, J = 10.4, 7.7 Hz, 1 H), 3.95 (br. d, J = 6.0 Hz, 1 H), 5.13–5.30 (m, 2 H), 5.75 (ddt, J = 17.6, 9.8, 6.2 Hz, 1 H), 5.97 (d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.6 (CH_2), 30.8 (CH_3), 33.6 (C), 40.7 (CH), 46.1 (CH_2), 51.1 (CH_2), 118.8 (CH_2), 132.6 (CH), 133.6 (C), 150.7 (CH), 166.1 (C=O) ppm. HRMS: calcd. for $C_{13}H_{20}INO$ $[M + H]^+$ 334.0662; found 334.0664.

(*E*)-1-Allyl-4-iodomethyl-3-(2-methylpropylidene)pyrrolidin-2-one (3) and (*E*)-1-Allyl-4-methyl-3-(2-methylpropylidene)pyrrolidin-2-one (4): Treatment of **1** (100 mg, 0.67 mmol) according to the general procedure in the presence of isopropyl iodide (670 µL, 6.7 mmol, 10 equiv.) and diethylzinc (0.6 mL, 0.6 mmol, 0.9 equiv.) led to **3** (147 mg, 0.462 mmol, 69%, *E*/*Z* = 80:20) and **4** (28.4 mg, 0.147 mmol, 22%, *E*/*Z* = 78:22) after FC (10% AcOEt/pentane). Diethylzinc was added in portions (0.4 mL at first, an additional 0.2 mL after 1 h). Treatment of **1** (100 mg, 0.67 mmol) according to the general procedure in the presence of isopropyl iodide (1.33 mL, 13.4 mmol, 20 equiv.) and diethylzinc (0.6 mL, 0.6 mmol, 0.9 equiv.) led to **3** (180 mg, 0.563 mmol, 84%, *E*/*Z* = 80:20) and **4** (7 mg, 0.036 mmol, 5%, *E*/*Z* = 78:22) after FC (10% AcOEt/pentane). Diethylzinc was added in portions (0.4 mL at first, an additional 0.2 mL after 1 h). Treatment of **1** (100 mg, 0.67 mmol) according to the general procedure in the presence of isopropyl iodide (670 µL, 6.7 mmol, 10 equiv.) and dimethylzinc (0.5 mL, 1 mmol, 1.5 equiv.) led to **3** (141 mg, 0.442 mmol, 66%, *E*/*Z* = 80:20). Treatment of **1** (100 mg, 0.67 mmol) according to the general procedure in the presence of isopropyl iodide (670 µL, 6.7 mmol, 10 equiv.) and triethylborane (1.34 mL, 1.34 mmol, 2 equiv.) led to **3** (158 mg, 0.496 mmol, 74%, *E*/*Z* = 80:20). Data for (*E*)-**3** (major isomer): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, J = 6.8 Hz, 3 H), 1.09 (d, J = 6.8 Hz, 3 H), 2.53 (dsept., J = 10.9, 6.4 Hz, 1 H), 3.06 (pseudo t, J = 10.8 Hz, 1 H), 3.17 (dd, J = 10.4, 1.9 Hz, 1 H), 3.23–3.33 (m, 2 H), 3.49 (ddd, J = 10.4, 7.4, 0.8 Hz, 1 H), 3.90–4.05 (m, 2 H), 5.16–5.26 (m, 2 H), 5.74 (ddt, J = 17.4, 9.8, 6.0 Hz, 1 H), 6.42 (dd, J = 10.9, 1.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7 (CH_2), 22.7 (CH_3), 22.9 (CH_3), 29.2 (CH), 37.0 (CH), 46.0 (CH_2), 51.6 (CH_2), 118.9 (CH_2), 132.1 (C), 132.4 (CH), 143.2 (CH), 167.8 (C=O) ppm. HRMS: calcd. for $C_{12}H_{18}INO$ $[M + H]^+$ 320.0505; found 320.0500. Data for (*Z*)-**3** (minor isomer): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, J = 6.6 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 3.12 (t, J = 9.0 Hz, 1 H), 3.08 (dd, J = 9.6, 3.8 Hz, 1 H), 3.02 (superimposed m, 1 H), 3.31 (dd, J = 3.6, 9.5 Hz, 1 H), 3.48 (dd, J = 7.2, 9.8 Hz, 1 H), 3.94 (br. d, J = 6.1 Hz, 2 H), 4.01

