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Synthesis of homopropargyl alcohols via insertion of allenyl carbenoids into acyclic organozirconium bonds

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ABSTRACT

Insertion of allenyl carbenoids (3-tosyloxy-1-lithioalk-1-ynes) into organozirconium complexes gave allenyl-zirconocenes via a 1,2-zirconate rearrangement. Trapping of the allenyl-zirconium species with aldehydes and ketones gave, after hydrolysis, a series of homopropargyl alcohols. Enantioenriched products were prepared by insertion of the lithium carbenoid derived from (*S*)-but-3-yn-2-yl 4-toluenesulfonate into alkyl- and alkenyl-chlorozirconocenes.

Propargyl/allenyl metallics are an important class of intermediates, which have found wide application in carbon–carbon bond forming reactions.[1] Negishi reported an interesting convergent access to allenyl zirconocene **4** by insertion of 1-lithio-3-chloro-1-propyne (**2**) into octylzirconocene chloride **1** via 1,2-rearrangement of the ate-complex **3** (Scheme 1).[2,3] Species such as **2** are termed allenyl carbenoids as 1,3-elimination of lithium chloride would generate an allenyl carbene.

The reaction of triorganozincates with propargyl chlorides and mesylates[4] and the insertion of lithiated propargyl chloride and lithiated propargyl ethers into boranes presumably follow a similar pathway.[5,6] The insertion of Me_3SiCHN_2 into alkynyl boranes provides a similarly convergent route to allenyl boranes.[7]

We have reported the insertion of allenyl carbenoids into a variety of zirconacycles, and elaboration of the resultant η^3-propargyl zirconium species by addition of aldehydes. For example, insertion of **2** into unsaturated zirconacycle **6** followed by $BF_3{\cdot}Et_2O$ promoted addition of butanal gave the α-allenic alcohol **9** via rearrangement of the ate-complex **7** to **8** (Scheme 2).[8]

Following our interest in the elaboration of acyclic organozirconium species by insertion of carbenoids,[9] we wished to extend Negishi's method (Scheme 1) for the convergent formation of acyclic propargylic zirconium species by insertion of allenyl carbenoids. Since enantiomerically pure propargyl alcohols are readily available[10] we were particularly keen to see if chirality derived from the carbenoid precursor **11** could be transferred to the product **14** (Scheme 3). It is not known if carbenoid **11** or allenyl zirconocene **13** are configurationally stable, or if the rearrangement of **12** to **13** or the addition of an aldehyde to **13** would be stereospecific. There is no literature precedent for chiral allenyl carbenoids. There are reports of both configurational stability, and instability for alkyl and alkenyl carbenoids.[11–16] It is known that a variety of allenylmetallic species react with aldehydes with excellent transfer of chirality to afford homopropargyl alcohol products.[7,17]

Propargyl/allenyl zirconocenes **16** have been formed by the insertion of zirconocene equivalents into propargyl ethers **15** with subsequent aldehyde addition to give homopropargylic alcohols **17** (Scheme 4), but the overall stereochemistry of the reaction has not been reported.[18]

In this Letter, we describe the syntheses of homopropargyl alcohols via insertion of allenyl carbenoids into various bis-alkyl/aryl/alkynyl biscyclopentadienyl zirconium complexes and alkyl/alkenyl chlorozirconocenes followed by reaction with aldehydes. Synthesis of enantioenriched products has also been achieved in some cases by insertion of carbenoids derived from enantiomerically pure propargyl tosylates into organochlorozirconocenes.

Treatment of zirconocene dichloride with 2 equiv of an organolithium reagent gave the corresponding acyclic organozirconocene species **18**, which inserted the γ-organolithium reagent **19**, formed from the corresponding alkyne by in situ metallation with LDA or LiTMP at −78 °C, to provide the ate complex **20**. Subsequent 1,2-metallate rearrangement afforded the allenic Zr intermediate **21**, which was trapped with benzaldehyde in the presence of $BF_3{\cdot}Et_2O$ to give homopropargyl alcohols **22a–f** (Scheme 5, Table 1) in modest yields and diastereocontrol, the latter favouring the *anti*-isomer. Trapping the allenyl zirconocene intermediate **21** with

