ORGANOMETALLICS

Metallotropic Equilibrium and Configurational Stability of 3-Chloro-1-(trimethylsilyl)propargyl and -allenyl Metals: Comparative Study among Lithium, Titanium, and Zinc

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Supporting Information

ABSTRACT: A comparative study of the metallotropic equilibrium between 1-chloro-3-(trimethylsilyl)propargyl and -allenyl metals was undertaken by means of lithio-, titano-, and zinco-carbenoids. The lithium and zinc species were shown to react mainly in their allenic metallotropic forms, whereas the titanium species proved to react in both its propargylic and allenic forms. The configurational stability of these organometallics was next examined using a modification of the Hoffmann test. In each case, the organometallic was reacted with a chiral enantiopure electrophile. A comparison of the diastereo-



meric ratios obtained at low and high conversion rates of the reagent allows assessment of its configurational stability. The lithium species thus exhibited a configurational lability at -125 °C in Trapp mixture on the time scale of its reaction with (+)-camphor, while the titanium analogue proved to be configurationally stable at -40 °C in THF/Et₂O on the time scale defined by its reaction with (*S*)-*N*-tritylprolinal. In the context of its reaction with the same electrophile, the zinc bromide species was proven to be partially labile from -80 °C in THF and its dynamic kinetic resolution was investigated.

INTRODUCTION

Reactions of propargyl and allenyl metals with electrophiles have been extensively investigated and provide synthetically useful intermediates.^{1–6} The regio- and stereoselectivities of these reactions are both sensitive to the metal itself and the bulkiness of its substituents. For example, allenyl stanannes,⁷ indiums,⁷ and zincs^{8–13} react with aldehydes in a highly regio- and stereoselective manner, while the magnesium,¹⁴ chromium,¹⁵ boron,^{16–19} and titanium²⁰ analogues generally react less selectively. Particularly interesting are configurationally stable chiral propargyl and allenyl metals.^{2,7,8,21–27} The racemization process involves intra- or intermolecular dissociative carbon– metal bond pathways, and thus the level of the configurational stability is specific to each species. The existence of a metallotropic equilibrium between the propargylic (*P*) and allenic (*A*) forms may also have an impact on the configurational stability of the organometallic (Scheme 1).^{23c,28}

Scheme 1. Metallotropic Equilibrium between Propargyl (P) and Allenyl (A) Metals



Little information is available on the configurational stability of propargyl and allenyl metallo-carbenoids, reagents for which R^1 is a leaving group in Scheme 1,²⁹ probably due to their

thermal sensitivity.³⁰ For the past decade, our group has been interested in the preparation of 3-chloro-1-(trimethylsilyl)allenyl metals and their reactions with electrophiles. In racemic form, these reagents have proven highly useful for the stereoselective preparation of acetylenic epoxides and aziridines.³¹ In order to extend the scope of our developed methodology, we envisioned preparing these species in enantioenriched form. Achievement of this prospect requires first investigating their configurational stability. A study was thus conducted using the Hoffmann test, which is based on the kinetic resolution of the organometallic by a chiral electrophile and has the advantage of not requiring use of enantiomerically pure organometallics.³² Two experiments are needed for this test. The first is carried out with 1 equiv of the racemic electrophile. The diastereomeric ratio thus observed is the intrinsic selectivity s of the reaction and corresponds to the upper attainable stereoselectivity under the reaction conditions used. The second experiment is carried out under the same conditions with the enantiopure electrophile. The level of configurational stability of the organometallic reagent on the time scale defined by its reaction with the electrophile used is inferred from a comparison of the diastereomeric ratios obtained in the two experiments.^{33,34}

Herein, we report a comparative study on 3-chloro-1-(trimethylsilyl)-substituted lithio-, titano-, and zinco-carbenoids M-1. First, the addition reaction of the racemic species M-1

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with achiral aldehydes has been studied in order to gain insight into the rate of the metallotropic equilibrium. Then, their configurational stabilities have been investigated by means of the Hoffmann test using chiral enantiopure aldehydes (Scheme 2).



RESULTS AND DISCUSSION

Preparation of Metallo-Carbenoids M-1. Usually propargyl- and allenylmetals are prepared by the reduction of propagylic or allenic halides with metals or by the metalation of the corresponding hydrocarbons with alkyllithiums.^{1a,35} As for us, we succeeded in preparing the lithio-carbenoid Li-1 (Met = Li) in racemic form by the deprotonation of (3-chloroprop-1-ynyl)trimethylsilane³⁶ with 1 equiv of *n*BuLi in the presence of 1 equiv of TMEDA within 15 min at -95 °C in Et₂O (Scheme 3).³⁷





This initially gave the racemic propargyllithium (P)-Li-1, which isomerized into its metallotropic allenic form (A)-Li-1 (vide infra), thereby producing a mixture of (P)-Li-1 and (A)-Li-1 forms in equilibrium. Under these conditions, no detectable self-coupling product was observed.