(dsept., J = 10.0, 6.6 Hz, 1 H), 5.17–5.29 (m, 2 H), 5.73 (dd, J = 1.5, 10.2 Hz, 1 H), 5.66–5.85 (superimposed m, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.8 (CH$_2$), 23.0 (CH$_3$), 23.3 (CH$_3$), 25.8 (CH), 39.1 (CH), 45.7 (CH$_2$), 51.4 (CH$_2$), 118.8 (CH$_2$), 131.2 (C), 132.6 (CH), 147.1 (CH), 167.5 (C=O) ppm. HRMS: calcd. for $C_{12}H_{18}INO$ [M + H]$^+$ 320.0505; found 320.0502. Data for (*E*)-**4** (major isomer): ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.03 (d, J = 6.6 Hz, 3 H), 1.08 (d, J = 6.6 Hz, 3 H), 1.19 (d, J = 7.2 Hz, 3 H), 2.58 (dsept., J = 10.6, 6.6 Hz, 1 H), 2.89 (dd, J = 1.9, 9.8 Hz, 1 H), 3.03 (pseudo tt, J = 1.9, 7.2 Hz, 1 H), 3.50 (dd, J = 7.7, 9.8 Hz, 1 H), 3.90 (br. dd, J = 15.2, 6.2 Hz, 1 H), 4.03 (br. dd, J = 15.2, 6.0 Hz, 1 H), 5.15–5.24 (m, 2 H), 5.74 (ddt, J = 17.4, 9.8, 6.0 Hz, 1 H), 6.27 (dd, J = 1.9, 10.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 22.0 (CH$_3$), 22.8 (CH$_3$), 23.1 (CH$_3$), 28.6 (CH), 29.0 (CH), 46.0 (CH$_2$), 52.7 (CH$_2$), 118.2 (CH$_2$), 132.9 (CH), 134.8 (C), 140.6 (CH), 168.6 (C=O) ppm. HRMS: calcd. for $C_{12}H_{19}NO$ [M + H]$^+$ 194.1539; found 194.1536.

General Procedure for the Reaction of Dialkylzinc Reagents with Amide 1: The mediator (R$_2$Zn or Et$_3$B) was added under an atmosphere of argon at room temperature to a 0.2-M solution of substrate in dichloromethane. The reaction was stirred at the same temperature whilst air (20 mL) was injected through a needle into the solution for 1 h. After stirring for 6 h at room temperature, the reaction was quenched by adding aqueous NH$_4$Cl, D$_2$O or ND$_4$Cl. The reaction mixture was extracted with CH$_2$Cl$_2$ (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by FC on silica gel (see Table 2).

Deuterated Compound 5: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.00 (br. d, J = 6.0 Hz, 2 H), 4.16 (br. d, J = 5.7 Hz, 2 H), 5.11–5.27 (m, 4 H), 5.65–5.85 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 46.7 (CH$_2$), 50.9 (CH$_2$), 76.1 (t, J = 7.7 Hz, **C**C-D), 79.3 (t, J = 39.0 Hz, C-D), 118.6 (CH$_2$), 118.7 (CH$_2$), 132.2 (CH), 132.8 (CH), 153.6 (C=O) ppm. HRMS: calcd. for $C_9H_{10}DNO$ [M + H]$^+$ 151.0976; found 151.0973.

