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Zirconium-catalyzed methylalumination of heterosubstituted arylethynes: Factors affecting the regio-, stereo-, and chemoselectivities

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Dedicated to Professor Gerhard Erker on the occasion of his 60th birthday.

Abstract

The Zr-catalyzed methylalumination of heterosubstituted arylethynes containing O, S, Cl, and Si can proceed in high yields (>70%) and in a highly regio- and stereoselective manner ($\geqslant 98$–99%), although SO$_2$Ph, Br, and Cl in a benzylic position present serious chemoselectivity-related problems. The low regioselectivity of 60% initially observed with *o*-ethynylphenol (**1a**) has been elevated to $\geqslant 98\%$ through the use of either a catalytic amount of Zr(ebi)Cl$_2$ or Zr(2-Me-Ind)$_2$Cl$_2$ or, more conveniently, the stoichiometric amount of ZrCp$_2$Cl$_2$, ZrCp$_2$MeCl, or ZrCp$_2$Me$_2$ in conjunction with the use of a deficient amount (0.9 molar equiv.) of I$_2$ for subsequent iodinolysis.
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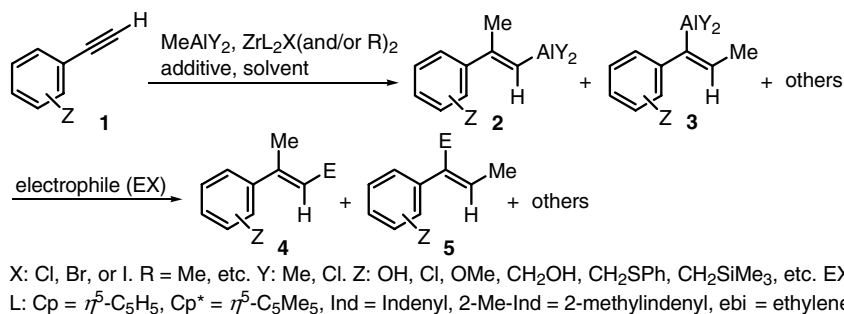
1. Introduction

The Zr-catalyzed carboalumination, especially methylalumination, of terminal alkynes reported first by the authors' group in 1978 [1] has since been developed into a preferred method for the synthesis of methyl-substituted (*E*)-trisubstituted alkenes representing a wide variety of natural products and related compounds of biological and medicinal importance. A recent survey indicates that well over 100 complex natural products have been synthesized by using this reaction in one or more crucial steps [2]. In the absence of any heterofunctional groups in the alkyne substrates, this reaction is highly stereoselective ($\geqslant 98$–99% *syn* addition), regioselective (generally ca. 95%), and dependably and widely applicable. Furthermore, the regioselectivity can be improved to $\geqslant 98$–99% through the use of bulky derivatives of ZrCp$_2$Cl$_2$, such as, Zr(ebi)Cl$_2$, where ebi is ethylenebis(indenyl), as recently reported by

Lipshutz [3]. Alternatively, high regioselectivity levels ($\geqslant 98$–99%) can also be attained through the use of a controlled amount of electrophile, such as I$_2$, for derivatization of methylalumination products, since the desired terminally aluminated products, in general, are considerably more reactive than the internally aluminated byproducts, presumably because of greater steric hindrance around the alkenylcarbon–Al bond in the latter [4].

The presence of one or more heterofunctional groups in the terminal alkynes can exert significant influences on selectivity. In terms of chemoselectivity, most of the carbonyl groups can be competitively reduced, and it is therefore advisable to introduce them later. Fortunately, halogens including Cl, Br, and I are accommodated except perhaps in the allylic, propargylic, benzylic, and other similarly activated positions, a particularly noteworthy example of this class being the preparation of (*E*)-1,4-diiodo-2-methyl-1-butene from 4-iodo-1-butyne [5]. Perhaps more importantly, hydroxyl groups can be accommodated widely even in the propargylic position, provided that free unprotected alcohols are used in conjunction with one

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Scheme 1.

2. Results and discussion

The results summarized in Table 1 indicate the following:

(1) All except the PhSO$_2$-containing **1h** (Entry 8) undergo the Zr-catalyzed methylalumination in high yields (72–93%).

(2) With halobenzylethynes (**1i** and **1j**), methylation of benzyl halides takes place concurrently to produce **6** (Entries 9 and 10). These benzylic halogens must therefore be introduced later via halogenation of **4f**, for example.

(3) It is noteworthy that both phenolic and benzylic OH groups can be readily accommodated without protection (Entries 1, 3, 4, and 6).

(4) In the case of **1a** containing an OH group in the ortho position, however, a drastically lower regioselectivity of 60% for the expected major product, i.e., β-**4a**, was observed. Fortunately, this problem has been solved through modification of the methylalumination procedure, as discussed later.

