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

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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 (≥ 98 –99%), although SO_2Ph , 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 ≥ 98 % through the use of either a catalytic amount of $\text{Zr}(\text{ebi})\text{Cl}_2$ or $\text{Zr}(2\text{-Me-Ind})_2\text{Cl}_2$ or, more conveniently, the stoichiometric amount of ZrCp_2Cl_2 , ZrCp_2MeCl , or ZrCp_2Me_2 in conjunction with the use of a deficient amount (0.9 molar equivalent) of I_2 for subsequent iodinolysis.

Keywords

Methylalumination with Me_3Al ; Heterosubstituted arylethynes; (*E*)-1-Iodo-2-arylpropenes; ZrCp_2Cl_2 and its derivatives; Regio- and stereoselectivities

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 (≥ 98 –99% *syn* addition), regioselective (generally ca. 95%), and dependably and widely applicable. Furthermore, the regioselectivity can be improved to ≥ 98 –99% through the use of bulky derivatives of ZrCp_2Cl_2 , such as, $\text{Zr}(\text{ebi})\text{Cl}_2$, where ebi is ethylenebis(indenyl), as recently reported by Lipshutz [3]. Alternatively, high regioselectivity levels (≥ 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].

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

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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 additional equivalent of Me₃Al 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 ⁱPr₃Si (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 Me₃Al (3 molar equiv.) and ZrCp₂Cl₂ (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 H₂O and one additional equivalent of Me₃Al were used to *in situ* generate methylaluminoxane, leading to acceleration of the reaction, as originally devised by Wipf [6].

The results summarized in Table 1 indicate the following.

1. All except the PhSO₂-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 equivalent of I₂ 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 ¹³C 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 7 cases studied, the Zr-catalyzed methylalumination of arylethynes (**1**) that are arylally 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.

M = Al or Zr group.

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 $\text{Zr}(\text{2-Me-Ind})_2\text{Cl}_2$ or $\text{Zr}(\text{ebi})\text{Cl}_2$ [3], either of which is commercially available, in place of ZrCp_2Cl_2 . This modification with $\text{Zr}(\text{2-Me-Ind})_2\text{Cl}_2$ and $\text{Zr}(\text{ebi})\text{Cl}_2$ 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 equivalents of I_2 instead of the usual amount of 1.5 molar equivalents, 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 [5], which called for the use of the stoichiometric amount of ZrCp_2Me_2 along with Me_3Al (3 molar equiv.). We accordingly ran the reaction of **1a** with Me_3Al (3 equiv) and ZrCp_2Me_2 (1 equiv.) and indeed obtained >99% regioisomerically pure **4a** in 61% yield upon iodinolysis with 1.5 equivalent of I_2 . The use of 1.5 molar equivalents of ZrCp_2Me_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_2MeCl or ZrCp_2Cl_2 in place of ZrCp_2Me_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_2MeCl (Entry 15) and a 74% yield and a β/α ratio of >98/2 observed with ZrCp_2Cl_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 $\text{Me}_3\text{Al-ZrCp}_2\text{Cl}_2$, $\text{Me}_3\text{Al-ZrCp}_2\text{MeCl}$ and $\text{Me}_3\text{Al-ZrCp}_2\text{Me}_2$ reagent systems would all undergo alkyne methylmetalation but that the reaction of the $\text{Me}_3\text{Al-ZrCp}_2\text{Me}_2$ 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.

Synthesis of **4a**

(a) With ZrCp_2Cl_2 , ZrCp_2MeCl , or ZrCp_2Me_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 $\text{Pd}(\text{PPh}_3)_4$ [9] and dissolved in 1 mL of CH_2Cl_2 , was added at 0 °C to a mixture of Me_3Al (0.3 mL, 3.0 mmol) and ZrCp_2Cl_2 (292 mg, 1.0 mmol) in 2 mL of CH_2Cl_2 pretreated with H_2O (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_2O (3 x 10 mL), washed with brine, and dried over MgSO_4 . After filtration and concentration, chromatography on silica gel (10% Et_2O in hexanes) afforded **4a** of >98% isomeric purity in 74% yield. The use of one molar equivalent of ZrCp_2MeCl or ZrCp_2Me_2 in place of ZrCp_2Cl_2 also gives **4a** of $\geq 99\%$ isomeric purity in 71 or 64% yield, respectively.

