DOI: 10.1002/ejoc.200801188

$AlCl_3$-Promoted Facile *E*-to-*Z* Isomerization Route to (*Z*)-2-Methyl-1-buten-1,4-ylidene Synthons for Highly Efficient and Selective (*Z*)-Isoprenoid Synthesis

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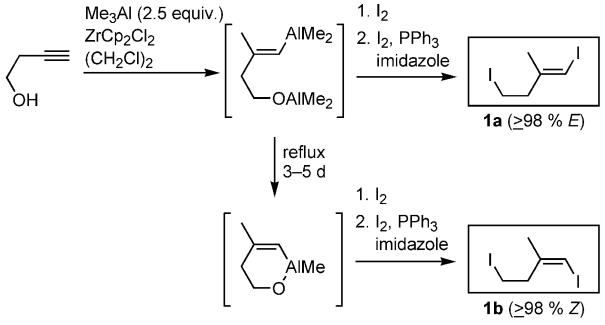
Dedicated to Professor Alain Krief

Keywords: Carboalumination / Zirconium / Isomerization / Stereoselectivity / Terpenoids

Zr-catalyzed methylalumination of 3-butyn-1-ols followed by $AlCl_3$-promoted stereoisomerization at 50 °C for 6 h provides 4-iodo-3-methyl-3-buten-1-ols **2b** and **6** (≥98 % Z configuration) in 87 and 67 % yields, respectively. (*Z*)-1,4-Diiodo-2-methyl-1-butene (**1b**) obtainable by iodination of **2b** is a valuable synthon for efficient and selective syntheses of (*Z*)-alkene-containing isoprenoids.

Introduction

Stereo- and regioselective synthesis of 1,5-dienes and oligoenes thereof representing various terpenoidal natural products had provided a major synthetic challenge until the development of the Pd-catalyzed homoallyl–/homopropargyl–alkenyl coupling route first reported in 1980.[1] In sharp contrast with the intrinsically capricious allyl–allyl coupling route requiring typically several steps for the formation of just one critical C–C bond linking two allylic moieties,[2] the Pd-catalyzed cross-coupling reaction of alkenyl iodides with either homopropargylzinc or homoallylzinc reagents reliably proceeds in high yields with strict (≥98 %) control of regio- and stereochemical identities, with little or no sign of β-elimination.[1,3–5] Particularly attractive is the two-step preparation of (*E*)-1,4-diiodo-2-methyl-1-butene (**1a**)[3a] with a ≥98 % *E* configuration (Scheme 1) from homopropargyl alcohol by Zr-catalyzed methylalumination, ZMA hereafter, which permits one-pot homologation of (all-*E*)-isoprenoid skeletons by one "one isoprene equivalent" that has been applied to highly efficient and selective syntheses of coenzyme Q_n (n = 3 and 10) and menaquinone-3.[3a] For the synthesis of (*Z*)-trisubstituted alkene-containing isoprenoids, (*Z*)-1,4-diiodo-2-methyl-1-butene (**1b**) with a ≥98 % stereoisomeric purity was prepared by heating to reflux the reaction mixture containing the *E*-isomer in $(CH_2Cl)_2$ for 3–5 d (Scheme 1).[6] Compound **1b** has also been successfully used for the synthesis of (*Z*)-trisubstituted alkene-containing farnesols and (2*E*, 6*Z*, 10*E*)-geranylgeraniol.[3a] As attractive as it is, the rather harsh conditions for isomerization pointed to the obvious need for improvement.



Scheme 1. Zr-catalyzed carboalumination and double-iodination routes to (*E*)- or (*Z*)-1, 4-diiodo-2-methyl-1-butene (summary of the previous results).

Herein we report our recent findings that have led to a remarkably mild and highly satisfactory procedure for the preparation of **1b** with a ≥98 % stereoisomeric purity in 75 % yield in 2 steps from 3-butyn-1-ol, which thereby makes the ZMA–Pd-catalyzed alkenylation–homoallylation tandem protocol highly satisfactory, not only for the synthesis of (all-*E*)-isoprenoids, but also for (*Z*)-trisubstituted alkene-containing isomers.

