Synthesis of Geminal Dimetal-Substituted Terminal Alkenes Utilizing a Cuprate Rearrangement: Toward an Efficient and General Access to Trisubstituted Olefins

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Abstract: Preparation of 1,1-dimetalated-1-alkenes was realised via metaleate rearrangements in the opening of lithiodihydrofuran 6 by reaction with dilithium stannyl-, silyl-, alkyl- and aryl(cyano)cuprates and quenching with electrophilic agents. Several hetero (E)- and (Z)-1,1-dimetalated alkene derivatives were so produced in good to high yields and total stereocontrol.

Key words: metaleate rearrangement, lithium, copper, tin, trisubstituted olefins

The trisubstituted olefin functional array is an important structural subunit largely found in natural biologically active compounds. The synthesis of these products remains an important challenge particularly in the case of a Z-trisubstituted double bond-containing segment. Even if considerable progress has been made in construction of such elements, the current methods are far from ideal.

As a representative example, the antitumoral agent epothilone D (1) structure encompasses a C12–C13 Z-double bond, which is essential for cytotoxicity (Scheme 1). Several synthetic approaches were based on the formation and the use of a methyl-substituted (Z)-iodomethylvinyl moiety 2.1 Another target was griseoviridin (3), a streptogramin antibiotic, which presents a thioacrylamide core whose construction was already described by different authors2 and ourselves.3 In a distinct perspective, we sought for a new approach exploiting a direct coupling between D-cysteine (4) and the (Z)-vinyl iodide 5.

Owing to these particular goals, we wanted to get a general and efficient access to trisubstituted olefins, and the present manuscript builds on previously published work by Kocienski et al.,4 and us,5 to develop a general method for the synthesis of geminal dimetal-substituted terminal olefins using a cuprate rearrangement. This reaction is related to 1,2-metalate rearrangement (dyotropic rearrangement), which takes place when the lithiodihydrofuran 6 is treated with a cuprate to form the first intermediate vinylic derivative IV and the cuprate V after rearrangement. This latter was reported to be trapped with NH4Cl or MeI4,5 to deliver VI, and then olefin 7, but at this time other electrophilic agents EX were not checked (Scheme 2).
In this paper, toward a further practical synthesis of targets 2 and 5, we wish to report the extension of this methodology to the stereoselective elaboration of (Z)-1-halo-1-methyl-1-alkenes and (Z)-1-halo-1-tributyltin- or (Z)-1-halo-1-triylsilyl-1-alkenes, respectively.

A sequence based on treatment of the lithiodihydrofuran 6 with dilithium dimethyl(cyano)cuprate (8a, Me₂CuCNLi₂)² followed by a Bu₃SnCl quench, led to the production of the expected pure (Z)-1-methyl-1-tributyltin (Z)-9 in 61% yield (Scheme 3). It was earlier reported¹ that the corresponding (E)-9 isomer was prepared in 86% yield, via an inverse sequence (reaction of dilithium bistributyltin(cyano)cuprate (8c, 3 equivalents)³ and MeI trap).

Aromatic transfer can be also effected using this method, and reaction of 6 with dilithium diphenyl(cyano)cuprate (8b)¹⁰ (Ph₂CuCNLi₂, 1.1 equiv) afforded compounds (E)-10 (72% yield) and (Z)-11 (57% yield) as pure isomers after quenching with NH₄Cl, and Bu₃SnCl, respectively. When 1 equivalent of the cuprate 8b, and 3.0 equivalents of phenyllithium were employed, yields improved to 89 and 77%, respectively.

As signified above, another important challenge was to investigate the scope of this methodology in the construction of (Z)-1-halo-1-metalted-1-alkenes. Starting from lithiodihydrofuran 6, treatment with dilithium bistributyltin(cyano)cuprate (8c) led to an intermediate vinylcuprate which was trapped with N-iodosuccinimide (NIS)⁷ (Scheme 4) to give the iodotin derivative (Z)-12 as the only isomer in 75% yield.³ When a N-bromosuccinimide (NBS), or N-chlorosuccinimide (NCS) quench followed the same reaction between cuprate 8c and lithiodihydrofuran 6, the (E)-13 or (E)-14 derivative was prepared as pure stereocontrolled compound in 63 or 56% yield, respectively (Scheme 4). Using chlorotributyltin (Bu₃SnCl), as the electrophilic agent, the 1,1-distannyl derivative 15 was also produced in high yield (>95%).

