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Zirconium-Catalyzed Hydroalumination of C═O Bonds: Site-Selective De-*O*-acetylation of Peracetylated Compounds and Mechanistic Insights

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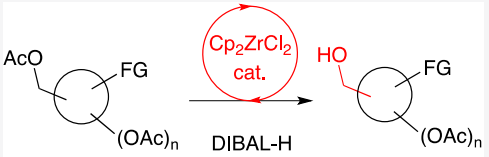
ABSTRACT: An unprecedented hydroalumination of C ═ O bonds catalyzed by zirconocene dichloride is reported herein and applied to the site-selective deprotection of peracetylated functional substrates. A mixed metal hydride, with 1:1 zirconium/aluminum stoichiometry, is also shown to be the reductive species. A catalytic cycle is finally proposed for this transformation with no precedent in the field of zirconium catalysis.



FG = ketal, thioketal, enol ether, azide, acetamide, Boc, *t*Bu ester

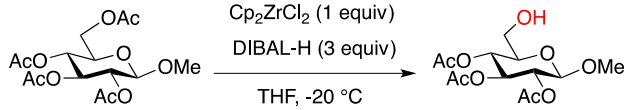
INTRODUCTION

Zirconium-mediated processes have undergone numerous developments in organic synthesis for decades.[1] Recently, the chemistry of zirconocenes has been pushed toward an exquisite level of sophistication with the emergence of dual C−C/C−H bond activation processes,[2] chemoselective transmetallations,[3] insertion reactions giving branched products instead of the usual linear ones,[4] formation of frustrated Lewis pairs,[5] and new synthetic approaches toward heterocycles.[6] Moreover, the reduction of carboxylic acid derivatives,[7] and more particularly of amides,[8] by zirconium hydrides is a matter of strong interest. These transformations can indeed be achieved with remarkable chemoselectivity,[9] and involve intermediates having a versatile reactivity.[10,11] However, to the best of our knowledge, the reduction of C═O bonds by zirconium hydrides has never been achieved with the main group metal hydride used as the stoichiometric reductant and a catalytic amount of zirconium complex.[12] In this context, we recently reported that a mixture of Cp_2ZrCl_2 and DIBAL-H in tetrahydrofuran (THF) induce the selective de-*O*-acetylation of the primary position of peracetylated compounds on a broad scope of polyfunctional substrates (Scheme 1a).[13] Schwartz's reagent Cp_2ZrHCl, which was initially believed to be formed in situ under our conditions,[14] was eventually discarded as the reductive species. Our preliminary mechanistic studies rather suggested that mixed zirconium/aluminum hydrides would be involved in this site-selective deprotection process.

The formation of clusters from mixtures of Cp_2ZrCl_2 and organoaluminum compounds in THF has previously been monitored by ^1H NMR spectroscopy,[15] but the structure of these aggregates remains elusive in this polar solvent.[16] On the other hand, several zirconium/aluminum mixed metal hydrides were fully characterized in apolar solvents, and extensive reactivity studies revealed their critical role in zirconium-catalyzed hydro- and carboaluminations of alkenes and

Scheme 1. Zirconium-Mediated Site-Selective Deprotection of Peracetylated Substrates

(a) Previous work: site-selective de-*O*-acetylation

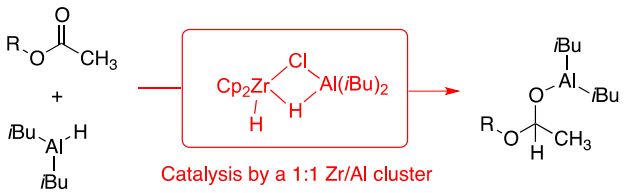


85 %, 2 mmol

Scope: Carbohydrates, Terpenes, Amino Acids

Large functional group tolerance

(b) This work: Zr-catalyzed hydroalumination of C=O bond



Catalysis by a 1:1 Zr/Al cluster

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alkynes.[17] Herein, we report that a Zr/Al cluster with a 1:1 stoichiometry is the reductive species giving rise to the site-selective deprotection of peracetylated compounds previously reported by our group. Furthermore, this mixed metal hydride has also been shown to promote the catalytic hydroalumination of carbon−oxygen double bonds (Scheme 1b). A putative catalytic cycle is finally proposed for this transformation with no precedent in the field of zirconium catalysis.