1-Allyl-4-methyl-3-propylidenepyrrolidin-2-one (6): ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.08 (t, J = 7.6 Hz, 3 H), 1.18 (d, J = 7.0 Hz, 3 H), 2.21 (pseudo quint., J = 7.6 Hz, 2 H), 2.90 (dd, J = 1.9, 9.6 Hz, 1 H), 2.97–3.09 (m, 1 H), 3.50 (dd, J = 7.9, 9.6 Hz, 1 H), 3.90 (br. dd, J = 6.0, 15.1 Hz, 1 H), 4.04 (br. dd, J = 5.9, 15.1 Hz, 1 H), 5.11–5.25 (m, 2 H), 5.75 (ddt, J = 9.6, 17.4, 6.0 Hz, 1 H), 6.43 (dt, J = 2.1, 7.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0 (CH$_3$), 21.5 (CH$_3$), 22.3 (CH$_2$), 29.0 (CH), 45.9 (CH$_2$), 52.6 (CH$_2$), 118.2 (CH$_2$), 132.9 (CH), 135.5 (CH), 136.6 (C), 168.4 (C=O) ppm. HRMS: calcd. for $C_{11}H_{17}NO$ [M + H]$^+$ 180.1382; found 180.1382.

Deuterated Compound 7: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.08 (t, J = 7.6 Hz, 3 H), 1.14–1.21 (m, 2 H), 2.21 (pseudo quint., J = 7.6 Hz, 2 H), 2.90 (dd, J = 1.9, 9.6 Hz, 1 H), 2.97–3.09 (m, 1 H), 3.50 (dd, J = 7.9, 9.6 Hz, 1 H), 3.90 (br. dd, J = 6.0, 15.1 Hz, 1 H), 4.04 (br. dd, J = 5.9, 15.1 Hz, 1 H), 5.11–5.25 (m, 2 H), 5.75 (ddt, J = 9.6, 17.4, 6.0 Hz, 1 H), 6.43 (dt, J = 2.1, 7.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0 (CH$_3$), 21.5 (t, $J_{C,D}$ = 19.8 Hz, CH$_2$), 22.3 (CH$_2$), 29.0 (CH), 45.9 (CH$_2$), 52.6 (CH$_2$), 118.2 (CH$_2$), 132.9 (CH), 135.5 (CH), 136.6 (C), 168.4 (C=O) ppm. HRMS: calcd. for $C_{11}H_{16}DNO$ [M + H]$^+$ 181.1446; found 181.1442.

Deuterated Compound 8: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.03 (d, J = 6.6 Hz, 3 H), 1.08 (d, J = 6.6 Hz, 3 H), 1.13–1.20 (m, 2 H), 2.58 (dsept., J = 10.6, 6.6 Hz, 1 H), 2.89 (dd, J = 1.9, 9.8 Hz, 1 H), 3.03 (pseudo tt, J = 1.9, 7.2 Hz, 1 H), 3.50 (dd, J = 7.7, 9.8 Hz, 1 H), 3.90 (br. dd, J = 15.2, 6.2 Hz, 1 H), 4.03 (br. dd, J = 15.2, 6.0 Hz, 1 H), 5.15–5.24 (m, 2 H), 5.74 (ddt, J = 17.4, 9.8, 6.0 Hz, 1 H), 6.27 (dd, J = 1.9, 10.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.7 (t, $J_{C,D}$ = 19.8 Hz, CH$_2$), 22.8 (CH$_3$), 23.1 (CH$_3$), 28.6 (CH), 29.0 (CH), 46.0 (CH$_2$), 52.7 (CH$_2$), 118.2 (CH$_2$), 132.9 (CH), 134.8 (C), 140.6 (CH), 168.6 (C=O) ppm. HRMS: calcd. for $C_{12}H_{18}DNO$ [M + H]$^+$ 195.1602; found 195.1594.