During this work, the structures of all vinyltin derivatives were established by ¹H and ¹³C NMR analysis, based on the measure of ¹H, ¹³C, and ¹⁴N coupling constants.¹¹ An extension of this cuprate rearrangement is the preparation of vinylsilyl derivatives using a silylcuprate reagent. Thus, lithiodihydrofuran 6 was reacted with dilithium bis(trimethylsilyl(cyano)cuprate (8d) ([Me₃Si]₂CuCNLi₂).¹² We initially performed a NH₄Cl trap, and the silyl product (E)-16 was produced in 86% yield (Scheme 5). When Bu₃SnCl was used as the electrophilic agent, the vinylsilyltin (Z)-17 was cleanly delivered in 87% yield. Interestingly, addition of NIS (4 equiv) resulted in the formation of the stereodefined (Z)-iodosilyl derivative (Z)-18 in 76% yield. Elaboration of a (Z)-1-iodo-1-trimethylsilyle-1-alkene by this route appears to be an alternative proposal of the Lautens procedure.¹³

In conclusion, we have disclosed in this report a general route to hetero 1,1-bimetalated-1-alkenes in high yields and total stereocontrol based on a cuprate rearrangement effected on lithiodihydrofuran 6 followed by an appropriate trap. This methodology reveals also an open route to the preparation of substituted Z-alkenes. Elaboration of an intermediate 2 and the trisubstituted olefin subunit 5, for the application of this methodology toward total synthesis of epothilone D (1) and griseoviridin (3), are currently under investigation.

Scheme 3

Scheme 4

Scheme 5
All air and/or water sensitive reactions were carried out under argon with anhyd, freshly distilled solvents using standard syringe-cannula/ septa technique. All corresponding glassware was oven dried (110 °C) and/or carefully dried in line with a flameless heat gun. THF and Et2O were distilled from sodium-benzophene, CH3Cl2 from CaH2, Et3N and pyridine from KOH. Benzene and toluene were distilled from sodium-benzophene. Pentane and hexane were distilled from phosphoric anhydride. MeOH was distilled from the corresponding magnesium derivative. All reactions were monitored by TLC carried out on precoated plates of silica gel 60F 254 (Art. 9385) or aluminum oxide Merck 60F 254 (Art. 5580).

Visualization was accomplished with UV light, then 10% ethanolic (Merck, Art. 7735) or aluminum oxide Merck 60F 254 (Art. 5550).

TLC carried out on precoated plates of silica gel 60F 254 (Art. 5425) and IR (neat): 3420, 2950, 2920, 2860, 1620, 1466, 1375, 1301, 1080 cm-1.

5-Lithio-2,3-dihydrofuran (6)
A 1.7 M solution of tert-BuLi in hexane (1.8 mL, 3 mmol, 1.2 equiv) was slowly added to a solution of hexamethyldisilane [(Me3Si)2, 1.15 mL, 5.6 mmol, 2.04 equiv]. The mixture was stirred at -40 °C for 5 min, and then was added, via cannula, to a suspension of CuCN (225 mg, 2.5 mmol, 1 equiv) in Et2O at -40 °C (6 mL). The reaction mixture was stirred for 30 to 45 min between -20 to -30 °C.

Bis[(Trimethylsilyl)diolithiocyanocuprate (8d)
To a solution of hexamethyldisilane [(Me3Si)2] (250 mg, 1.15 mmol, 1 equiv) in THF (4 mL) at -40 °C, was added a 1.2 M hexane solution of BuLi (3.2 mL, 5.5 mmol, 2.04 equiv). The mixture was stirred at -40 °C for 5 min and then, at 20 °C for 10 min. The temperature of the cuprate was kept at -30 °C before use.

Bis[(Trimethylsilyl)diolithiocyanocuprate (8c)
Cuprate 8c was prepared according to Still’s procedure. To a solution of hexabutylditin [(Bu4Sn)2] (2.5 mL, 5 mmol, 2 equiv) in THF (4 mL) at -40 °C, was slowly added a 1.2 M hexane solution of BuLi (3.2 mL, 5.5 mmol, 2.04 equiv). The mixture was stirred for 20 min at -40 °C and then was added, via cannula, to a suspension of CuCN (225 mg, 2.5 mmol, 1 equiv) in Et2O at -40 °C (6 mL). The reaction mixture was stirred for 30 to 45 min between -20 to -30 °C.

Bis[(Tributyl)stannyl]dilithiocyanocuprate (8b)
To a suspension of dried CuCN (250 mg, 2.57 mmol, 1.1 equiv) in Et2O (4 mL) at -40 °C, was added a 2 M PhLi solution (cyclohexane, 190 mL, 175 mg, 2.5 mmol, 6 equiv). The mixture was stirred at -40 °C for 5 min, and at 20 °C for 10 min. The temperature of the cuprate was kept at -30 °C before use.