RESULTS AND DISCUSSION

Zirconium-Catalyzed Hydroalumination of C═O Bonds. The ability of mixed Zr/Al hydrides to catalyze hydroalumination of carbon−carbon multiple bonds[17] prompted us to investigate the possibility to achieve the reduction of C═O bonds by DIBAL-H in the presence of a catalytic amount of Cp_2ZrCl_2. De-*O*-acetylation of the model diester **1** with DIBAL-H and various amounts of zirconocene dichloride was first considered to establish a proof of concept. Addition of 3.0 equiv of aluminum hydride in one portion to a solution of compound **1** in THF at −20 °C selectively gave the de-*O*-acetylation product **2** after 1 h, albeit in only 38% conversion and 27% yield (Table 1, entry 1). Addition of a stoichiometric amount of Cp_2ZrCl_2 resulted in 91% conversion (entry 2), and full conversion could even be reached when aluminum hydride was added dropwise at a 1 mmol/h rate (entry 3). The rate of the C═O bond reduction by DIBAL-H is thus dramatically increased in the presence of Cp_2ZrCl_2.

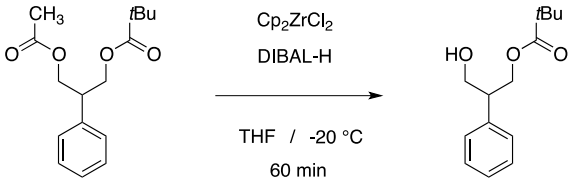
In this context, the use of a substoichiometric amount of zirconocene dichloride was next considered to develop reaction conditions catalytic in the zirconium complex. Addition of DIBAL-H (3 equiv) to a solution of diester **1** and Cp_2ZrCl_2 (0.3 equiv) resulted in a remarkable 75% conversion (entry 4). However, compound **2** was obtained in a modest 43% yield, presumably because of a competitive reduction of the pivalate when aluminum hydride is added in one portion. The dropwise addition of DIBAL-H (1 mL/h, entry 5) markedly improved the conversion of the substrate but increasing this rate of addition slightly diminished this conversion (entries 6 and 7). Finally, the use of 20 mol % of zirconocene dichloride and 3 equiv of DIBAL-H added at 1.8 mmol/h resulted in 68% conversion and gave the desired product **2** in 53% yield. The dropwise addition of DIBAL-H (3 equiv, 1 mL/h) alone (entry 9) only gave rise to 43% conversion of the substrate, and 32% of isolated alcohol **2**, thus confirming the catalytic effect of Cp_2ZrCl_2 for the reduction of the acetate C═O bond.

We next wondered if the site-selective deprotection of peracetylated substrates could also be achieved under these unprecedented catalytic reaction conditions. Our investigations started with peracetylated methyl-α-D-glucoside **3**, whose de-*O*-acetylation by DIBAL-H (3 equiv) and a stoichiometric amount of Cp_2ZrCl_2 (1 equiv) gave the primary alcohol **4** in 91% isolated yield (Table 2, entry 1).[13]

When aluminum hydride was added in one portion to a solution of the substrate (1 equiv) and a catalytic amount of Cp_2ZrCl_2 (20 mol %) at −20 °C, random acetate deprotection took place (entry 2). To our delight, the dropwise addition of the reducing agent (1.8 mmol/h) nicely restored a fully selective deprotection process (entry 3). After optimization, addition of DIBAL-H (5 equiv, 1.8 mmol/h) to a solution of Cp_2ZrCl_2 (30 mol %) and **3** in THF at −20 °C, followed by hydrolysis with 1 M aqueous citric acid and purification over a small plug of silica, gave the desired primary alcohol **4** in 85% isolated yield (entry 4).

Site-Selective Zirconium-Catalyzed De-*O*-acetylation of Polyfunctional Substrates by DIBAL-H. Substrates previously deprotected successfully by a stoichiometric amount of Cp_2ZrCl_2 and DIBAL-H were next subjected to these catalytic reaction conditions. For each substrate, optimization

Table 1. Cp_2ZrCl_2-Catalyzed Reduction of Primary Acetates by DIBAL-H

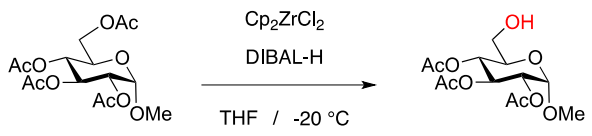


1 2

entry[a]	Cp_2ZrCl_2 (equiv)	DIBAL-H (equiv/mmol/h)	conversion[b] (%)
1	0.0	3.0/one portion	38[c]
2	1.0	3.0/one portion	91
3	1.0	3.0/1.0	100
4	0.3	3.0/one portion	75[d]
5	0.3	3.0/1.0	89
6	0.3	3.0/1.5	83
7	0.3	3.0/1.8	70
8	0.2	3.0/1.8	68[e]
9	0.0	3.0/1.8	41[f]

[a]Reaction performed on 0.25 mmol of **1**. [b]Determined on the crude product by ^{1}H NMR. [c]27% yield. [d]43% yield. [e]53% yield. [f]32% yield.