The lithio-carbenoid Li-1 exhibits a limited stability at -95 °C but can still be transmetalated with 1 equiv of $Ti(OiPr)_4$ and $ZnBr_2$ to give Ti-1 (Met = $Ti(OiPr)_3$) and Zn-1 (Met = ZnBr), respectively, as mixtures of the two corresponding metallotropic forms. Alternatively, the zinco-carbenoid Zn-1 could be prepared in THF at -80 °C by the lithiation of (3-chloroprop-1-ynyl)trimethylsilane using 2 equiv of LDA in the presence of 2 equiv of ZnBr₂.^{31a}

Attempts to characterize metallo-carbenoids M-1 by lowtemperature NMR experiments were unsuccessful. Although the TMEDA required for the formation of M-1 and the lithium salt (LiBr or LiO*i*Pr) generated during the preparation should have an influence on both the metallotropic equilibrium and the configurational stability of M-1, we were not able to determine their role.³⁹ In addition, metallo-carbenoids M-1, and more particularly the lithio-carbenoid Li-1, should form aggregates associated through carbon-metal bonds. However, throughout this paper, reagents M-1 will only be considered as monomeric species for a simplified view.⁴⁰

Study of the Metallotropic Equilibrium Involving Metallo-Carbenoids M-1. With carbonyl functions, in most cases it is believed that the reaction of propargyl and allenyl metals proceeds by a cyclic S_E2' process, giving allenic and homopropargylic alcohols, respectively.^{2,41,42} The regioselectivity of the reaction, i.e. the ratio between allenic and acetylenic products obtained, is thus highly informative as to the rate of the metallotropic equilibrium. The reaction of lithio-, titano-, and zinco-carbenoids M-1 with achiral aldehydes was then investigated (Scheme 4).

Scheme 4. Addition of Metallo-Carbenoids M-1 to Aldehydes



When the lithio-carbenoid Li-1 was reacted with aldehydes for 1 h at -95 °C, mixtures of homopropargylic and allenic alcohols, **2** and **3**,³⁸ respectively, were obtained in high yields (Table 1, entries 1-5).³⁷ Except for the reaction with benzaldehyde (Table 1, entry 5), homopropargylic alcohols 2 were obtained with good to high anti selectivity, explained by the favored "Chodkiewicz-Yamamoto"-type transition state model M1.⁴³ The relative configuration of the minor allenic alcohols 3, which could arise from transition state model M2, could not be determined. Even though products 2 were always formed as the major isomers, a variation of the 2:3 ratio depending on the aldehyde was observed. This variation is a good indication that the Curtin-Hammett principle applies. This means that the metallotropic equilibrium is faster than the reactions of (P)-Li-1 and (A)-Li-1 with the aldehydes so that $2:3 = k_A:k_P$. In order to explain both the variation in the 2:3 ratio and the predominant formation of 2, the rate constants should be such that $k_e \gg k_A > k_P$ at -95 °C in Et₂O.

The reaction of titano-carbenoid Ti-1 was first investigated with cyclohexanecarboxaldehyde at different temperatures in THF/Et₂O. In each case, the corresponding homopropargylic and allenic adducts **2** and **3** were obtained with modest regioselectivities and variable stereoselectivities (Table 1, entries 6-10). The best regio- and stereoselectivities, however, were attained within 3 h at -40 °C (Table 1, entry 8). Note that partial thermal decomposition of Ti-1 was observed above -20 °C.

Table 1. Study of the Metallotropic Equilibrium Involving M-1 (Scheme 4)

entry	M-1 ^a	R	T (°C)	2:3 ^b	dr of 2^c	dr of 3^c	yield (%) ^d
1	Li-1	cHex	-95	89:11	71:29	68:32	83
2	Li-1	iPr	-95	82:18	72:28	66:34	87
3	Li-1	tBu	-95	96:04	90:10	80:20	75
4	Li-1	nBu	-95	83:17	69:31	58:42	60
5	Li-1	Ph	-95	69:31	65:35	58:42	79 ^e
6	Ti-1	cHex	-80	52:48	98:02	98:02	80
7	Ti-1	cHex	-60	35:65	98:02	98:02	90
8	Ti-1	cHex	-40	30:70	92:08	98:02	67
9	Ti-1	cHex	-20^{f}	38:62	80:20	93:07	74
10	Ti-1	cHex	0 ^{<i>f</i>}	71:29	68:32	75:25	50
11	Ti-1	iPr	-40	30:70	92:08	98:02	59
12	Ti-1	tBu	-40	65:35	92:08	>98:02	63
13	Ti-1	nBu	-40	50:50	85:15	96:04	76
14	Ti-1	Ph	-40	75:25	82:18	75:25	75 ^e
15	Ti-1	(E)-crotyl	-40	59:41	91:09	79:21	61 ^e
16	Zn-1	cHex	-80 to -20	>98:02	83:17		76
17	Zn-1	iPr	-80 to -20	>98:02	95:05		75
18	Zn-1	<i>t</i> Bu	-80 to -20	>98:02	>98:02		82
19	Zn-1	nBu	-80 to -20	>98:02	86:14		81
20	Zn-1	Ph	-80 to -20	>98:02	64:36		83
21	Zn-1	crotyl	-80 to -20	>98:02	84:16		82

^{*a*}Conditions: Li-1 (Met = Li), reactions carried out for 1 h at -95 °C in Et₂O; Ti-1 (Met = Ti(OiPr)₃), reactions carried out for 3 h at the indicated temperature in THF/Et₂O; Zn-1 (Met = ZnBr), reactions carried out for 1 h at -80 °C and then 45 min at -20 °C in THF. ^{*b*}Determined by ¹H NMR analysis at 400 MHz of the crude reaction mixture. ^{*c*}dr of products 2 and 3 determined by ¹H NMR analysis at 400 MHz of the crude reaction mixture. ^{*d*}Combined isolated yield in 2 and 3. Unless otherwise stated, analytically pure 2 and 3 could be isolated by flash chromatography. ^{*c*}Inseparable mixtures of 2 and 3 were obtained. ^{*f*}Partial decomposition of Ti-1 was observed.