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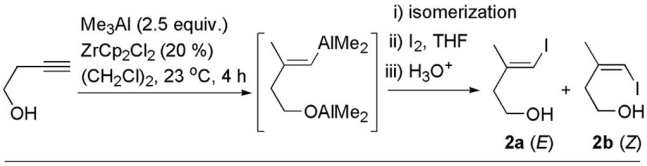
Results and Discussion

In the hope of promoting the sluggish stereoisomerization mentioned above, Lewis acid promoted stereoisomerization was considered. Although both organoalanes and $ZrCp_2Cl_2$ used for the ZMA reaction are considered to be Lewis acids, more effective Lewis acids were evidently needed. We therefore chose and added to the completed ZMA reaction mixture methylaluminoxane (MAO) used for promoting the Zr-Al-cocatalyzed Kaminsky modification of the Ziegler–Natta alkene polymerization,[7] $AlCl_3$, $MeAlCl_2$, Me_2AlCl, as well as $BF_3{\cdot}OEt_2$ and $InCl_3$. The results summarized in Table 1 indicate the following: (i) $AlCl_3$ and MAO are both effective in accelerating the desired *E*- to *Z*-isomerization, but $AlCl_3$ is the promoter of choice (Entries 3 and 7). (ii) It appears to be mandatory to use more than 1 equiv. $AlCl_3$ (Entries 5–7) at moderately elevated temperatures, e.g. 50 °C (Entries 4 and 7). (iii) Under the conditions employed, $MeAlCl_2$, Me_2AlCl, $BF_3{\cdot}OEt_2$ and $InCl_3$ are not effective (Entries 8–11).

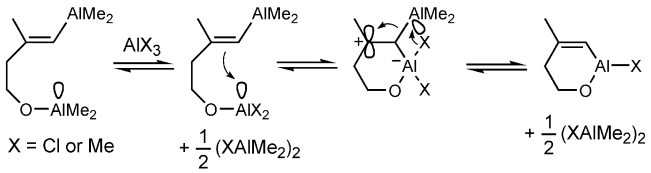
Table 1. Lewis acid promoted stereoisomerization of the ZMA reaction mixture obtained from 3-butyn-1-ol.



Entry	Additive (quantity)	*T* [°C]	Time [h]	**2a** + **2b** [%]	**2b**/**2a**
1[a]	none	–	0	91	≤2/98
2[a]	none	reflux	72	60	≥98/2
3[b]	MAO (3 equiv.)	reflux	24	61	≥98/2
4	$AlCl_3$ (2 equiv.)	–5	12	72	≤2/98
5	$AlCl_3$ (0.25 equiv.)	50	12	82	1/50
6	$AlCl_3$ (1.1 equiv.)	50	6	89	3/1
7	$AlCl_3$ (2 equiv.)	50	6	87	≥98/2
8	$MeAlCl_2$ (2 equiv.)	50	6	88	1/4
9	Me_2AlCl (2 equiv.)	50	6	86	1/45
10	$InCl_3$ (2 equiv.)	50	12	70	1/4
11	$BF_3{\cdot}OEt_2$	23	12	[c]	[c]

[a] Previously reported data.[6] [b] Observed by Dr. Z. Tan in our laboratories. [c] Complex product mixture obtained.

Although mechanistic details of the $AlCl_3$-promoted stereoisomerization remain to be further clarified, it is not unreasonable to envision the reaction in terms of a polar cyclization process shown in Scheme 2, which is consistent with (i) the high efficiency of Al–Cl bonded species that are expected to undergo kinetically facile O⇌Cl ligand exchange and [1, 3] Cl migration owing to the presence of 3 lone pairs of electrons as opposed to none for the Me group and (ii) the formation of the thermodynamically more favorable double Cl-bridged alane dimers as opposed to the Me-bridged alane dimers. If this latter item (ii) is indeed a significant factor, the observed isomerization may well be stoichiometric in chloroalanes.

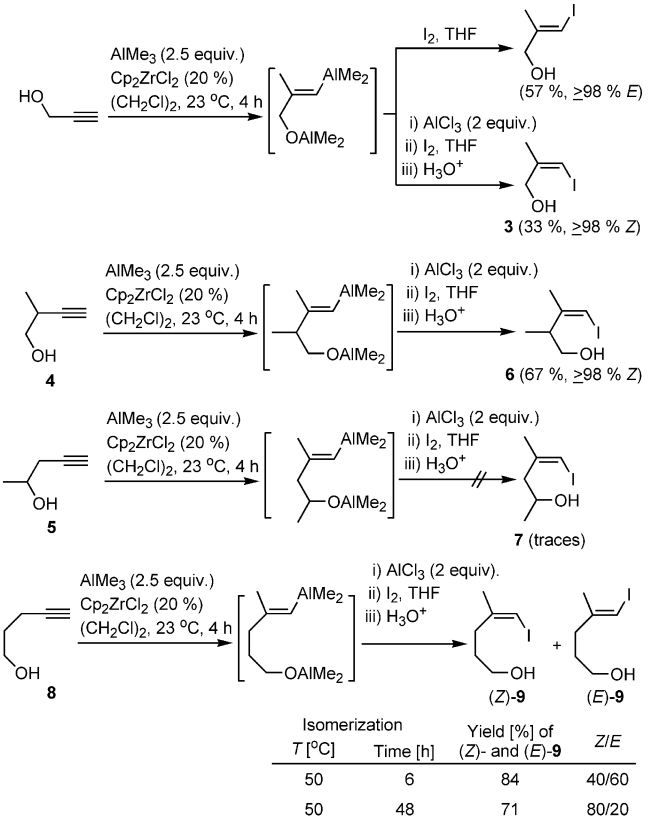


Scheme 2. Mechanistic hypothesis for AlX_3-promoted stereoisomerization.