Table 2. Cp_2ZrCl_2-Catalyzed Site-Selective De-*O*-acetylation of Peracetylated Glucoside 3



3 4

entry	Cp_2ZrCl_2 (equiv)	DIBAL-H (equiv/mmol/h)	conversion[a] (%)	selectivity[a] (%)
1	1.0	3.0[b]	100	96[c]
2	0.2	3.0[b]	complex mixture	
3	0.2	3.0/1.8	84	96
4	0.3	5.0/1.8	100	99[d]

[a]Determined on the crude product by ^{1}H NMR. [b]Addition in one portion. [c]91% isolated yield. [d]85% isolated yield.

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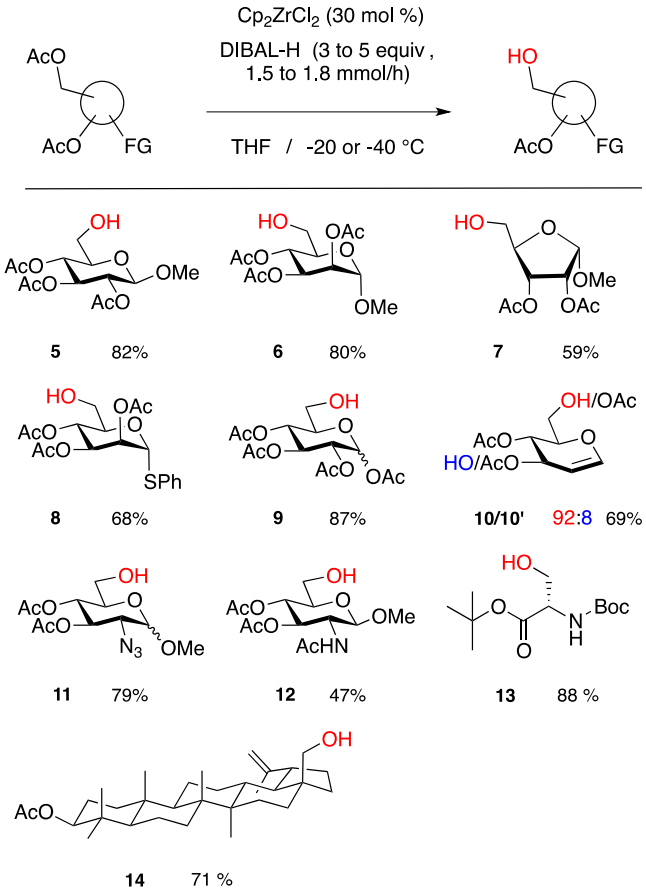
of the conversion and selectivity required some slight adjustments of the temperature and/or rate of addition of aluminum hydride. Overall, the formation of the desired products was achieved by the dropwise addition of DIBAL-H (3 to 5 equiv, 1.5 or 1.8 mmol/h) to a solution of the substrate (1 equiv) and zirconocene dichloride (30 mol %) in THF at −20 or −40 °C (Scheme 2).

Scheme 2. Zirconium-Catalyzed Site-Selective Deprotection of Peracetylated Substrates



First, site-selective de-*O*-acetylation of peracetylated methyl *β*-gluco- and *α*-mannopyranosides and of methyl *α*-ribofuranoside gave the primary alcohols **5**, **6**, and **7** in 59 to 82% yields. Deprotection of glycosyl donors, preactivated as a phenyl thioglycoside, an anomeric acetate, or a glycal, into compounds **8**, **9**, and **10** was then successfully achieved under catalytic reaction conditions. De-*O*-acetylation of the primary position of 2-deoxy 2-acetamido and 2-azido sugars also gave **11** and **12** with complete chemoselectivity. Finally, compounds **13** and **14** were obtained from acetylated *N*-Boc serine *tert*-butyl ester and peracetylated betulin without any side-reaction on the amino acid protecting groups and electron-rich *α*-olefin. Based on the low weight of the crude product obtained after the deprotection of ribofuranoside and 2-deoxy 2-acetamido sugar, the moderate yields in products **7** and **12** might be due to competitive de-*O*-acetylation of secondary positions that would have given rise to water-soluble side products.