(5) Despite the fact that the internally metalated α isomer of the product contains a benzylic metal, which is normally strongly favored, the high regioselectivity level of the ⩾93% favoring the β isomer has been observed except in the case of **1a**. In particular, the β/α ratios observed for the iodinolysis products **4** were ⩾98–99% with no indication of the presence of the α isomer at the detection level of S/N ratios of ⩾50–100, except in the cases of **1a**, **1b**, and **1c** (Entries 1–3). In the cases of **1b** and **1c**, however, the use of 0.9 molar equiv. of I$_2$ led to the β/α ratio of 99/1, even though the products yields were necessarily lower (80% for **4b** and 81% for **4c**).

(6) In all cases where the Zr-catalyzed methylalumination proceeded, a uniformly high stereoselectivity level of ⩾98–99% by ^{13}C NMR spectroscopy has been observed. Attempt to induce synthetically useful, clean stereoisomerization similar to that observed with 3-methyl-4-alumino-3-buten-1-ol [7] has thus far been unsuccessful. Despite some difficulties, observed with **1a**, **1h**, **1i**, and **1j**, it is gratifying to find that, in all of the other seven cases studied, the Zr-catalyzed methylalumination of arylethynes (**1**) that are arylically and benzylically substituted with heterofunctional groups containing O, S, Cl, and Si proceeds satisfactorily as detailed above and summarized in Table 1.
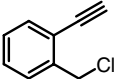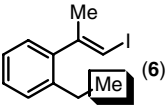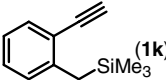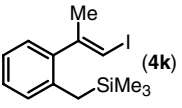
The uniquely lower regioselectivity of 60% observed with **1a** was then dealt with. In this case, the formation of metal-containing five-membered species (**7**) was thought to be favorable and critical. If so, the corresponding formation of six-membered species (**8**) must be comparatively insignificant, as judged by the results observed with **1f** (Entry 6 in Table 1). Rather than probing structural and mechanistic details, we opted for varying some of the readily changeable reaction parameters, which led to the experimental results that are summarized in Table 2.

additional equivalent of Me$_3$Al for in situ generation of aluminum alkoxides [5]. Although, remote OH groups protected with silyl, benzyl, and other groups may be better tolerated, their presence in the propargylic, homopropargylic and other related positions can be problematic, even though the ^{i}Pr$_3$Si (TIPS) group may be tolerated [3]. With these precautions, hydroxyl-containing 1-alkynes including various hydroxyl-substituted enynes have indeed been employed in highly stereo- and regioselective manners [2].

In conjunction with application of the Zr-catalyzed methylalumination to the synthesis of arylated alkene-containing natural products, we recently ran the Zr-catalyzed methylalumination of *o*-ethynylphenol (**1a**) with Me$_3$Al (3 molar equiv.) and ZrCp$_2$Cl$_2$ (5 mol%), and observed an unexpectedly low regioselectivity of about 60%, as detailed below. We then noted that, even though phenylethyne was one of the first substrates used in this reaction [1a], little has since been investigated on the use of its heterosubstituted derivatives. Below, we describe the results of our investigation of the Zr-mediated methylalumination of heterofunctionalized arylethynes, which has, in fact, proceeded, in most cases, normally and satisfactorily. Since some of the reactions of *o*-substituted phenylethynes were sluggish, one molar equivalent of H$_2$O and one additional equivalent of Me$_3$Al were used to in situ generate methylaluminoxane, leading to acceleration of the reaction, as originally devised by Wipf [6] (see Scheme 1).

Table 1
Zr-catalyzed methylalumination of heterosubstituted arylethynes

Entry	1	Main product	Yield (%)[a] $\beta + \alpha$	β/α[b]
1	(1a)	(4a)	85	60/40
2	(1b)	(4b)	90 81[c]	93/7 99/1[c]
3	(1c)	(4c)	93 80[c]	95/5 >98/2[c]
4	(1d)	(4d)	89	98/2
5	(1e)	(4e)	92	>99/1
6	(1f)	(4f)	76	>98/2
7	(1g)	(4g)	86	>98/2
8	(1h)	–	0	–
9	(1i)	(6)	72	>98/2

(continued on next page)

Table 1 (continued)

Entry	1	Main product	Yield (%)[a] $\beta + \alpha$	β/α[b]
10	(1j)	(6)	76	>98/2
11	(1k)	(4k)	85	>98/2

[a] Isolated yield.
[b] Based on ^{1}H and ^{13}C NMR.
[c] 0.9 molar equiv. of I_2 was used.