Since our efforts have been focused on the improvement of the synthesis of the single most important (*Z*)-isoprene equivalent **1b** obtainable via **2b**, relatively little effort has thus far been given to the exploration of the scope of the $AlCl_3$-promoted stereoisomerization of alkenylalanes that has just been developed. Nonetheless, some preliminary results described below do provide indications of its scope and limitations. 1-Alkynes lacking proximal OH or any heterofunctional group, e.g. 1-octyne, are known to undergo the ZMA reaction,[8] but such alkenylalane products show no sign of stereoisomerization upon heating to 50 °C in the presence of $AlCl_3$ (2.0 equiv.). As has long been known,[9] treatment of propargyl alcohol with Me_3Al (2.5 equiv.) and $ZrCp_2Cl_2$ (0.2 equiv.) in $(CH_2Cl)_2$ at 23 °C for 4 h followed by iodinolysis produced (*E*)-3-iodo-2-methyl-2-propen-1-ol (≥98% *E*) in 57% yield. When the ZMA reaction mixture was treated with anhydrous $AlCl_3$ (2.0 equiv.) at 50 °C for 6 h and then subjected to iodinolysis, (*Z*)-3-iodo-2-methyl-2-propen-1-ol (**3**) with a ≥98% *Z* geometry was obtained albeit in only 33% yield. It should be reminded that **3** can be readily and selectively prepared in higher yields by treating propargyl alcohol with MeMgBr in the presence of a catalytic amount of CuI followed by iodinolysis.[10]

As previously reported, 2-methyl-3-butyn-1-ol (**4**) and 4-pentyn-2-ol (**5**) can be converted into the expected iodinated alcohols **6** and **7** with ≥98% *Z* configuration in 61 and 50% yields, respectively, but the isomerization step requires the heating to reflux of the ZMA-product-containing mixtures for 3–5 d.[3a,6] Under the $AlCl_3$-promoted conditions (heating at 50 °C for 6 h in the presence of 2 equiv. $AlCl_3$), **6** (≥98% *Z*) was obtained in 67% yield. To our disappointment, however, our attempts to prepare **7** under the same conditions as described above led to extensive decomposition of the ZMA product from **5**. In the case of 4-pentyn-1-ol (**8**), the product is not clean but interesting and promising. As summarized at the bottom of Scheme 3, application of the standard ZMA and $AlCl_3$-promoted isomerization protocol reported herein gave a roughly 40:60 mixture of the *Z* and *E* isomers of **9** in 84% combined yield when the ZMA reaction product was heated to 50 °C for 6 h in the presence of 2 equiv. $AlCl_3$. After prolonged heating at 50 °C for a total of 48 h, the *Z*/*E* ratio was improved to 80:20, but the yield of **9** decreased to 71%. When the ZMA product mixture was heated to reflux in the presence of $AlCl_3$ (2 equiv.), however, most of the alkenylalane products de-

composed. Chromatographic purification of the 80:20 mixture of the *Z* and *E* isomers of **9** gave ≥98% pure (*Z*)-**9** in 52% yield. Further improvement is clearly desirable.



Isomerization T [°C]	Time [h]	Yield [%] of (*Z*)- and (*E*)-**9**	*Z*/*E*
50	6	84	40/60
50	48	71	80/20

Scheme 3. Application of the ZMA–$AlCl_3$-promoted isomerization protocol to other proximally OH-substituted 1-alkynes.

Conclusions

Zr-catalyzed methylalumination of 3-butyn-1-ol and its 2-methyl derivative **4** followed by $AlCl_3$-promoted stereoisomerization at 50 °C for 6 h provides ≥98% *Z* 4-iodo-3-methyl-3-buten-1-ols **2b** and **6** in 87 and 67% yields, respectively. Iodination of **2b** gives (*Z*)-1,4-diiodo-2-methyl-1-butene (**1b**) with a ≥98% isomeric purity in 75% yield from 3-butyn-1-ol. The procedural development reported herein has finally made the Pd-catalyzed homoallyl–alkenyl coupling route to 1,5-diene-containing oligomeric isoprenoids of any geometric combination both highly selective and practically convenient.