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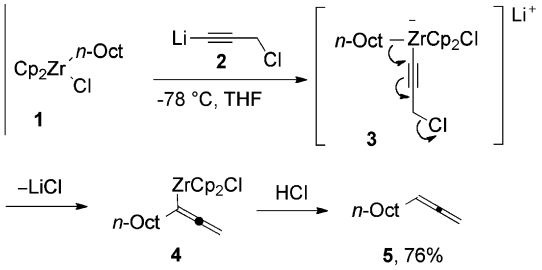
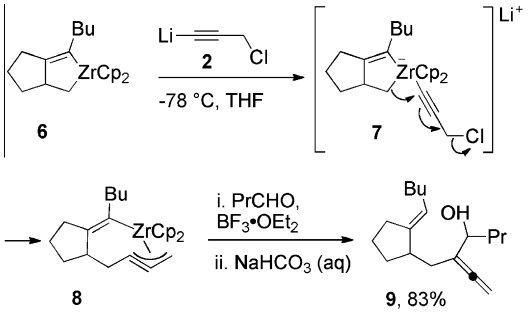
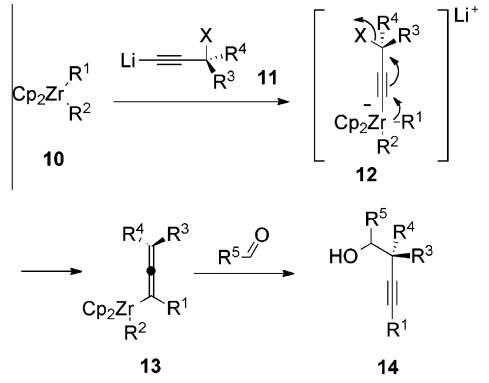


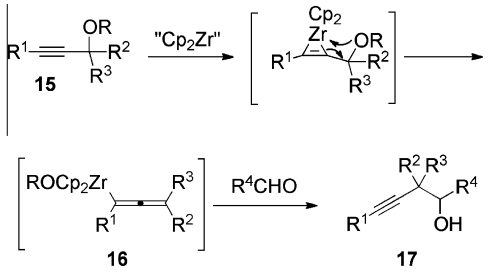
Scheme 1. Insertion of an allenyl carbenoid into octylzirconocene chloride.



Scheme 2. Insertion of an allenyl carbenoid into a zirconacycle.



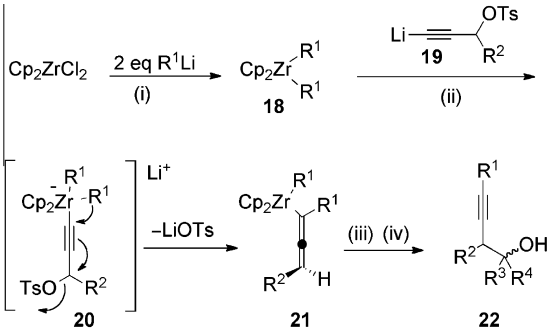
Scheme 3. Proposed convergent stereoselective synthesis of homopropargyl alcohols.



Scheme 4. Formation of propargyl zirconocenes by insertion.

acetone afforded the corresponding tertiary alcohol **22g** in only a 25% yield.

The *anti:syn* relationship of the products **22a–f** was assigned by ^{1}H NMR data correlation with the literature data.[4] The proton adjacent to the hydroxy group was shifted upfield in all *anti*-isomers reported by Harada,[4] and this trend is well retained for the major isomers of compounds **22a–f**.



Scheme 5. Insertion of an allenyl carbenoid into bisalkyl/alkynyl Zr species. Reagents and conditions: (i) THF, −78 °C, 0.5 h; (ii) 1.0 equiv **19**, −78 to −50 °C, 1 h; (iii) (a) for R^3 = Ph, R^4 = H, 1.5 equiv PhCHO, $BF_3{\cdot}OEt_2$, −60 °C to rt over 1 h, then rt, 3 h, (b) for $R^3 = R^4$ = Me, 3.0 equiv Me_2CO, $BF_3{\cdot}OEt_2$, −60 °C to rt over 1 h, then rt, 2 h, then reflux 20 h; (iv) MeOH, aq $NaHCO_3$, rt, 12–16 h.