Table 2
Optimization of regioselectivity in the Zr-catalyzed methylalumination of 2-ethynylphenol
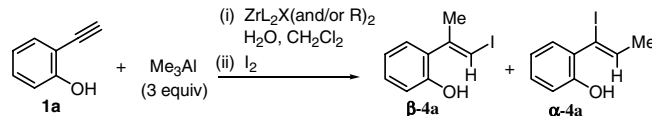
Entry	ZrL$_2$X (and/or R)$_2$[a]	Molar equiv. of ZrL$_2$X$_2$	Molar equiv. of I_2	Product yield (%)[b] $\beta + \alpha$	β/α[c]	1a (%)
1	ZrCp$_2$Cl$_2$	0.05	1.5	85	60/40	0
2	ZrCp$_2$Cl$_2$	1.0	1.5	88	88/12	0
3	ZrCp$_2$Cl$_2$	1.0	0.9	**74**	**>98/2**	0
4	ZrCp$_2^*$Cl$_2$	0.2	–	0	–	86
5	ZrInd$_2$Cl$_2$	0.05	1.5	81	60/40	0
6	Zr(2-Me-Ind)$_2$Cl$_2$	0.05	1.5	82	86/14	0
7	Zr(2-Me-Ind)$_2$Cl$_2$	0.05	0.9	70	**99/1**	0
8	Zr(ebi)Cl$_2$	0.05	1.5	80	90/10	0
9	Zr(ebi)Cl$_2$	0.05	0.9	70	**>98/2**	0
10	ZrCp$_2$Me$_2$	0.05	1.5	31	>99/1	22
11	ZrCp$_2$Me$_2$	1.0	1.5	61	>99/1	0
12	ZrCp$_2$Me$_2$	1.5	1.5	**64**	**>99/1**	0
13	ZrCp$_2$MeCl	0.15	1.5	41	66/34	46
14	ZrCp$_2$MeCl	1.0	1.5	**84**	**97/3**	0
15	ZrCp$_2$MeCl	1.0	0.9	**71**	**99/1**	0

[a] Cp = η^5-C$_5$H$_5$, Cp* = η^5-C$_5$Me$_5$, Ind = Indenyl, 2-Me-Ind = 2-methylindenyl, ebi = ethylenebis(indenyl).
[b] Isolated yield.
[c] Based on ^{1}H and ^{13}C NMR.
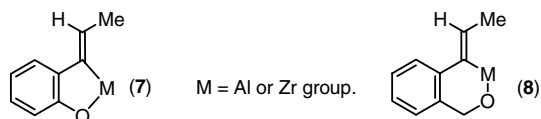
As can be gleaned from Table 2, a couple of reasonable solutions have now been found. One involves the use of a catalytic amount (5 mol%) of bulky ligand-containing Zr complexes, such as Zr(2-Me-Ind)$_2$Cl$_2$ or Zr(ebi)Cl$_2$ [3], either of which is commercially available, in place of ZrCp$_2$Cl$_2$. This modification with Zr(2-Me-Ind)$_2$Cl$_2$ and

Zr(ebi)Cl$_2$ led to the β/α ratios of 86/14 and 90/10, respectively, the combined yields being 80–82% (Entries 6 and 8). As expected, the use of only 0.9 molar equiv. of I_2 instead of the usual amount of 1.5 molar equiv., improved the β/α ratio in each case to >98–99/1, with a concomitant decrease in the product yield to ca. 70% (Entries 7 and 9).

Another method for obtaining regioisomerically pure methylmetalation products was originally reported in 1981 by us [8], which called for the use of the stoichiometric amount of ZrCp$_2$Me$_2$ along with Me$_3$Al (3 molar equiv.). We accordingly ran the reaction of 1a with Me$_3$Al

(3 equiv.) and ZrCp$_2$Me$_2$ (1 equiv.) and indeed obtained >99% regioisomerically pure **4a** in 61% yield upon iodinolysis with 1.5 equiv. of I$_2$. The use of 1.5 molar equiv. of ZrCp$_2$Me$_2$ did improve the yield of >99% pure **4a** to 64%. In view of the modest product yield observed above, we then employed one molar equivalent of ZrCp$_2$MeCl or ZrCp$_2$Cl$_2$ in place of ZrCp$_2$Me$_2$ and found that the β/α ratio would decrease to 97/3 (Entry 14) or 88/12 (Entry 2), respectively, but a significantly higher product yield of 84% or 88%, respectively, was realized. Here again, a controlled amount (0.9 equiv.) of I$_2$ led to practically attractive combinations of product yields and regioselectivity, namely a 71% yield and a β/α ratio of 99/1 observed with ZrCp$_2$MeCl (Entry 15) and a 74% yield and a β/α ratio of >98/2 observed with ZrCp$_2$Cl$_2$ (Entry 3). The effects of using bulky ligand-containing Zr complexes on regioselectivity may not require any explanation. From our earlier and extensive structural and mechanistic studies [1c,9,10], it has been known that the Me$_3$Al–ZrCp$_2$Cl$_2$, Me$_3$Al–ZrCp$_2$MeCl and Me$_3$Al–ZrCp$_2$Me$_2$ reagent systems would all undergo alkyne methylmetalation but that the reaction of the Me$_3$Al–ZrCp$_2$Me$_2$ reagent system is only stoichiometric in zirconium. Relatively little beyond these basic findings is clearly known, and the reaction in an overall sense is unquestionably multimechanistic. At this point, we merely wish to present some facts of potential synthetic use by deferring structural and mechanistic investigation of potentially intriguing aspects of the reactions presented herein.