The titano-carbenoid Ti-1 was thus reacted with other aldehydes for 3 h at -40 °C (Table 1, entries 11–15). In all cases, the expected adducts 2 and 3 were isolated in good yields with low 2:3 ratios but quite good stereoselectivities for both 2 and 3. The *anti* configuration observed for 2 could again be explained by transition state model **M1**. Although still low, the regioselectivity of the reaction was highly impacted by the aldehyde itself, as seen by the variation in both the level and the sense of the 2:3 ratio. As for Li-1, this is characteristic of Ti-1 existing in its two metallotropic forms that interconvert much more quickly than they react with aldehydes at -40 and -80 °C in THF-Et₂O, meaning that 2:3 = $k_A:k_P$ with rate constants such as $k_e \gg k_A \approx k_P$. These results are in sharp contrast with the reported reactivity of 3-alkyl-substituted propargyl/allenyl titanium(IV) species with aldehyde.

Finally, the reaction of the zinco-carbenoid Zn-1 with aldehydes was examined (Table 1, entries 16-21).³⁸ In all cases, the reaction was complete within 2 h between -80 and -20 °C and only homopropargylic alcohols 2, obtained via M1, were formed in excellent yields and mostly with high *anti:syn* ratios. This result could be explained in two ways. Along the lines of the works of Gaudemar on 3-alkyl-substituted allenylzincs, ^{42a,b,45}

the metallotropic equilibrium might be totally displaced in favor of (*A*)-Zn-1. Alternatively, it might be that a rapid equilibrium occurs but the exclusive formation of 2 is the result of a Curtin–Hammett situation with rate constants such that $k_e \gg k_A \gg k_p$.

In conclusion, for each of the three metallo-carbenoids M-1 the regioselectivity of the reaction appears to depend only on **2**:**3** = k_A : k_P (Scheme 5).

Scheme 5. General Trends of the Metallotropic Equilibrium Involving M-1

$(\pm)-2 \stackrel{\text{RCHO}}{\longleftarrow} k_A \stackrel{\text{H}}{\leftarrow} CI$	$(\pm)^{-(A)-M-1}$	$\begin{array}{c} H \\ H \\ Met \\ (\pm)-(P)-M-1 \end{array} \xrightarrow{\text{RCHO}} (\pm)-3 \\ \hline \\ k_{P} \end{array}$
Met = Li	$k_{\rm e} >> k_A > k_P$	at –95 °C in Et ₂ O
Met = Ti(O <i>i</i> Pr) ₃	$k_{\rm e} >> k_A \approx k_P$	at –80 °C and –40 °C in THF/Et ₂ O
Met = ZnBr	k _e >> k _A >> k _P or only (A)-Zn-1 exists	at –80 °C to –20 °C in THF

Study of the Configurational Stability of Metallo-Carbenoids M-1. In order to examine the configurational behavior of metallo-carbenoids M-1, we used a modified version of the Hoffmann test that only required the use of an enantiopure electrophile. To this end, the first experiment was carried out at a low conversion rate (C_G) of the organometallic. In practice, to have good control of C_G , the reaction was run using 0.1–0.2 equiv of electrophile. These conditions mimic the reaction of the organometallic with 1 equiv of the racemic electrophile according to Hoffmann calculated curves plotting the variation of the diastereomeric ratio (dr) against the conversion rate of a configurationally stable organometallic.⁴⁶ These curves allow us to know the intrinsic selectivity *s* of the reaction, which is very close to the observed dr at low C_G (Figure 1).

The configurational stability of lithio-carbenoid Li-1 was first examined at -125 °C in a 4/4/1 THF/Et₂O/pentane mixture as solvent (Trapp mixture⁴⁷) using (+)-camphor (4) as the electrophile. Under these conditions within 1 h, the reaction of Li-1 with 0.2 equiv of 4 led to a $C_{\rm G}$ value of 20%. *Exo* acetylenic epoxides 5 were obtained with dr(5a:5b) = 92:08 (Scheme 6). The exclusive formation of acetylenic adducts 5 was explained by the reaction of (*A*)-Li-1 with 4 being much faster than that of (*P*)-Li-1. Thus, in a simplified view only the reaction of (*A*)-Li-1 was taken into consideration. The *exo* stereochemistry and the *S* configuration of carbon atom C11 of the major isomer 5a were assigned by NOE experiments, indicating a significant effect of 4% between H^{3α} and H¹¹ (Scheme 6).

The stereochemistry of the minor isomer **5b** could not be determined. However, on the basis of reported works showing that the addition of organometallics occurs from the less hindered face of camphor, i.e. the *endo* face, ⁴⁸ **5b** was assumed to be also *exo* but with an *R* configuration for carbon atom C11. The predominant formation of **5a** could be rationalized by the nucleophilic attack of the *aR* enantiomer of (*A*)-Li-1 via the favored transition state model **M3a**, wherein the chlorine atom and the camphor ring adopt an *anti* relationship in order to minimize steric interaction. On the other hand, the *aS* enantiomer of (*A*)-Li-1 approaches via disfavored transition state model **M3b**, giving the minor isomer **5b** (Scheme 6).

Following the equations developed by Hoffmann, an observed 5a:Sb ratio of 92:08 at a C_G value of 20% is



Observed dr = 90:10 at 15% C_G for s = 10 (dr = 91:09)



Scheme 6. Addition of Racemic Li-1 to Enantiopure (+)-Camphor (4)



associated with the intrinsic selectivity $s = k_{aR} k_{aS} = 14.1$ at -125 °C in Et₂O. It also represents the upper theoretical limit that can be reached at complete conversion of Li-1, under identical reaction conditions.