Table 1
Yields and *anti:syn* relationship of the secondary alcohols **22a–f**

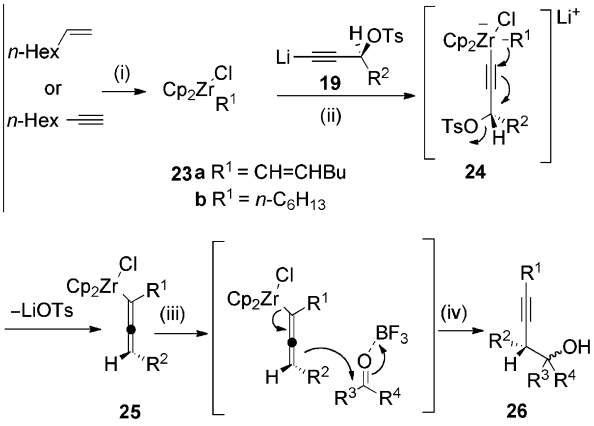
R^1	R^2	R^3	R^4	*anti:syn*	Product	Isolated yield (%)
n-Bu	*n*-Hex	Ph	H	77:23	**22a**	35
Me	*n*-Hex	Ph	H	79:21	**22b**	40
Ph	*n*-Hex	Ph	H	79:21	**22c**	35
PhCC	*n*-Hex	Ph	H	62:38	**22d**	62
Ph	Me	Ph	H	81:19	**22e**	39
Me	Me	Ph	H	73:27	**22f**	37
Me	*n*-Hex	Me	Me	—	**22g**	25

Asymmetric synthesis of the secondary alcohols **22e** and **22f** was attempted by insertion of the enantiomerically pure carbenoid **19** [R^2 = Me, derived from commercially available (*S*)-but-3-yn-2-ol] into the acyclic organozirconium system **18** (R^1 = Ph, Me). The products **22e** and **22f** obtained were analysed by chiral HPLC on a Diacel® OD-H column and in both cases were racemic.

The insertion of allenyl carbenoid **19** has been extended to the organochlorozirconocenes. Hydrozirconation with the Schwartz reagent[19] of 1-octene or 1-octyne provided the corresponding organochlorozirconocene complexes **23a** and **23b**, which underwent insertion of the allenyl carbenoid **19** to give the 'ate' complex **24** (Scheme 6). Subsequent 1,2-metallate rearrangement afforded the allenyl zirconium intermediate **25**, which was further elaborated through addition of an aldehyde or ketone to provide secondary and tertiary alcohols **26**, respectively (Table 2). Yields and diastereoselectivity were similar to the products from **18**. Remarkably, we found that the yields and diastereoselectivity for the formation of **26a** and **26b** were almost identical when $BF_3{\cdot}Et_2O$ was not used for the aldehyde addition. In the formation of **22b** and **22c** $BF_3{\cdot}Et_2O$ was required for reasonable yields. It is notable that the 1,2-zirconate rearrangement of **24** to **25** required the reaction mixture to be warmed to room temperature, in marked contrast to the rearrangement of **20**, which occurred below −50 °C.

Regardless of the modest yields, asymmetric synthesis of the secondary alcohols **26a** and **26b** was attempted by the insertion of the carbenoid **19** derived from (*S*)-but-3-yn-2-yl *p*-toluenesulfonate into organochlorozirconocenes **23a** and **23b**. For the formation of **26a**, $BF_3{\cdot}Et_2O$ was used for the benzaldehyde addition, but for **26b** it was not. Analysis by chiral HPLC (on a Diacel® OD-H column) revealed that alcohols **26a** and **26b** were obtained in 71% and 62% enantiomeric excesses, respectively.

In order to determine the absolute stereochemistry of alcohols **26a**,**b** they were hydrogenated to give alcohol **27** (Scheme 7). The low yield for this hydrogenation may be due to hydrogenolysis of the benzyl alcohol moiety.



Scheme 6. Allenyl carbenoid insertion into organochloro-zirconocenes. Reagents and conditions: (i) 1.0 equiv Cp_2ZrHCl, rt, 1 h; (ii) 1.0 equiv **19**, −78 °C to rt, over 1 h; (iii) (a) for R^3 = Ph, R^4 = H, 1.5 equiv PhCHO, $BF_3{\cdot}OEt_2$, −78 °C to rt over 1 h, then rt, 2 h, (b) for $R^3 = R^4$ = Me, 3.0 equiv Me_2CO, −78 °C to rt over 1 h, then reflux 20 h, (c) for R^3 = *n*-Hex, R^4 = H, 3.0 equiv *n*-HexCHO, −78 °C to rt over 1 h, then rt, 3 h; (iv) MeOH, aq $NaHCO_3$, rt, 12–16 h.