The following two procedures, one for the synthesis of 2-[(*E*)-(1′-iodo-2′-propenyl)]phenol (**4a**) from **1a** and the other for that of 2-[(*E*)-(1′-iodo-2′-propenyl)]benzyl alcohol (**4f**) from **1f**, are representative.

3. Representative experimental procedures

3.1. Synthesis of **4a**

3.1.1. With ZrCp$_2$Cl$_2$, ZrCp$_2$MeCl, or ZrCp$_2$Me$_2$ as a promoter

2-Ethynylphenol (118 mg, 1.0 mmol), prepared by treatment of 2-iodophenol with ethynylzinc bromide in the presence of 5 mol% of Pd(PPh$_3$)$_4$ [9] and dissolved in 1 mL of CH$_2$Cl$_2$, was added at 0 °C to a mixture of Me$_3$Al (0.3 mL, 3.0 mmol) and ZrCp$_2$Cl$_2$ (292 mg, 1.0 mmol) in 2 mL of CH$_2$Cl$_2$ pretreated with H$_2$O (18 μL, 1.0 mmol) at −30 °C. The reaction mixture was stirred for 4 h at 23 °C, treated with a solution of I$_2$ (229 mg, 0.9 mmol) in 2 mL of THF at −78 °C, and gradually warmed to 0 °C. The resultant mixture was poured slowly into 10 mL of ice-water with stirring, extracted with Et$_2$O (3 × 10 mL), washed with brine, and dried over MgSO$_4$. After filtration and concentration, chromatography on silica gel (10% Et$_2$O in hexanes) afforded **4a** of >98% isomeric purity in 74% yield. The use of one molar equivalent of ZrCp$_2$MeCl or ZrCp$_2$Me$_2$ in place of ZrCp$_2$Cl$_2$ also gives **4a** of ≥99% isomeric purity in 71% or 64% yield, respectively.

3.1.2. With a catalytic amount of Zr(ebi)Cl$_2$ or Zr(2-Me-Ind)$_2$Cl$_2$

This experiment was performed in a manner similar to that described above, except that 5 mol % of either Zr(ebi)Cl$_2$ or Zr(2-Me-Ind)$_2$Cl$_2$ was used as a catalyst. In cases where 1.5 molar equiv. of I$_2$ was used for iodonolysis, **4a** was obtained in 80–82% yield, but the β/α ratio was 90/10 or 86/14, respectively. The use of 0.9 molar equiv. of I$_2$ reduced the yield of **4a** to about 70%, but the β/α ratio increased to 98/2–99/1.

3.2. Synthesis of **4f**

The starting 2-ethynylbenzyl alcohol (**1f**) was prepared in 72% yield by treating consecutively 2-iodobenzyl alcohol (Aldrich) with (i) MeMgBr (1 equiv.) and (ii) ethynylmagnesium bromide (1.3 equiv.) pretreated with dry ZnBr$_2$ (1.3 equiv.) and 5 mol% of Pd(PPh$_3$)$_4$ in THF [9]. To a solution of Me$_3$Al (0.4 mL, 4.0 mmol) and Cp$_2$ZrCl$_2$ (58 mg, 0.2 mmol) in 2 mL of CH$_2$Cl$_2$ was added H$_2$O (18 μL, 1.0 mmol) at −78 °C. After stirring for 30 min at −78 °C, the reaction mixture was warmed to 23 °C and kept at this temperature for 30 min. To the resultant mixture was added 2-ethynylbenzyl alcohol (132 mg, 1.0 mmol) in 3 mL of CH$_2$Cl$_2$ at −78 °C. The resultant reaction mixture was stirred for 3 h at 23 °C and treated with a solution of I$_2$ (508 mg, 2.0 mmol) in 3 ml of THF at −78 °C. After stirring for 30 min at −78 °C, the reaction mixture was warmed to 0 °C, stirred further for 30 min, quenched by careful addition of saturated aqueous Na$_2$S$_2$O$_3$, extracted with ether, washed with brine, dried over MgSO$_4$, and concentrated. Purification by column chromatography (silica gel, 70/30 hexanes-EtOAc) afforded 208 mg (76%, E/Z > 98/2 by ^{13}C NMR) of the title compound as a colorless oil.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2007.05.052.

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