When the reaction was carried out with 1.1 equiv of 4, a $C_{\rm G}$ value of 77% was observed within 1 h at -125 °C on the basis of recovered unreacted 4 upon hydrolysis. *Exo* acetylenic epoxides 5 were isolated in 62% combined yield with an unchanged 5a:5b ratio of 92:08. Interestingly, this result strongly suggests that Li-1 is already configurationally labile at -125 °C in Trapp mixture: it racemizes much more quickly

than it is trapped by 4. This situation corresponds to the best possible dynamic kinetic resolution with rate constants such that $k_r \gg k_{aR} > k_{aS}$. This result is in accordance with the configurational behavior reported for 3-alkyl-1-silyl-substituted allenyllithiums,^{23c} which are labile below -93 °C in Et₂O, and can be correlated to the rapid metallotropic equilibrium involving Li-1.

The configurational stability of racemic titano-carbenoid Ti-1 was next evaluated by means of the modified Hoffmann test. (*S*)-*N*-Tritylprolinal (**6**), known to react with various organometallics with high diastereoselectivities,⁴⁹ was used as the electrophile. The study was conducted in a THF/Et₂O mixture at -40 °C, conditions for which the best regio- and stereoselectivities were observed in reactions with aldehydes (see Table 1). When Ti-1 was reacted with 0.1 equiv of **6**, a $C_{\rm G}$ value of 10% was reached. The two allenic products 7**a**,**b** were obtained in a 7**a**:7**b** ratio of 66:34, corresponding to the low intrinsic selectivity s = 2 according to Hoffmann equations (Scheme 7).

The configuration of the newly created stereogenic carbon atom in both isomers was assumed to be S from the coupling constant

Scheme 7. Addition of Racemic Ti-1 to Enantiopure (S)-N-Tritylprolinal (6)



of 2.8 Hz between H^a and H^b and earlier works on additions of organometallics to $6.^{49}$ The configuration of the allenic moiety in both products could not, however, be determined.

As allenic alcohols 7a,b were exclusively obtained, (*P*)-Ti-1 was assumed to react much more quickly than (*A*)-Ti-1 ($k_P \gg k_A$). Everything thus happened as if only the propargylic metallotropic form (*P*)-Ti-1 were present.

When the reaction was conducted under the same conditions with 1.2 equiv of **6**, Ti-1 was completely consumed ($C_{\rm G} = 100\%$), affording adducts **7a**,**b** in 60% combined yield with no selectivity (**7a**:**7b** = 50:50). This result suggests that (*P*)-Ti-1 is configurationally stable at -40 °C in THF/Et₂O on the time scale defined by its reaction with **6**. Interestingly, despite the rapid equilibrium between its two metallotropic forms, the configurational stability of Ti-1 is maintained so that $k_r \ll k_R$ and k_s . A study of the configurational stability of Ti-1 could not be undertaken at higher temperatures due to its partial thermal decomposition.

As a general trend, organozincs are thought to be more covalently bonded with a barrier of inversion higher than that of their lithium and titanium analogues.⁵⁰ We have recently shown that zinco-carbenoid Zn-1 is partially configurationally stable at 20 °C in Et₂O but configurationally stable at -15 °C in the presence of HMPA in the time scale defined by its reaction with enantiopure N-tert-butanesulfinimines.⁵¹ However, no information is available on the configurational stability of Zn-1 in THF, which is the solvent of choice for its reaction with aldehydes.³⁷ To this end, we carried out the modified Hoffmann test at -80 °C in THF, using 0.2 equiv of (S)-Ntritylprolinal (6) (Scheme 8). Under these conditions, within 2 h, a $C_{\rm G}$ value of 20% was reached. A mixture of the two diastereomeric acetylenic chlorohydrins 9a,b was obtained with dr = 90:10 in favor of 9a (Table 2, entry 1). As before, the exclusive formation of acetylenic adducts 9 was rationalized by the reactivity of (A)-Zn-1 being greater than that of (P)-Zn-1 $(k_A \gg k_P)$, and thus everything happened as if (A)-Zn-1 were the only existing metallotropic form. The anti and syn relative configurations of the two newly created stereogenic carbon atoms of 9a,b were deduced from chemical correlations (see the Supporting Information).

The *anti* stereoselectivity of the reaction was explained by transition state models **M4a,b**, analogous to those postulated and validated by PM3 calculations for the nucleophilic addition reaction of organometallics to 6.⁴⁹ In **M4a,b** the organometallic attacks from the *re* face of the aldehyde that lies over the pyrrolidine ring and adopts a pseudo-axial position in a *trans* relationship with the trityl group. Accordingly, the *aR* enantiomer of (*A*)-Zn-1 leads to **9a** via the favored transition state model **M4a**, in which the chlorine atom is not interacting with the pyrrolidine cycle. The minor isomer **9b** iself could result from the approach of the *aS* enantiomer via the disfavored transition state model **M4b**.