Table 2
Yields and *anti:syn* relationship of the alcohols **26a**–**d**

R^1	R^2	R^3	R^4	*anti:syn*	Product	Isolated yield (%)
n-Oct	Me	Ph	H	79:21	**26a**	76
n-Oct	Me	Ph	H	75:25	**26a**	61[a]
(*E*)-1-Oct	Me	Ph	H	69:31	**26b**	40
(*E*)-1-Oct	Me	Ph	H	70:30	**26b**	34[a,b]
n-Oct	*n*-Hex	*n*-Hex	H	89:11	**26c**	44
n-Oct	*n*-Hex	Me	Me	—	**26d**	50

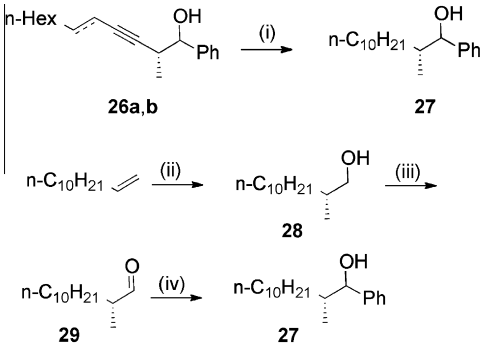
[a] From the insertion of enantiomerically pure carbenoid.
[b] $BF_3{\cdot}Et_2O$ was not used.

The independent enantioselective synthesis of alcohol **27** was achieved in three steps from 1-dodecene (Scheme 7). Enantioselective methylalumination of dodecene with $AlMe_3$ and bis[3-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)indenyl]-zirconium dichloride catalyst followed by oxidation with O_2 gave alcohol **28** in a 66% yield and 67% enantiomeric excess, the major enantiomer possessing the *R* absolute configuration.[20] Swern oxidation of alcohol **28** to aldehyde **29** followed by addition of phenylmagnesium bromide gave the (2*R*)-alcohol **27** as a 3:2 *syn*:*anti* mixture, each of which was formed in 43% enantiomeric excess.

Chiral HPLC using a Diacel® OD-H column of samples of alcohol **27** synthesised by hydrogenation of alcohols **26a**,**b** and by the independent synthesis revealed that for both alcohols **26a** and **26b** the (2*R*) enantiomer was the major.

The result is consistent with both the 1,2-metallate rearrangement **24** to **25**, and the addition of aldehyde (irrespective of the presence of $BF_3{\cdot}Et_2O$) to be *anti*-processes as shown in Scheme 2. Of course, both could be *syn*, but given the available precedent for both S_N2' nucleophilic displacement of propargylic systems to be *anti* we consider this unlikely.[1b] Although many allenylmetallics react with aldehydes via a chelate transition state (S_E2', a *syn*-process) the bulk of the zirconocene fragment, relatively low Lewis acidity of the zirconium centre, and the absence of a strong effect of adding $BF_3{\cdot}Et_2O$ all suggest that an *anti*-process for aldehyde addition is reasonable.

The reasons for the complete loss of stereochemical integrity in the formation of **22e**,**f**, and partial loss in the formation of **26a**,**b** are not clear. It may be significant that competition studies on the insertion of carbenoid **19** (R^2 = Me) into Cp_2ZrBu_2 and $Cp_2Zr(C_8H_{17})$(Cl) species showed insertion only into the latter. The relatively slow insertion into **18** may give time for the carbenoid to racemise.[12,13]



Scheme 7. Synthesis of alcohol **27**. Reagents and conditions: (i) H_2, 5% Pd/C, EtOAc, rt, 2 h, 56% from **26a**, 58% from **26b;** (ii) (a) bis(1-neomenthylindenyl)$_2$ $ZrCl_2$, $AlMe_3$, 1,2-dichloroethane, rt, 7 days, (b) O_2, 5 h (c) 15% aq NaOH, 66%; (iii) DMSO, CH_2Cl_2, $(COCl)_2$, −60 °C, 15 min, Et_3N, −60 °C to rt, 1 h, 95%; (iv) (a) PhMgBr, Et_2O, −78 °C to rt, 3 h, (b) aq NH_4Cl, 53%.

In conclusion we report a three component coupling of propargyl tosylates, acyclic organozirconium species and aldehydes/ketones to afford homopropargyl alcohols. The key step is a convergent synthesis of propargyl/allenyl zirconium species via insertion of lithiated propargyl tosylates into acyclic organozirconium complexes. We have also demonstrated that it is possible for the absolute stereochemistry of readily available propargyl alcohols to be retained through this sequence, although improvements in yields and enantiomeric excesses are needed before it constitutes a useful synthetic method. Chiral propargyl tosylate insertion into other organometallic species, particularly organozinc and organoboranes, may overcome the limitations of the organozirconium method.