Having shown that the regio- and chemoselective deprotection of peracetylated compounds by DIBAL-H could be achieved with a catalytic amount of Cp_2ZrCl_2 on a broad scope of polyfunctional substrates, we next investigated the mechanism of this unprecedented zirconium-catalyzed reduction of C═O bonds by aluminum hydride.

Identification of the Reductive Species and Proposition of a Catalytic Cycle for the Zirconium-Catalyzed Hydroalumination of C═O Bonds. Intrigued by the tolerance of acetamides toward reaction conditions used to promote this site-selective reduction of acetates, we previously showed that Schwartz's reagent was not the reductive species.[13] These preliminary mechanistic studies in THF also revealed that a mixed metal hydride should be involved. However, since Zr/Al clusters have not been identified in THF,[15,16] we wanted to transpose the de-*O*-acetylation reaction in toluene to identify the active species. Indeed, in this apolar solvent, extensive structural and reactivity studies have been performed to rationalize zirconium-catalyzed hydroalumination of alkenes by mixtures of Cp_2ZrCl_2 and aluminum hydrides.[17] They revealed that only mixed metal hydrides **15a**/**b** and **16a**/**b** (Figure 1), with 1:1 or 1:2

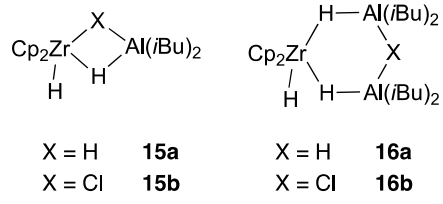


Figure 1. Possible Zr/Al clusters involved in the catalytic hydroalumination of C═O bonds.

zirconium/aluminum stoichiometries, respectively, and chlorine/hydride bridging ligands, must be considered as possible reductive species from the complex equilibrium depicted in Scheme S1.[17,18]

To identify the reductive and catalytic species involved in this unprecedented zirconium-catalyzed hydroalumination of C═O bonds, deprotection of peracetylated methyl-*α*-D-glucoside **3** in toluene was chosen as a model reaction. Our rationale was that the primary alcohol **4** would be selectively obtained in high yield when the proper mixed metal hydride would be present in the reaction mixture. Otherwise, low conversion and/or selectivity would be observed.

In our preliminary communication, deprotection of **3** took place in low conversion and poor selectivity when DIBAL-H (3 equiv) was added to a mixture of the substrate and Cp_2ZrCl_2 (3.5 equiv) in toluene at −20 °C (Table 3, entry 1).[13] In this apolar solvent, we suspected that strong aggregation of aluminum hydride might have prevented a fast reduction of zirconocene dichloride into the active species. The reaction of the substrate with dimeric and trimeric DIBAL-H would then lead to random deprotection.

In a new experimental protocol, Cp_2ZrCl_2 and DIBAL-H were premixed for 10 min at −20 °C to allow the reduction of the zirconium complex by aluminum hydride before addition of **3** to the reaction mixture. Under these slightly modified reaction conditions, we were pleased to obtain **4** with an 85:15 selectivity (entry 2). When THF was used as an additive (50, 10, or 1.5 equiv, entries 3 to 5, respectively), de-*O*-acetylation took place with almost complete regioselectivity. THF is thus not essential as the solvent and probably plays a key role in the dissociation of DIBAL-H aggregates. With a single equivalent of Cp_2ZrCl_2 and a Zr/Al ratio ranging from 1:2 to 1:4, selectivity could be increased to 95:5, but the conversion of **3** remained partial (entries 6−8). Finally, 1.5 equiv of

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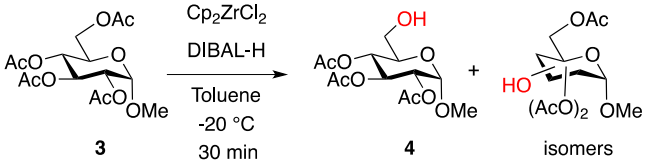
Table 3. Cp_2ZrCl_2-Mediated Site-Selective De-*O*-acetylation of 1 in Toluene



entry	Cp_2ZrCl_2 (equiv)	DIBAL-H (equiv)	conversion[c] (%)	selectivity[c] (%)
1[a]	3.5	3.0	17	54:46
2[b]	3.5	3.0	44	85:15
3[bd]	3.5	3.0	56	97:3
4[be]	3.5	3.0	83	98:2
5[bf]	3.5	3.0	45	96:4
6[b]	1	2.0	32	87:13
7[b]	1	3.0	47	83:17
8[b]	1	4.0	47	95:5
9[b]	1.5	6.0	94[g]	90:10