Diphenyldilithiocyanocuprate (8a)
To a solution of hexamethyldisilane [(Me3Si)2] (2.5 mL, 11.5 mmol, 2 equiv) in THF (4 mL) at -40 °C, was slowly added a 1.6 M hexane solution of BuLi (1.8 mL, 3.0 mmol, 1.2 equiv) in THF (2 mL) at -60 °C. The stirring was maintained for 10 min at -60 °C and the flask was rapidly put in an ice bath for 50 min.

Dimethyldilithiocyanocuprate (8a)
To a suspension of dried CuCN (250 mg, 2.75 mmol, 1.1 equiv) in Et2O (4 mL) at -40 °C, was added a 1.6 M MeLi solution in Et2O (3.5 mL, 5.6 mmol, 2.04 equiv). The mixture was stirred at -40 °C for 5 min, and at 20 °C for 10 min. The temperature of the cuprate was kept at -30 °C before use.

Phenyl Transfer
(3E)-4-Phenylbut-3-enol ([E]-10)
A. Prepared according to the general procedure using dihydrofuran 6, diphenyldiacetoacetate 8b (1.1 equiv.) and NH2Cl trap; yield: 265 mg (72%).

B. Prepared according to the general procedure using dihydrofuran 6, PhLi (3 equiv), diphenyldiacetoacetate 3b (1 equiv) and NH2Cl trap; yield: 330 mg (89%).

(3Z)-4-Phenyl-4-(tributylstannyl)but-3-enol ([Z]-11)
A. Prepared according to the general procedure using dihydrofuran 6, diphenyldiacetoacetate 8b (1.1 equiv.) and Bu3SnCl (4.0 equiv) trap; yield: 620 mg (57%).

B. Prepared according to the general procedure using dihydrofuran 6, PhLi (3 equiv), diphenyldiacetoacetate 3b (1 equiv) and Bu3SnCl trap (4.0 equiv) trap; yield: 840 mg (77%).
13C NMR (50 MHz, CDCl3); δ = 11.1 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = 327.0 Hz, J117Sn = 313.0 Hz, 13.6 [3 C, Sn(CH2CH2CH2CH3)], 27.3 [3 C, Sn(CH2CH2CH2CH3}], J119Sn = J117Sn = 55.0 Hz, 29.0 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = J117Sn = 38.0 Hz, 41.6 [C–2], 62.4 [C–1], 125.4 [C–3], 126.7 [2 CH_2, C(CH3)], 139.3 [C–3], 147.5 [C(CH3)4 or C(CH2)], 149.2 [4 C or C(CH3)]

MS (Cl, CH2)= for major Sn isotope, m/z = 337, 307, 306, 304, 252, 250, 249.

Anal. Calcd for C6H9OSn: C, 60.44; H, 8.76; O, 3.66; Sn, 27.15. Found: C, 60.87; H, 9.18.

Tributylstannyl Transfer (3Z)-4-Iodo-4- tributylstannyl|but-3-enol (Z)-12
Prepared according to the general procedure using dihydrofuran 6, tributylstannylycyanole 8e (1.1 equiv), and NIS trap (4.0 equiv); yield: 910 mg (75%).

IR (neat): 3324, 2950, 2920, 2870, 2850, 1594, 1461, 1376, 1180, 1044, 907, 733, 690, 664, 597 cm⁻¹.

1H NMR (200 MHz, CDCl3–D2O): δ = 0.85 [t, J = 8.0 Hz, 6 H, Sn(CH2CH2CH2CH3)], 0.96 [t, J = 8.0 Hz, 9 H, Sn(CH2CH2CH2CH3)], 1.30 [m, 6 H, Sn(CH2CH2CH2CH3)], 1.48 [m, 6 H, Sn(CH2CH2CH2CH3)], 2.45 (q, J = 6.5 Hz, 2 H, H-2), 3.69 (t, J = 6.5 Hz, 2 H, H-1), 6.14 (t, J = 6.5 Hz, J_HSn = J_HSn = 42.0 Hz, 1 H, H-3).

13C NMR (50 MHz, CDCl3); δ = 11.1 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = 348.0 Hz, J117Sn = 332.0 Hz, 13.6 [3 C, Sn(CH2CH2CH2CH3)], 27.3 [2 C, Sn(CH2CH2CH2CH3)], J119Sn = J117Sn = 60.0 Hz, 28.6 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = J117Sn = 20.0 Hz, 42.6 [C–2, J119Sn = J117Sn = 32.0 Hz, 60.9 (C–1), 110.0 (C–4), 145.2 (C–3, J119Sn = J117Sn = 20.0 Hz).

MS (Cl, CH2)= for major Sn isotope, m/z = 377, 322, 307, 252.


Silyl Transfer (3E)-4-((Trimethylsilyl)but-3-enol (E)-13
Prepared according to the general procedure using dihydrofuran 6, trimethylstannylycyanole 8d (1.1 equiv), and NIS trap (4.0 equiv); yield: 690 mg (63%).