At -80 °C in THF, the intrinsic selectivity of the reaction is then $s = k_{aR} \cdot k_{aS} = 9.8$ according to Hoffmann equations. The reaction was next carried out with 0.80 and 1.50 equiv of **6** under the same conditions. In both cases, a longer reaction time of 7 h was necessary in order to reach C_G values of 75% and 80% with dr values of 70:30 and 66:34, respectively (Table 2, entries 2 and 3). This decrease of dr was a good fit with the theoretical curve calculated for the variation of dr as a function of C_G for a configurationally stable chiral organometallic (Figure 2). Thus, it could be concluded that Zn-1 is configurationally stable with $s = k_{aR} \cdot k_{aS} = 9.8$ at -80 °C in THF on the time scale defined by its reaction with **6**. Subsequently, we Scheme 8. Addition of Zn-1 to Enantiopure (S)-N-Tritylprolinal (6)



Table 2. Study of the Configurational Stability of Zn-1 (Scheme 8)

entry	amt of 6 (equiv)	Т (°С)	time (h)	$\stackrel{C_{\mathrm{G}}}{(\%)^a}$	dr ^b	yield (%) ^c
1	0.20	-80	2	20	90:10	100
2	0.80	-80	7	75	70:30	70
3	1.50	-80	7	80	66:34	nd^d
4	0.15	-20	1	15	77:23	100
5	1.30	-20	1	100	63:37	56
6	1.30	-20	7	100	81:19	65

"Measured by ¹H NMR analysis at 400 MHz on the basis of recovered unreacted **6** in the crude reaction mixture. ^{*b*} dr = (9a + 10a):(9b + 10b), determined by ¹H NMR analysis at 400 MHz on the crude reaction mixture. ^{*c*} Combined yield of purified 9a,b and 10a,b. ^{*d*}Not determined.

studied the configurational stability of Zn-1 in THF at -20 °C. Within 1 h, the reaction with 0.15 equiv of 6 led to a mixture of chlorhydrins 9a,b. They were accompanied by about 15% of epoxides 10a,b, which came from intermediates 9a,b, respectively, by intramolecular displacement of the chlorine. The diastereoselectivity of the reaction is thus given by dr = (9a + 10a): (9b + 10b) = 77:23 at $C_G = 15\%$ (Table 2, entry 4). This corresponds to the intrinsic selectivity s = 3.2 according to Hoffmann equations. At $C_G = 100\%$, reached using 1.30 equiv of 6, a dr value of 63:37 was observed. It significantly deviated from 50:50,



 $_{\Delta}~$ Reaction carried out at -20 °C by the slow addition of 6 over 6 h and an additional 1 h of stirring



the dr which would have been obtained in the case of a configurationally stable organometallic. A partial racemization of Zn-1 on the time scale of its reaction with 6 was then suspected.

To confirm this interpretation, we performed an additional experiment by slowly adding 1.30 equiv of **6** over a period of 6 h and waiting an additional 1 h prior to hydrolysis. As expected, slowing down the addition rate of **6** resulted in an increased dr of 81:19. Under these conditions, a higher kinetic resolution was attained by giving more time to the mismatched *aS* enantiomer of (*A*)-Zn-1 to racemize into its matched *aR* enantiomer. Thus, Zn-1 was shown to be partially configurationally labile from -20 °C in THF. The striking difference in behavior of Zn-1 in comparison to that of its 3-alkyl-substituted analogues, which are reported to be configurationally stable up to 40 °C, ^{3,9,22,25c,d,52} remains unexplained.

We next envisioned running kinetic resolution experiments to evaluate the time during which Zn-1 is still configurationally stable at -80 °C in THF. With this aim, the reaction was conducted at -80 °C between Zn-1 and 2 equiv of 6 for a given time, after which cyclohexanecarboxaldehyde was added in order to trap the remaining Zn-1. Upon hydrolysis, 9a and the corresponding chlorohydrin 2 were obtained with anti:syn ratios of 90:10 and 84:16, respectively (Scheme 9). After 2 h of reaction, under these conditions, **2:9a** = 25:75, giving $C_G = 25\%$ (Table 3, entry 1). The enantiomeric ratio (er) of the major anti chlorohydrin, isolated in 25% yield, was assigned to be 63:37 by the use of 50 wt % of $Eu(hfc)_3$ as a europium shift reagent. The R,S absolute configuration of the chlorohydrin was deduced from its conversion into a known homopropargylic alcohol⁵³ via successive treatments with DBU and LiAlH₄ (see the Supporting Information). The formation of the anti isomer could thus be explained by transition state model M5, wherein the *aS* enantiomer of Zn-1 reacts with 6. All these results indicated that unreacted (A)-Zn-1 was enantioenriched in its aS enantiomer.

Scheme 9. Synthesis of Enantioenriched Chlorhydrins



Further experiments were thus carried out under the same conditions while increasing the reaction time between Zn-1 and 6 (Table 3, entries 2–5). In all cases, the *anti* chlorohydrin was isolated as the main isomer in 29–33% yields with up to 78:22 er obtained after 3.5 h of reaction (Table 3, entry 4). Up to 3.5 h of reaction, the observed er was a good fit with the theroretical calculated curve er = $f(C_G)$ obtained in the case of a configurationally stable organometallic with s = 9.8 (Figure 3), suggesting that Zn-1 is configurationally stable over 3.5 h at -80 °C in THF.

Table 3. Kinetic Resolution of Zn-1 (Scheme 9)

entry	time $(h)^a$	yield (%) ^b	er ^c
1	2	25	63:37
2	2.5	nd^d	69:31
3	3	29	77:23
4	3.5	nd^d	78:22
5	4	33	69:31

^{*a*}Reaction time at -80 °C with 6 prior to addition of cyclohexylcarboxaldehyde. ^{*b*}Yield in purified chlorohydrin 2 based on cyclohexanecarboxaldehyde. ^{*c*}Measured by addition of 50 wt % of Eu(hfc)₃ to a CD₃Cl solution of purified chlorohydrin 2. ^{*d*}Not determined.