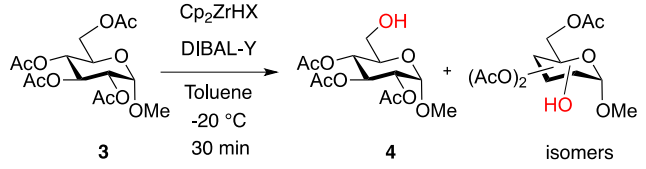
[a]Addition of DIBAL-H to a mixture of **3** and Cp_2ZrCl_2. [b]Addition of **3** after premixing of DIBAL-H and Cp_2ZrCl_2 for 10 min. [c]Determined on the crude product by ^{1}H NMR. [d]THF (50 equiv) as an additive. [e]THF (10 equiv) as an additive. [f]THF (1.5 equiv) as an additive. [g]73% isolated yield.

zirconocene dichloride and 6 equiv of DIBAL-H gave rise to almost full conversion, and the primary alcohol **4** could be obtained in 73% isolated yield after purification by silica gel flash chromatography (entry 9).

Having shown that site-selective de-*O*-acetylation of **3** could be achieved in toluene, we next investigated the nature of the bridging ligand to discriminate clusters **15a** and **16a** (X = H) from **15b** and **16b** (X = Cl). Based on previous works by Dzhemilev,[19] Cp_2ZrHCl or Cp_2ZrH_2 was mixed with either DIBAL or iBu$_2$AlCl to obtain 1:1 and 1:2 clusters with a chlorine bridging ligand on one side or with exclusively hydride bridging ligands on the other side. With Cp_2ZrHCl alone, the starting material was fully recovered (Table 4, entry 1), thus confirming that Schwartz's reagent was not the active species. Addition of DIBAL-H or iBu$_2$AlCl to Cp_2ZrHCl resulted in random deprotection of **3** (entries 2 and 3).

Cp_2ZrH_2, which is more soluble than Schwartz's reagent in toluene, was then considered as the zirconium source. Used alone (entry 4) or after premixing with DIBAL-H (entry 5), this zirconium complex gave poor conversion and regioselectivity. However, Cp_2ZrH_2 in mixture with iBu$_2$AlCl resulted in 66% conversion of **3**, together with the formation of **4** with a very good site-selectivity (entry 6). Clusters **15a** and **16a** with only hydride bridging ligands were thus ruled out from being involved in the deprotection of **3** by zirconium-catalyzed hydroalumination of the primary acetate.

Table 4. Identification of the Bridging Ligand in Zr/Al Clusters



entry[a]	X = (equiv)	Y = (equiv)	conversion[b] (%)	selectivity[b] (%)
1	Cl (3.5)		0	
2	Cl (3.5)	H (3)	96	56:44
3	Cl (3.5)	Cl (3)	35	49:51
4	H (3.5)		0	
5	H (1)	H (1)	29	69:31
6	H (1)	Cl (1)	66	88:12

[a]Addition of **3** after premixing of DIBAL-Y and Cp_2ZrHX for 10 min. [b]Determined on the crude product by ^{1}H NMR.

To determine if the active cluster was **15b** or **16b**, with a chlorine bridging ligand and a 1:1 or 1:2 zirconium/aluminum stoichiometry, density-functional theory (DFT) calculations were finally performed. The capacity of Zr/Al clusters to reduce a model ester was studied using the Gaussian 09 software package. Following a recent report,[20] geometry optimizations were carried out with the B3LYP functional, the LANL2DZ ECP basis set for Zr and Al, and the 6-31G(d) basis set for the other elements. Energies were refined by single-point calculations at the M06 level, using the def2-TZVP basis set for Zr and Al and the 6-31G(d,p) basis set for the other elements. Solvation correction for toluene was obtained with the PCM method. The values presented are ΔG_{298} (kcal/mol). Of the many combinations attempted to transfer a hydride from Zr or Al to the carbonyl functionality, only two could be modeled.[18] The first one consists of using the 1:1 Zr/Al cluster **15b** composed of Cp_2ZrHCl and iBu$_2$AlH (Scheme 3). After the cleavage of the Zr−H−Al bridge, the formation of **I** by complexation of the substrate appears to be slightly endergonic by 0.5 kcal/mol. This activation of carbonyl by the zirconium fragment is then followed by Al to C hydride transfer through a six-membered transition state ($\mathbf{TS_{I–II}}$) in which the Cl atom binds Zr and Al. This step requires only 3.5 kcal/mol of free energy of activation and is strongly exergonic by 43.0 kcal/mol. It yields ketal **II** with oxygen engaged in a four-membered ring with the Zr, Al, and Cl atoms. The low barrier of the hydride transfer validates the capability of a 1:1 cluster to promote the reduction.