(*E*)-*N*,*N*-Diallylpent-2-enamide (9): ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.06 (t, J = 7.4 Hz, 3 H), 2.23 (pseudo quint.d, J = 7.4, 1.3 Hz, 2 H), 3.82–4.18 (m, 4 H), 5.09–5.27 (m, 4 H), 5.66–5.89 (m, 2 H), 6.14 (dt, J = 15.9, 1.3 Hz, 1 H), 6.99 (dt, J = 15.1, 6.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.0 (CH$_3$), 26.0 (CH$_2$), 48.8 (CH$_2$), 49.5 (CH$_2$), 117.0 (CH$_2$), 117.6 (CH$_2$), 119.7 (CH), 133.5 (CH), 133.8 (CH), 148.8 (CH), 167.3 (C=O) ppm. HRMS: calcd. for $C_{11}H_{17}NO$ [M + H]$^+$ 180.1382; found 180.1378.

(*E*)-*N*,*N*-Diallyl-4-methylpent-2-enamide (10): ^{1}H NMR (300 MHz, CDCl$_3$): characteristic signals: δ = 2.40 (oct.d, J = 6.8, 1.1 Hz, 1 H), 6.05 (dd, J = 15.1, 1.1 Hz, 1 H), 6.84 (dd, J = 15.1, 6.8 Hz, 1 H) ppm.

General Procedure for the Reaction of Dialkylzinc Reagents and Alkyl Iodides with Ester 11: Alkyl iodide (10 equiv.) was added under an atmosphere of argon at room temperature to a 0.2-M solution of substrate **11** in dichloromethane. The mediator (R$_2$Zn or Et$_3$B) was then introduced, and the reaction was stirred at the same temperature whilst air (20 mL) was injected through a needle into the solution for 1 h. After stirring for 6 h, the reaction was quenched by adding aqueous NH$_4$Cl. The reaction mixture was extracted with CH$_2$Cl$_2$ (×3). The organic layer was dried, filtered and concentrated. The crude product was purified by FC on silica gel (see Table 3).

Allyl Propynoate (11): Substrate **11** was prepared according to a known procedure.[28] To a solution of propiolic acid (4 mL, 64.87 mmol) in DMF (25 mL) was added NaHCO$_3$ (10.9 g, 129.74 mmol, 2 equiv.) portionwise. After 1 h stirring at room temperature, allyl bromide (8.4 mL, 97.3 mmol, 1.5 equiv.) was added, and the reaction was stirred for one night. The reaction was diluted with Et$_2$O (25 mL) and washed several times with water. The organic layer was dried (MgSO$_4$), filtered and concentrated in vacuo. Compound **11** was isolated in 97% yield (6.9 g, 63.21 mmol).^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.91 (s, 1 H), 4.70 (br. d, J = 5.8 Hz, 2 H), 5.31 (br. dd, J = 10.4, 1.0 Hz, 1 H), 5.39 (br. dd, J = 17.1, 1.0 Hz, 1 H), 5.94 (ddt, J = 17.1, 10.4, 5.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 67.1 (CH$_2$), 74.9 (CH), 75.4 (C), 119.9 (CH$_2$), 131.2 (CH), 152.7 (C=O) ppm.