(b) With a catalytic amount of $\text{Zr}(\text{ebi})\text{Cl}_2$ or $\text{Zr}(\text{2-Me-Ind})_2\text{Cl}_2$

This experiment was performed in a manner similar to that described above, except that 5 mol % of either $\text{Zr}(\text{ebi})\text{Cl}_2$ or $\text{Zr}(\text{2-Me-Ind})_2\text{Cl}_2$ was used as a catalyst. In cases where 1.5 molar equivalent of I_2 was used for iodolysis, **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 equivalent of I_2 reduced the yield of **4a** to about 70%, but the β/α ratio increased to 98/2~99/1.

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 $\text{Pd}(\text{PPh}_3)_4$ in THF [9]. To a solution of Me_3Al (0.4 mL, 4.0 mmol) and Cp_2ZrCl_2 (58 mg, 0.2 mmol) in 2 mL of CH_2Cl_2 was added H_2O (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_2Cl_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 $\text{Na}_2\text{S}_2\text{O}_3$, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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X: Cl, Br, or I. R = Me, etc. Y: Me, Cl. Z: OH, Cl, OMe, CH_2OH , CH_2SPh , CH_2SiMe_3 , etc. EX = I_2 , NBS, etc.
 L: Cp = $\eta^5\text{-C}_5\text{H}_5$, Cp* = $\eta^5\text{-C}_5\text{Me}_5$, Ind = Indenyl, 2-Me-Ind = 2-methylindenyl, ebi = ethylenebis(indenyl)

Scheme 1.

Table 1

Entry

1

1

2

Entry

1

3

Entry

1

(1d)

4

(1e)

5

Entry

1

(1f)

6

Entry

1

(1g)

7

Entry

1

8

(1h)

Entry

1

9

(1i)

10

(1j)

Entry

1

11

[a] isolated yield.

[b] based on ^1H and ^{13}C NMR.

[c] 0.9 molar equivalent of I_2 was used.

Table 2

<div> </div>					
Entry	ZrL ₂ X(and/or R) ₂ ^[a]	Mol. Eq. of ZrL ₂ X ₂	Mol. Eq. of I ₂	Product Yield (%) ^[b] β + α	β + α ^[c] 1a (%)
1	ZrCp ₂ Cl ₂	0.05	1.5	85	60/40
2	ZrCp ₂ Cl ₂	1.0	1.5	88	88/12
3	ZrCp ₂ Cl ₂	1.0	0.9	74	>98/2
4	ZrCp ₂ *Cl ₂	0.2	-	0	-
5	ZrInd ₂ Cl ₂	0.05	1.5	81	60/40
6	Zr(2-Me-Ind) ₂ Cl ₂	0.05	1.5	82	86/14
7	Zr(2-Me-Ind) ₂ Cl ₂	0.05	0.9	70	99/1
8	Zr(ebi)Cl ₂	0.05	1.5	80	90/10
9	Zr(ebi)Cl ₂	0.05	0.9	70	>98/2
10	ZrCp ₂ Me ₂	0.5	1.5	31	>99/1
11	ZrCp ₂ Me ₂	1.0	1.5	61	>99/1
12	ZrCp ₂ Me ₂	1.5	1.5	64	>99/1
13	ZrCp ₂ MeCl	0.15	1.5	41	66/34
14	ZrCp ₂ MeCl	1.0	1.5	84	97/3
15	ZrCp ₂ MeCl	1.0	0.9	71	99/1

^[a] Cp = η⁵-C₅H₅, Cp* = η⁵-C₅Me₅, Ind = Indenyl, 2-Me-Ind = 2-methylindenyl, ebi = ethylenebis(indenyl).

^[b] isolated yield.

^[c] based on ¹H and ¹³C NMR.