Nevertheless, the 1:2 Zr/Al cluster **16b** was also studied (Scheme 4). In this case, the formation of **III** by complexation of the substrate to the open cluster is endergonic by 10.5 kcal/mol. Reaching the eight-membered reduction transition state $\mathbf{TS_{III–IV}}$ requires 7.5 kcal/mol. The transformation is also less exergonic (−22.1 kcal/mol). Thus, the 1:1 cluster is suggested to be the most efficient species.

Having identified the reductive species, we undertook additional DFT calculations to identify a chemical pathway, allowing the product release and regeneration of the Zr/Al cluster **15b** from intermediate **II**. Based on previous work on the formation of Zr/Al clusters from Cp_2ZrCl_2 and DIBAL-H,[17] we identified two possible chemical pathways giving back **15b** from **II** (Scheme 5). In the first one, the release of the product from **II**, in the form of acetal **V**, would give Schwartz's reagent **17**. In a second step, cluster **15b** would be regenerated by the complexation of DIBAL-H (eq 1). The second possible pathway would first involve complexation of DIBAL-H to the bridging chlorine atom of **II** to give **IV**. This intermediate would then spontaneously isomerize into **VI**, before the release of **V** and regeneration of **15b** (eq 2). Calculation of the free energies revealed that the association of DIBAL-H with **17** (ΔG_{298} = −45.7 kcal/mol) or **II** (ΔG_{298} = −26.9 kcal/mol) is highly exergonic, whereas decomplexation of acetal **V** from **II** (ΔG_{298} = +39.0 kcal/mol) or **VI** (ΔG_{298} = +30.7 kcal/mol) is strongly endergonic. Because of the large energy cost of both dissociative steps (from **II** to **17** in eq 1 and from **VI** to **15b** in

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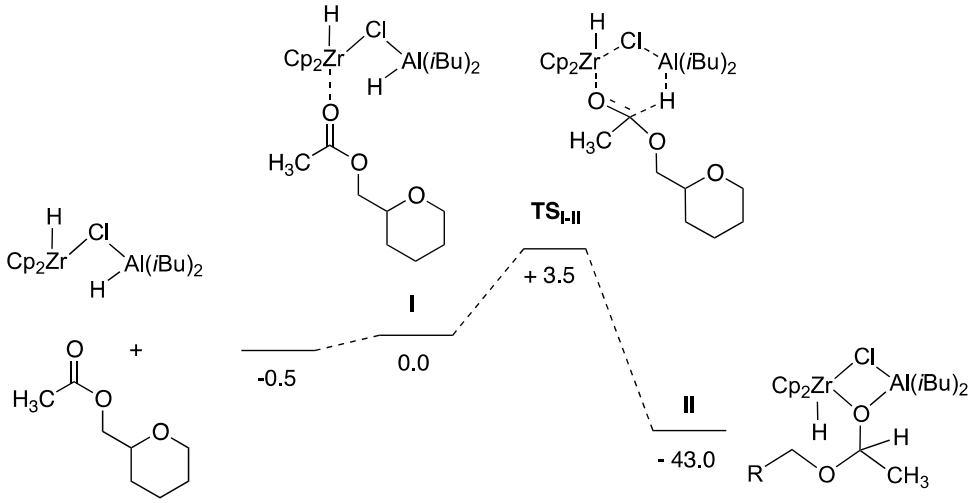
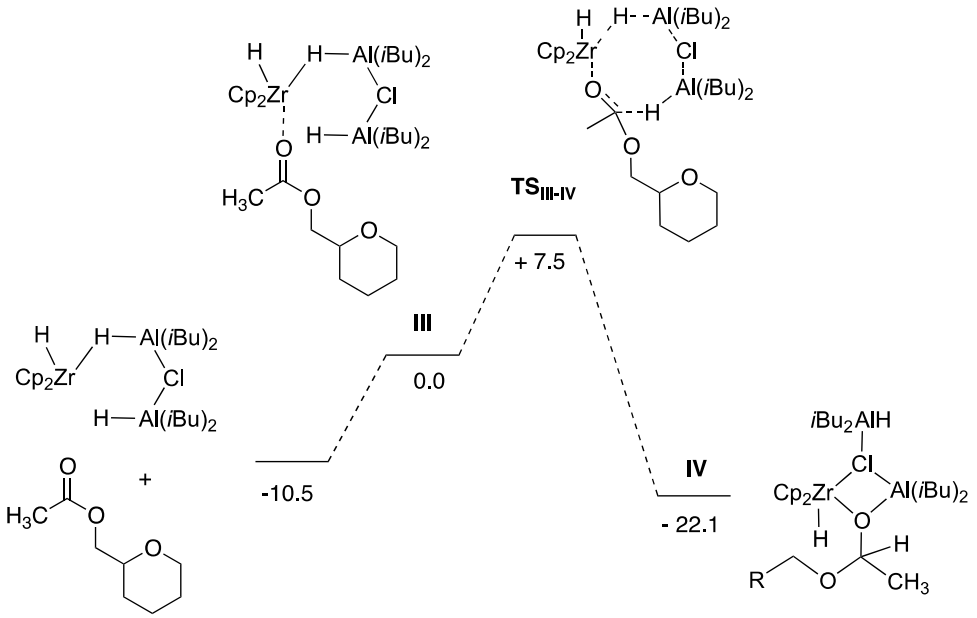
Scheme 3. Computed Hydride Transfer with a 1:1 Zr/Al Cluster (kcal/mol)