Surprisingly, a drop in the er was noted for a longer reaction time (Table 3, entry 5), which could not be explained by racemization of the electrophile, since recovered unreacted **6** showed no loss of its optical purity. Conversely, racemization of Zn-1 could be invoked. Indeed, the reaction rate between Zn-1 and **6** might become slower and slower while $C_{\rm G}$ increases, which might give more and more time for Zn-1 to racemize. Unfortunately, this phenomenon precludes the practical use of the kinetic resolution of Zn-1 in order to access highly enantio-enriched allenylzinc species and their use in asymmetric synthesis.

CONCLUSION

3-Chloro-1-(trimethylsilyl)-substituted metallo-carbenoids M-1 were shown to exist in rapid metallotropic equilibria between propargylic and allenic forms. The allenic form of Li-1 exhibited a greater reactivity toward aldehydes than the propargylic form, giving predominantly homopropargylic alcohols at -95 °C in Et₂O. The same behavior was observed for Zn-1 between -80 and -20 °C in THF. On the other hand, the allenic and propargylic forms of Ti-1 proved to have similar reactivities at -80 and -40 °C in a THF/Et₂O mixture, affording mixtures of homopropargylic and allenic alcohols.

The configurational stability of metallo-carbenoids M-1 was also investigated by means of a modification of the Hoffmann test. Li-1 proved to be configurationally labile at -125 °C in

Trapp mixture on the time scale defined by its reaction with (+)-camphor, whereas Ti-1 exhibited configurational stability at -40 °C in THF/Et₂O on the time scale defined by its reaction with (*S*)-*N*-tritylprolinal. With the latter electrophile, Zn-1 was demonstrated to be configurationally stable over 4 h at -80 °C but partially labile at -20 °C in THF. Further studies and synthetic applications using metallo-carbenoids M-1 are being undertaken in our group and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. Experiments involving organometallics were carried out in dried glassware under a positive pressure of dry nitrogen. Liquid nitrogen was used as a cryoscopic fluid. A three-necked, roundbottomed flask equipped with an internal thermometer, a septum cap, and a nitrogen inlet was used. Anhydrous THF and Et2O were obtained by distillation over sodium-benzophenone ketyl. CH₂Cl₂ and TMEDA were obtained by distillation over CaH₂. (+)-Camphor was sublimed prior to use. Commercial zinc bromide was melted under argon and immediately after cooling to room temperature dissolved in anhydrous THF or Et₂O. n-BuLi (2.50 M commercial solution in hexane) was titrated with N-pivaloyl-o-toluidine.⁵⁴ All other reagents and solvents were of commercial quality and were used without further purification. Flash chromatography was carried out over silica gel (230-400 mesh). ¹H and ¹³C NMR spectra were recorded with a dual probe $({}^{13}C/{}^{1}H)$. Chemical shifts are reported in δ units relative to an internal standard of residual chloroform (δ 7.27 ppm for ¹H NMR and δ 77.16 ppm for ¹³C NMR) or C₆D₆ (δ 7.15 ppm for ¹H NMR and δ 128.6 ppm for ¹³C NMR). Elemental analyses were performed at the Service de Microanalyses de l'Université Pierre et Marie Curie-Paris 6, case 55, 4 place Jussieu, 75252 Paris Cedex 05.

Typical Procedure for the Reaction of Li-1 with Aldehydes. At -95 °C, to a solution of (3-chloroprop-1-ynyl)trimethylsilane (0.80 mL, 5.00 mmol) in Et₂O (20 mL) and TMEDA (0.75 mL, 5.00 mmol) was added *n*-BuLi (2.30 M in hexanes, 2.17 mL, 5.00 mmol) at such a rate that the internal temperature did not exceed -95 °C. The reaction mixture was stirred for 15 min while it turned orange. The aldehyde (5.00 mmol) in Et₂O (5 mL) was added to the reaction mixture at -95 °C over a period of 5 min. After 1 h of stirring at -95 °C, a 1 M aqueous HCl solution (10 mL) was added, the layers were separated,



Figure 3. Configurational stability of Zn-1 over 4 h at -80 °C in THF.

and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. Purification of the crude material by flash chromatography allowed isolation of 2 and 3 (see Table 1, entries 1–5).

(1R, 25, 3'5, 4R)-1, 7, 7-Trimethyl-3'-(trimethylsilyl)ethynylspiro-[bicyclo[2.2.1]heptane-2,2'-oxirane] (5a). The title compound was obtained following the above procedure by the reaction between (3-chloroprop-1-ynyl)trimethylsilane (1.61 mL, 10.00 mmol) and (+)-camphor (4; 1.40 g, 9.00 mmol) in a Trapp mixture. Purification by flash chromatography (5% Et₂O/pentane) afforded a mixture of 5a and 5b (1.46 g, 5.58 mmol, 5a:5b = 92:08, 62%) as a colorless oil.

Data for **5a** are as follows. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ 3.27 (s, 1 H), 1.92 (dt, *J* = 13.8, 3.9 Hz, 1 H), 1.84–1.75 (m, 2 H), 1.72–1.60 (m, 2 H), 1.55–1.52 (d, *J* = 13.8 Hz, 1 H), 1.24 (m, 1 H), 0.95 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 3 H), 0.16 (s, 9 H). ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ 101.9, 92.3, 73.7, 48.8, 48.2, 46.8, 44.8, 39.4, 30.7, 27.9, 19.7, 19.3, 10.6, –0.3. IR (neat): ν 2959, 2170, 1652, 1242, 1035, 846 cm⁻¹. MS (ESI): *m/z* (%) 285 (24) [*M* + Na⁺], 251 (100), 223 (42). HMRS (ESI): *m/z* calcd for C₁₆H₂₆OSi + Na⁺ 285.1645 [*M* + Na⁺], found 285.1641.