1H NMR (200 MHz, CDCl3–D2O): δ = 0.87 [t, J = 8.0 Hz, 6 H, Sn(CH2CH2CH2CH3)], 0.96 [t, J = 8.0 Hz, 9 H, Sn(CH2CH2CH2CH3)], 1.29 [m, 6 H, Sn(CH2CH2CH2CH3)], 1.50 [m, 6 H, Sn(CH2CH2CH2CH3)], 2.58 (q, J = 6.5 Hz, 2 H, H-2), 3.69 (t, J = 6.5 Hz, 2 H, H-1), 6.30 (t, J = 6.5 Hz, J_HSn = J_HSn = 33.0 Hz, 1 H, H-3).

13C NMR (50 MHz, CDCl3); δ = 10.7 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = 348.0 Hz, J117Sn = 333.0 Hz, 13.6 [3 C, Sn(CH2CH2CH2CH3)], 27.2 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = J117Sn = 58.5 Hz, 28.7 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = J117Sn = 20.0 Hz, 36.0 (C–2, J119Sn = J117Sn = 27.5 Hz, 61.3 (C–1), 132.1 (C–4), 139.9 (C–3, J119Sn = J117Sn = 30.0 Hz).

Anal. Calcd for C12H14OSiSn: C, 43.67; H, 7.56; Br, 18.16; O, 3.64; Sn, 26.97. Found: C, 43.92; H, 7.78.

(3E)-4-Chloro-4-tributylstannyl|but-3-enol (E)-14
Prepared according to the general procedure using dihydrofuran 6, tributylstannylycyanole 8e (1.1 equiv), and NCS trap (6.0 equiv); yield: 553 mg (56%).

1H NMR (200 MHz, CDCl3–D2O); δ = 0.87 [t, J = 8.0 Hz, 6 H, Sn(CH2CH2CH2CH3)], 0.99 [t, J = 8.0 Hz, 9 H, Sn(CH2CH2CH2CH3)], 1.20 [m, 6 H, Sn(CH2CH2CH2CH3)], 1.47 [m, 6 H, Sn(CH2CH2CH2CH3)], 2.58 (q, J = 6.5 Hz, 2 H, H-2), 3.67 (t, J = 6.5 Hz, 2 H, H-1), 5.85 (t, J = 6.5 Hz, J_HSn = J_HSn = 30.0 Hz, 1 H, H-3).

13C NMR (50 MHz, CDCl3); δ = 10.4 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = 347.5 Hz, J117Sn = 332.0 Hz, 13.6 [3 C, Sn(CH2CH2CH2CH3)], 27.2 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = J117Sn = 57.0 Hz, 28.6 [3 C, Sn(CH2CH2CH2CH3)], J119Sn = J117Sn = 20.2 Hz, 32.5 (C–2, J119Sn = J117Sn = 26.0 Hz, 61.5 (C–1), 131.7 (C–4), 137.6 (C–3).

Anal. Calcd for C12H12ClOSn: C, 48.58; H, 8.41; Cl, 8.96; O, 4.04; Sn, 30.00. Found: C, 48.82; H, 8.68.
13.6 [3 C, Sn(CH₂CH₂CH₂CH₃)], 27.4 [3 C, Sn(CH₂CH₂CH₂CH₃)], \( J_{C-Sn}^1 = J_{C-Sn}^{17} \) (58.0 Hz). 29.2 [3 C, Sn(CH₂CH₂CH₂CH₃)], \( J_{C-Sn}^{119} = J_{C-Sn}^{17} \) (19.0 Hz). 42.4 \( J_{C-Sn}^{119} = J_{C-Sn}^{17} \) (57.5 Hz). 62.1 (C-1), 147.6 (C-4), 150.7 (C-3), \( J_{C-Sn}^{119} = J_{C-Sn}^{17} \) (20.0 Hz).

MS (CI, CH₄): for major \(^{120}\)Sn isotope, \( J_{C-Sn} \), Anal. Calcd for \( C_7 H_{15} IOSi \): C, 31.12; H, 5.60; I, 46.97; O, 5.92; Si, 9.17.

References


11. When 1.1 equiv of I₂ was used as the trap, the reaction gave a mixture of the expected iodotin derivative (Z)-12 (9% yield), the unsubstituted vinyltin (51% yield) and the 1,1-ditin compound 15 (22% yield). It was interesting to note that when the reaction of the cuprate with an electrophile other than proton, see: (a) Piers, E.; Chong, J. *J. Org. Chem.* 1982, 47, 1602. (b) See also: Piers, E.; Chong, J. *J. Org. Chem.* 1982, 47, 1604.