Scheme 4. Computed Hydride Transfer with a 1:2 Zr/Al Cluster (kcal/mol)



eq 2), these two pathways were ruled out. On the other hand, a release of **V** from **VI**, concomitant with the complexation of the substrate (eq 3), was found to be a slightly endergonic process (ΔG_{298} = +6.0 kcal/mol). This third chemical pathway giving **I** from **VI** was thus chosen to close the catalytic cycle depicted in Scheme 6.

From the complex equilibrium between the Zr/Al clusters depicted in Scheme S1, the mixed metal hydride **15b** has been identified as the reductive species. Dissociation of the Zr−H−Al bridge would first give the Lewis acidic cluster **VII.** Complexation of the carbonyl oxygen atom of the substrate would then give the bipyramidal intermediate **I**. A 1,6-hydride transfer from aluminum to the carbonyl carbon atom would deliver the μ-oxo-μ-chloro Zr/Al cluster **II**. After the formation of **IV** by complexation of DIBAL-H to chlorine and isomerization into **VI**, acetal **V** would be released, concomitantly with the association of the substrate, to regenerate **I**. The formation of the product would occur during the work-up by acidic hydrolysis of **V**.

CONCLUSIONS

We report herein that a catalytic amount of Cp_2ZrCl_2 promotes a fast hydroalumination of C=O bonds in THF. Following this finding, the site-selective de-*O*-acetylation of functional peracetylated substrates, previously reported with a stoichiometric amount of zirconium complex, was developed under these new catalytic reaction conditions. A mixed metal hydride with a 1:1 Zr/Al stoichiometry was also identified as the reductive species based on mechanistic studies performed in toluene and on DFT calculations. Finally, a putative catalytic cycle was proposed for this unprecedented zirconium-catalyzed hydroalumination of C=O bonds.

EXPERIMENTAL SECTION

General Information and Method. All reactions were conducted under an argon atmosphere in distilled THF (sodium/benzophenone). All reagents were used as received unless otherwise indicated. Reactions were monitored by thin-layer chromatography with a silica gel 60 F254 precoated aluminum plate (0.25 mm). Visualization was performed under UV light and phosphomolybdic