Typical Procedure for the Reaction of Ti-1 with Aldehydes. At -95 °C, to a solution of TMEDA (0.60 mL, 4.00 mmol) and (3-chloroprop-1-ynyl)trimethylsilane (0.64 mL, 4.00 mmol) in Et₂O (10 mL) was added dropwise n-BuLi (2.30 M in hexanes, 1.70 mL, 4.00 mmol). The resulting yellow solution was stirred for 2 min at -95 °C prior to the addition of Ti(O-*i*-Pr)₄ (1.18 mL, 4.00 mmol) in THF (4 mL). The reaction mixture was stirred at -95 °C for 10 min, at which time it turned orange, and then warmed to the appropriate temperature (see Table 1, entries 6-15) over a period of 30 min. The aldehyde (6.00 mmol) in THF (6 mL) was then added. After 3 h of stirring at the same temperature, the reaction mixture was hydrolyzed with a 2/1 mixture of a saturated aqueous NH₄Cl solution and NH₃ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and filtered, and the solvents were removed in vacuo. Purification of the crude material by flash chromatography afforded 2 and 3 (see Table 1, entries 6-15).

(15)-4-Chloro-2-(trimethylsilyl)-1-((S)-1-tritylpyrrolidin-2-yl)buta-2,3-dien-1-ols (7). The title compound was obtained following the above procedure by the reaction between (3-chloroprop-1-ynyl)trimethylsilane (0.32 mL, 2.00 mmol) and (S)-N-tritylprolinal (4; 0.82 g, 2.40 mmol). Purification by flash chromatography (4.9%/ 0.1% EtOAc/Et₃N/cyclohexane) afforded a mixture of 7a and 7b (0.58 g, 7a:7b = 50:50, 60%). Further purification by flash chromatography (4.9%/0.1% EtOAc/Et₃N/cyclohexane) gave analytically pure 7a as a white amorphous solid, while a pure sample of 7b could not be obtained.

Data for 7a are as follows. Mp: 115 °C dec. $[\alpha]_D^{20} = -9.8^{\circ}$ (c = 1.24in CHCl₃). ¹H NMR (CDCl₃, 400 MHz, 25 °C): δ 7.55 (d, J = 7.3 Hz, 6 H), 7.27 (t, J = 7.6 Hz, 6 H), 7.18 (t, J = 7.2 Hz, 3 H), 6.07 (d, J =2.8 Hz, 1 H), 4.66 (t, J = 2.8 Hz, 1 H), 3.56 (ddd, J = 8.8, 6.0, 3.0 Hz, 1 H), 3.25 (ddd, J = 12.1, 10.8, 6.8 Hz, 1 H), 3.07 (ddd, J = 11.2, 7.8, 2.5 Hz, 1 H), 2.96 (bs, 1 H), 1.73–1.63 (m, 1 H), 1.33–1.25 (m, 1 H), 1.16–1.07 (m, 1 H), 0.14–0.01 (m, 1 H), -0.11 (s, 9 H). ¹³C NMR (CDCl₃, 100 MHz, 25 °C): δ 202.5, 144.5, 129.9, 127.8, 126.5, 113.1, 88.5, 78.3, 73.4, 63.9, 53.5, 26.0, 25.0, -1.4. IR (CHCl₃): ν 3468, 3084, 3057, 2955, 2874, 1935, 1596, 1489, 1447, 1366, 1320, 1250, 1217, 1104, 1012, 904, 842, 758, 745, 708, 629 cm⁻¹. Anal. Calcd for C₃₀H₃₄ClNOSi: C, 73.82; H, 7.02; N, 2.87. Found: C, 73.70; H, 7.17; N, 2.81.

Data for 7**b** are as follows. ¹H NMR (CDCl₃, 400 MHz, 25 °C): δ 7.55 (d, *J* = 7.3 Hz, 6 H), 7.27 (t, *J* = 7.6 Hz, 6 H), 7.18 (t, *J* = 7.2 Hz, 3 H), 5.91 (d, *J* = 2.6 Hz, 1 H), 4.74 (t, *J* = 2.7 Hz, 1 H), 3.57 (ddd, *J* = 8.8, 5.7, 3.0 Hz, 1 H), 3.23 (ddd, *J* = 12.1, 9.8, 7.0 Hz, 1 H), 3.06 (ddd, *J* = 11.4, 8.1, 2.5 Hz, 1 H), 2.93 (bs, 1 H), 1.61–1.51 (m, 1 H), 1.30–1.21 (m, 1 H), 1.13–1.03 (m, 1 H), 0.14–0.01 (m, 1 H), -0.06 (s, 9 H). ¹³C NMR (CDCl₃, 100 MHz, 25 °C): δ 202.6, 144.5, 129.9, 127.8, 126.5, 113.4, 87.7, 78.3, 73.7, 63.9, 53.5, 26.1, 25.0, –1.2. HMRS (ESI): *m*/*z* calcd for C₃₀H₃₄(³⁵Cl)NOSi + H⁺ 488.2176 [*M* + H⁺],

found 488.2183; m/z calcd for $C_{30}H_{34}(^{37}Cl)NOSi + H^+$ 490.2162 $[M + H^+]$, found 490.2149.