(*E*)-Allyl 4,4-Dimethylpent-2-enoate (12) and Allyl 2-Iodo-4,4-dimethylpent-2-enoate (15): Treatment of **11** (100 mg, 0.91 mmol) according to the general procedure in the presence of *tert*-butyl iodide (1.1 mL, 9.1 mmol, 10 equiv.) and diethylzinc (1.4 mL, 1.4 mmol, 1.5 equiv.) led to **12** (136 mg, 0.808 mmol, 89%) after FC (2–10% AcOEt/pentane). A trace amount of **15** was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Treatment of **11** (100 mg, 0.91 mmol) according to the general procedure in the presence of *tert*-butyl iodide (1.1 mL, 9.1 mmol, 10 equiv.) and diethylzinc (0.36 mL, 0.364 mmol, 0.4 equiv. in 2 portions, 0.2 equiv. every 2 h) led to **12** (31 mg, 0.184 mmol, 20%) and **15** (141 mg, 0.478 mmol, 53%) after FC (2–10% AcOEt/pentane). Treatment of **11** (100 mg, 0.91 mmol) according to the general procedure in the presence of *tert*-butyl iodide (1.1 mL, 9.1 mmol, 10 equiv.) and diethylzinc (0.18 mL, 0.182 mmol, 0.2 equiv., 2 × 0.1 equiv. every 2 h) led to **12** (16 mg, 0.094 mmol, 10%) and **15** (184 mg, 0.626 mmol, 69%) after FC (2–10% AcOEt/pentane). Data for **12**: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.07 (s, 9 H), 4.62 (dt, J = 5.6, 1.3 Hz, 2 H), 5.20–5.39 (m, 2 H), 5.76 (d, J = 15.9 Hz, 1 H), 5.95 (ddt, J = 17.2, 10.4, 5.7 Hz, 1 H), 6.99 (d, J = 15.9 Hz, 1 H) ppm. ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 29.0 (CH_3), 34.2 (C), 65.3 (CH_2), 116.8 (CH), 118.5 (CH_2), 132.8 (CH), 159.9 (CH), 167.3 (C=O) ppm. HRMS: calcd. for $C_{10}H_{16}O_2$ [M + H]$^+$ 169.1223; found 169.1219. Data for **15**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (s, 9 H), 4.68 (br. d, *J* = 5.9 Hz, 2 H), 5.27–5.48 (m, 2 H), 5.96 (ddt, *J* = 17.0, 10.6, 5.9 Hz, 1 H), 6.37 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.5 (CH_3), 38.9 (C), 66.8 (CH_2), 79.0 (C), 119.7 (CH_2), 131.5 (CH), 155.7 (CH), 166.8 (C=O) ppm. HRMS: calcd. for $C_{10}H_{15}IO_2$ [M + H]$^+$ 295.0189; found 295.0184.