Experimental

Formation of alcohols 26a by insertion of enantiomerically pure carbenoid

To a stirred suspension of Cp_2ZrHCl (258 mg, 1.0 mmol) in dry THF (10 mL) at rt was added 1-octene (0.125 mL, 0.80 mmol) dropwise over 3 min. After stirring the yellow solution for 1 h at rt, the reaction mixture was cooled to −78 °C and a solution of (*S*)-but-3-yn-2-yl 4-methylbenzenesulfonate (224 mg, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in dry THF (2 mL) and *n*-BuLi (0.4 mL of a 2.5 M solution in hexanes, 1.0 mmol) at −5 °C over 15 min]. The stirring was continued for 1 h during which time the reaction mixture was allowed to warm to rt. The reaction was re-cooled to −78 °C and a solution of benzaldehyde (0.30 mL, 3.0 mmol) in dry THF (1 mL) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.36 mL, 3.0 mmol). The mixture was warmed gradually to rt and stirred at the same temperature for 3 h before quenching with MeOH (5 mL), and a saturated aqueous solution of $NaHCO_3$ (6 mL). After overnight stirring, the mixture was poured onto H_2O (100 mL), and the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude product as a yellow oil (*anti:syn* diastereoisomers in the ratio of 75:25).

Purification of the crude material by column chromatography on SiO_2 (230–400 mesh) with hexane:EtOAc (10:1) as the eluent allows partial separation of the diastereoisomers to give a fraction of the *anti*-isomer as a yellow oil and a mixed fraction (yellow oil) of both isomers in a combined yield of 0.134 g (61%). Chiral HPLC (4.6 × 250 mm Diacel® OD-H column, 2% ^{i}PrOH in hexanes, 1 mL/min.): *anti*-isomer R_t 11.0 min (minor enantiomer) and 12.9 min

(major enantiomer); *syn*-isomer R_t 11.4 min (minor enantiomer) and 13.2 min (major enantiomer).

anti Diastereoisomer of 26a

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.45–7.24 (5H, m), 4.43 (1H, dd, *J* = 6.9, 3.5 Hz, C*H*OH), 2.76 (1H, m, C*H*Me), 2.64 (1H, d, *J* = 3.5 Hz, OH), 2.21 (2H, td, *J* = 6.9, 2.0 Hz, $CH_2C{\equiv}C$), 1.51 (2H, quin, *J* = 7.1 Hz), 1.43–1.20 (10H, m), 1.07 (3H, d, *J* = 6.9 Hz), 0.90 (3H, t, *J* = 6.6 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.68 (C), 128.16 (2CH), 127.76 (CH), 126.67 (2CH), 84.18 (C), 80.70 (C), 77.75 (CH), 35.67 (CH), 31.81 (CH_2), 29.16 (CH_2), 29.07 (CH_2), 28.93 (CH_2), 28.85 (CH_2), 22.63 (CH_2), 18.72 (CH_2), 17.81 (CH_3), 14.07 (CH_3). HRMS (EI): Found: $[M-H_2O]^+$, 254.2040. $[C_{19}H_{26}]^+$ requires: 254.2034. LRMS (CI): *m/z*: 273 ($[M+H]^+$, 54%), 255 ($[(M+H)^+-H_2O]$, 72%).

A pure sample of the minor *syn*-diastereoisomer was obtained by HPLC (4.6 × 250 mm Partisil® 60 Å 5 μm SiOH column, 0.7% ^{i}PrOH in hexanes, 1 mL/min; *anti*-isomer R_t 5.6 min; *syn*-isomer R_t 6.8 min.): ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.44-7.22 (5H, m), 4.71 (1H, m, CHOH), 2.86 (1H, m, CHMe), 2.25 (1H, d, *J* = 3.0 Hz, OH), 2.15 (2H, td, *J* = 6.9, 1.8 Hz, $CH_2C{\equiv}C$), 1.46 (2H, quin, *J* = 7.1 Hz), 1.37–1.21 (10H, m), 1.07 (3H, d, *J* = 7.1 Hz), 0.90 (3H, t, *J* = 6.3 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.52 (C), 127.99 (2CH), 127.51 (CH), 126.49 (2CH), 83.55 (C), 81.28 (C), 76.43 (CH), 34.35 (CH), 31.84 (CH_2), 29.18 (CH_2), 29.11 (CH_2), 28.93 (CH_2), 28.82 (CH_2), 22.65 (CH_2), 18.72 (CH_2), 15.86 (CH_3), 14.11 (CH_3).

Acknowledgments

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