Typical Procedure for the Reaction of Zn-1 with Aldehydes. At -80 °C, to a 1 M THF solution of ZnBr₂ (2.00 mL, 2.00 mmol) and (3-chloroprop-1-ynyl)trimethylsilane (0.32 mL, 2.00 mmol) in THF (6 mL) was added dropwise a freshly prepared 2 M THF solution of LDA (2 mL, 4.00 mmol) over a period of 1 h. After completion of the addition, the aldehyde (2.00 mmol) was added. The resulting mixture was stirred at -80 °C for 1 h and then warmed to -20 °C, at which temperature it was stirred for an additional 45 min. A 2/1 mixture of a saturated aqueous NH₄Cl solution and NH₃ (10 mL) was added, the layers were separated, and the aqueous layer was extracted with Et₂O (2 × 10 mL). The combined organic layers were dried over anhydrous MgSO₄ and filtered, and the solvents were removed in vacuo. Purification by flash chromatography afforded analytically pure chlorohydrins **2** (see Table 1, entries 16–21).

(–)-(15,2R)-2-Chloro-4-(trimethylsilyl)-1-((S)-1-tritylpyrrolidin-2yl)but-3-yn-1-ol (**9a**) and (–)-(15,2S)-2-chloro-4-(trimethylsilyl)-1-((S)-1-tritylpyrrolidin-2-yl)but-3-yn-1-ol (**9b**). The title compounds were obtained following the above procedure by the reaction between (3-chloroprop-1-ynyl)trimethylsilane (0.32 mL, 2.00 mmol) and (S)-N-tritylprolinal (**6**; 0.82 g, 2.40 mmol) for 7 h at -80 °C. Purification by flash chromatography (4.9%/0.1% EtOAc/Et₃N/cyclohexane) afforded analytically pure **9a** (0.57 g, 49%) and **9b** (0.25 g, 21%) as white solids.

Data for **9a** are as follows. Mp: 58–59 °C. $[\alpha]_D^{20} = -46.0^\circ$ (c = 1.42 in CHCl₃). ¹H NMR (CDCl₃, 400 MHz, 25 °C): δ 7.56 (d, J = 7.3 Hz, 6 H), 7.26 (t, J = 7.6 Hz, 6 H), 7.17 (t, J = 7.1 Hz, 3 H), 4.25 (dd, J = 8.3, 1.8 Hz, 1 H), 4.20 (d, J = 8.3 Hz, 1 H), 3.78 (ddd, J = 8.8, 3.8, 2.0 Hz, 1 H), 3.30 (dt, J = 12.4, 8.5 Hz, 1 H), 3.02 (ddd, J = 11.9, 8.7, 3.0 Hz, 1 H), 2.90 (bs, 1 H), 1.60–1.54 (m, 1 H), 1.36–1.32 (m, 1 H), 1.03–0.98 (m, 1 H), 0.36–0.29 (m, 1 H), 0.20 (s, 9 H). ¹³C NMR (CDCl₃, 100 MHz, 25 °C): δ 145.0, 129.8, 127.7, 126.3, 100.8, 93.3, 77.8, 77.3, 61.6, 52.2, 50.0, 25.3, 24.7, -0.1. IR (CHCl₃): ν 3460, 3056, 2957, 2361, 2178, 1596, 1489, 1447, 1250, 1010, 844, 758, 707 cm⁻¹. Anal. Calcd for for C₃₀H₃₄ClNOSi: C, 73.82; H, 7.02; N, 2.87. Found: C, 74.02; H, 7.02; N, 2.67.

Data for **9b** are as follows. Mp: 53–54 °C. $[\alpha]_D^{20} = -44.8^{\circ}$ (c = 0.93in CHCl₃). ¹H NMR (CDCl₃, 400 MHz, 25 °C): δ 7.56 (d, J = 7.6 Hz, 6 H), 7.26 (t, J = 7.6 Hz, 6 H), 7.18 (t, J = 7.2 Hz, 3 H), 4.27 (d, J = 9.4Hz, 1 H), 4.23 (bd, J = 9.9 Hz, 1 H), 3.92–3.88 (m, 1 H), 3.28 (ddd, J =12.1, 9.3, 7.6 Hz, 1 H), 3.07 (ddd, J = 11.8, 8.3, 2.8 Hz, 1 H), 2.99 (bs, 1 H), 1.55–1.45 (m, 1 H), 1.39–1.26 (m, 1 H), 1.14–1.06 (m, 1 H), 0.30–0.18 (m, 1 H), 0.10 (s, 9 H). ¹³C NMR (CDCl₃, 100 MHz, 25 °C): δ 144.8, 129.8, 127.7, 126.4, 99.5, 93.4, 79.2, 78.5, 62.3, 52.9, 52.8, 25.3, 25.2, -0.2. IR (CHCl₃): ν 3453, 3058, 2958, 2180, 1596, 1489, 1448, 1250, 1009, 845, 759, 708 cm⁻¹. HMRS (ESI): m/z calcd for C₃₀H₃₄CINOSi + H⁺ 486.2014 [M + H⁺], found 486.2009.

ASSOCIATED CONTENT

Supporting Information

Text and figures giving experimental procedures for compounds **3** and the determination of the configurations of compounds **9a,b**, ¹H and ¹³C spectra of all new analytically pure compounds, and ¹H spectra for the determination of the er of **2** with Eu(hfc)₃. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. **Notes**

The authors declare no competing financial interest.

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