(*E*)-Allyl 4-Methylpent-2-enoate (13) and Allyl 2-Iodo-4-methylpent-2-enoate (16): Treatment of **11** (100 mg, 0.91 mmol) according to the general procedure in the presence of isopropyl iodide (0.91 mL, 9.1 mmol, 10 equiv.) and diethylzinc (1.4 mL, 1.4 mmol, 1.5 equiv.) led to **13** (111 mg, 0.72 mmol, 78%, *E*/*Z* = 90:10) and **16** (22 mg, 0.08 mmol, 9%, *E*/*Z* = 35:65) after FC (2–10% AcOEt/pentane). Treatment of **11** (100 mg, 0.91 mmol) according to the general procedure, in the presence of isopropyl iodide (0.91 mL, 9.1 mmol, 10 equiv.) and diethylzinc (0.36 mL, 0.364 mmol, 0.4 equiv. in 2 portions, 0.2 equiv. every 2 h) led to **13** (30 mg, 0.195 mmol, 21%, *E*/*Z* = 90:10) and **16** (145 mg, 0.519 mmol, 57%, *E*/*Z* = 35:65) after FC (2–10% AcOEt/pentane). Treatment of **11** (100 mg, 0.91 mmol) according to the general procedure in the presence of isopropyl iodide (0.91 mL, 9.1 mmol, 10 equiv.) and diethylzinc (0.18 mL, 0.182 mmol, 0.2 equiv. in 2 portions, 0.1 equiv. every 2 h) led to **13** (14 mg, 0.093 mmol, 10%, *E* major) and **16** (153 mg, 0.545 mmol, 60%, *E*/*Z* = 35:65) after FC (2–10% AcOEt/pentane). Treatment of **11** (100 mg, 0.91 mmol) according to the general procedure in the presence of isopropyl iodide (0.91 mL, 9.1 mmol, 10 equiv.) and dimethylzinc (0.69 mL, 1.4 mmol, 1.5 equiv.) led to **13** (23 mg, 0.155 mmol, 17%, *E* major) and **16** (42 mg, 0.1504 mmol, 17%, *E*/*Z* = 40:60) after FC (2–10% AcOEt/pentane). Starting material was detected in the ^{1}H NMR spectrum of the crude mixture, bit owing to its low boiling point, part was evaporated with the solvent and could thus not be quantified. Treatment of **11** (100 mg, 0.91 mmol) according to the general procedure in the presence of isopropyl iodide (0.91 mL, 9.1 mmol, 10 equiv.) and triethylborane (1.82 mL, 1.82 mmol, 2 equiv.) led to **16** (240 mg, 0.85 mmol, 94%, *E*/*Z* = 35:65) after FC (5% AcOEt/pentane). Data for (*E*)-**13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.8 Hz, 6 H), 2.47 (oct.d, *J* = 6.8, 1.3 Hz, 1 H), 4.65 (dt, *J* = 5.7, 1.1 Hz, 2 H), 5.21–5.39 (m, 2 H), 5.81 (dd, *J* = 15.9, 1.3 Hz, 1 H), 5.96 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1 H), 6.99 (dd, *J* = 15.9, 6.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 31.4 (CH), 65.3 (CH_2), 118.4 (CH_2), 118.7 (CH), 132.8 (CH), 156.3 (CH), 167.0 (C=O) ppm. HRMS: calcd. for $C_9H_{14}O_2$ [M + H]$^+$ 155.1066; found 155.1061. Data for (*Z*)-**16**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.6 Hz, 6 H), 2.47 (dsept., *J* = 9.1, 6.6 Hz, 1 H), 4.63 (dt, *J* = 5.5, 1.5 Hz, 2 H), 5.20 (dq, *J* = 10.4, 1.5 Hz, 1 H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.89 (ddt, *J* = 17.2, 10.4, 5.5 Hz, 1 H), 6.93 (d, *J* = 9.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_3), 36.9 (CH), 67.5 (CH_2), 92.2 (C), 119.0 (CH_2), 132.1 (CH), 159.5 (CH), 168.2 (C=O) ppm. HRMS: calcd. for $C_9H_{13}O_2I$ [M + H]$^+$ 281.0032; found 281.0032. Data for (*E*)-**16**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 6.6 Hz, 6 H), 3.18 (dsept., *J* = 10.2, 6.6 Hz, 1 H), 4.70 (dt, *J* = 5.7, 1.3 Hz, 2 H), 5.30 (dq, *J* = 10.6, 1.3 Hz, 1 H), 5.42 (dq, *J* = 17.2, 1.3 Hz, 1 H), 5.96 (ddt, *J* = 17.2, 10.6, 5.7 Hz, 1 H), 6.72 (d, *J* = 10.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 (CH_3), 33.7 (CH), 67.4 (CH_2), 82.7 (C), 119.4 (CH_2), 132.2 (CH), 163.1 (CH), 163.6 (C=O) ppm.

(*E*)-Allyl Pent-2-enoate (14): Treatment of **11** (100 mg, 0.91 mmol) according to the general procedure in the presence of diethylzinc (1.4 mL, 1.4 mmol, 1.5 equiv.) led to **14** (77 mg, 0.55 mmol, 60%, *E*/*Z* = 90:10) after FC (100% Et_2O). Starting material was detected in the ^{1}H NMR spectrum of the crude mixture and was isolated in 11% yield, but owing to its low boiling point, part could be lost through evaporation. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.4 Hz, 3 H), 2.47 (quint.d, *J* = 7.4, 1.5 Hz, 1 H), 4.63 (dt, *J* = 5.7, 1.1 Hz, 2 H), 5.20–5.38 (m, 2 H), 5.84 (dt, *J* = 15.7, 1.7 Hz, 1 H), 5.95 (ddt, *J* = 16.1, 10.9, 5.7 Hz, 1 H), 7.05 (dt, *J* = 15.7, 6.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.5 (CH_3), 25.7 (CH_2), 65.2 (CH_2), 118.4 (CH_2), 120.5 (CH), 132.8 (CH), 151.5 (CH), 166.8 (C=O) ppm. HRMS: calcd. for $C_8H_{12}O_2$ [M + H]$^+$ 141.0910; found 141.0907.

Supporting Information (see footnote on the first page of this article): Full spectroscopic data for all new compounds.

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