Although tentative, the available data suggest that a cyclic mechanism requiring an appropriate proximal heterofunctional group, e.g. OH, is operative and that the role of $AlCl_3$ appears to displace the alkene-bound Me_2Al group with $AlCl_2$, which thereby facilitates configurational inversion through facile polar cyclization.

As suggested by the results shown in Scheme 3, the ZMA–$AlCl_3$-promoted isomerization process reported herein appears to be applicable to various other types of proximally heterofunctional trisubstituted (*Z*)-alkenyl derivatives containing Al, I and other functional groups, which may, in turn, be further converted to a wide variety of compounds including heterocycles, and explorations in such directions are in progress.

Experimental Section

General: All reactions were carried out under argon atmosphere. *$AlMe_3$ is highly pyrophoric!* Reactions were monitored by TLC and GC analysis of the reaction aliquots. GC analysis was performed on an HP6890 Gas Chromatograph using an HP-5 capillary column (30 m × 0.32 mm, 0.5 μM film) packed with SE-30 on Chromosorb W. Column chromatography was carried out on 230–400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on a Varian-Inova-300 spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum 2000 FT-IR spectrometer. LRMS and HRMS were obtained on Hewlett Packard 5995 GC-MS and Finnigan MATL95 mass spectrometers, respectively.

Preparation of (*Z*)-4-Iodo-3-methyl-3-buten-1-ol (2b). Representative Procedure for $AlCl_3$-Promoted *E*-to-*Z* Isomerization: To a solution of $ZrCp_2Cl_2$ (0.29 g, 1.0 mmol) in $(CH_2Cl)_2$ (20 mL) were sequentially added $AlMe_3$ (1.2 mL, neat, 12.5 mmol) and 3-butyn-1-ol (0.35 g, 5.0 mmol) at 0 °C. The resultant mixture was stirred at 23 °C for 4 h for completion of methylalumination. Anhydrous $AlCl_3$ powder (1.35 g, 10 mmol) was added to the above reaction mixture in one portion. After stirring at 50 °C for 6 h, the reaction mixture was quenched with a solution of I_2 (2.54 g, 10 mmol) in THF (20 mL) at –78 °C. The resultant mixture was stirred at –78 °C for 30 min and then poured into ice–water, extracted with diethyl ether, washed with brine, dried with $MgSO_4$, filtered and concentrated. Flash chromatography (silica gel, 30% EtOAc in hexanes) afforded (*Z*)-4-iodo-3-methyl-3-buten-1-ol (**2b**) (0.92 g, 87%, ≥98% *Z*) as a liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.89 (d, J = 1.2 Hz, 3 H), 2.46 (t, J = 6.9 Hz, 2 H), 2.84 (s, 1 H), 3.69 (t, J = 6.9 Hz, 2 H), 5.93 (q, J = 1.2 Hz, 1 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.81, 41.48, 59.80, 76.19, 144.25 ppm. IR (neat): $\tilde{\nu}$ = 3292, 1580 cm^{-1}. HRMS (CI): calcd. for M^+ 211.9700; found 211.9696.

It is also practical to use commercially available $AlMe_3$ in hexanes. The Zr-catalyzed carboalumination of 3-butyn-1-ol with 2 M $AlMe_3$ in hexanes under otherwise the same conditions as described above was complete in 5 h. The subsequent isomerization with $AlCl_3$ at 50 °C was somewhat slower requiring 18 h for ≥98% stereoisomerization in 82% yield.

Preparation of (*Z*)-1,4-Diiodo-2-methyl-1-butene (1b): Treatment of (*Z*)-4-iodo-3-methyl-3-buten-1-ol with PPh_3, I_2 and imidazole in CH_2Cl_2 as previously reported[3a,6] afforded the title compound in 86% yield with ≥98% stereoisomeric purity: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 3 H), 2.82 (t, J = 7.6 Hz, 2 H), 3.20 (t, J = 7.3 Hz, 2 H), 6.07 (s, 1 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 0.41, 23.00, 42.41, 77.02, 145.70 ppm.

Acknowledgments

We thank the National Institutes of Health (GM 36792) and Purdue University for support of this research. The favorable results with MAO as a promoter were obtained first by Dr. Z. Tan in our laboratories. We thank him for providing us with a promising lead. We also thank Albemarle, NICHIA Corporation, and Sigma-Aldrich for providing us with the organometallic compounds.

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Received: November 30, 2008
Published Online: January 28, 2009