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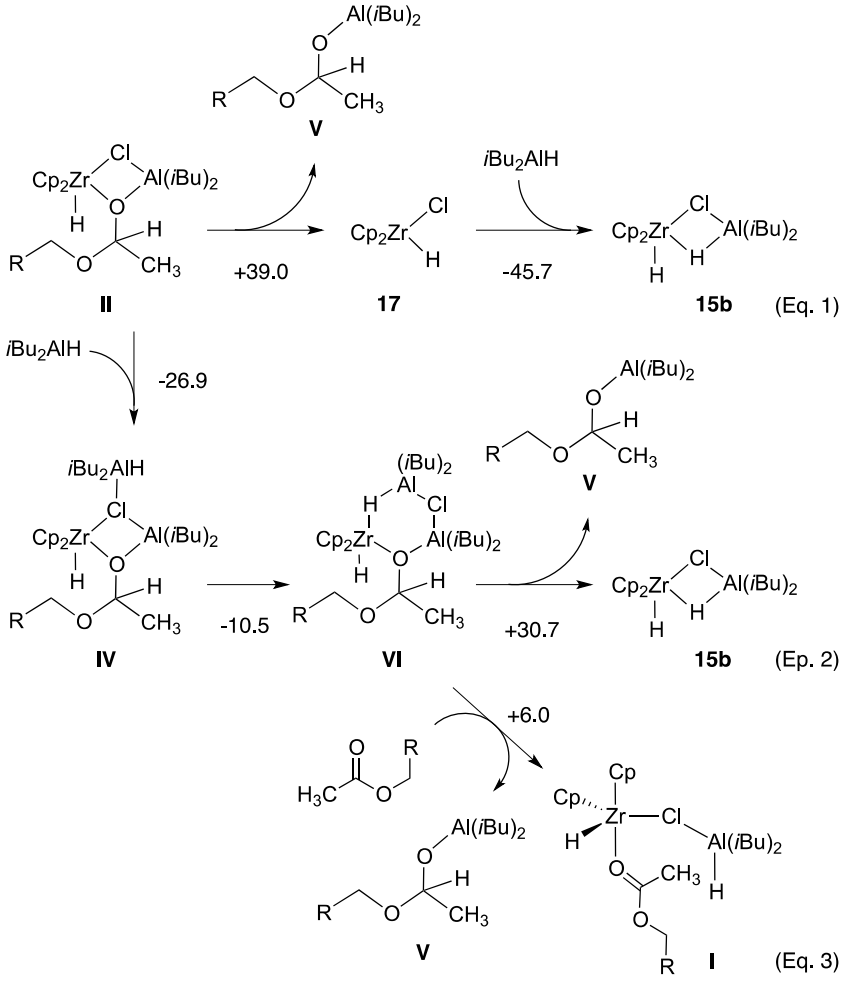
Scheme 5. Computed Free Energies (kcal/mol) of Possible Intermediates for the Closure of the Catalytic Cycle



acid oxidation. ^{1}H, NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra at 75 MHz. Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet, and m: multiplet. Coupling constants J are in Hz and chemical shifts are given in ppm and calibrated with $CDCl_3$ (residual solvent signals). Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. The ^{1}H and ^{13}C signals were assigned by COSY and HSQC experiments. Optical rotations were determined with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2/g and concentrations in g per 100 mL. Melting points are uncorrected. Compounds **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, and **14** have been fully characterized in a preliminary communication.[13]

Zirconium-Catalyzed Site-Selective De-*O*-acetylation in THF. *Compound* ***2***. To a solution of **1** (70 mg, 0.25 mmol) and Cp_2ZrCl_2 (15 mg, 0.05 mmol) in dry THF (2 mL), DIBAL-H (1 M in THF, 0.75 mL, 0.75 mmol, 1.8 mmol/h) was added dropwise via a syringe pump at −20 °C. After the end of the addition, the reaction mixture was diluted with dichloromethane (DCM) (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 4:1) to give **2** (31 mg, 53%) as a colorless liquid. R_f: 0.24 (silica, cyclohexane/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.38−7.22 (m, 5H$_{arom}$), 4.40 (dd, J = 11.2, 6.4 Hz, 1H, H$_2$), 4.33 (dd, J = 11.2, 6.4 Hz, 1H, H$_{2'}$), 3.83 (d, J = 6.4 Hz, 2H, H$_3$), 3.18 (quint, J = 6.4 Hz, 1H, H$_1$), 1.94 (s, 1H, OH), 1.16 (s, 9H, C(CH$_3$)$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 179.0 (C═O), 139.1 (C$_{quat\ arom}$), 128.9 (2 × CH$_{arom}$), 128.3 (2 × CH$_{arom}$), 127.5 (CH$_{arom}$), 65.0 (C$_2$), 63.9 (C$_3$), 47.6 (C$_1$), 40.0 (C(CH$_3$)$_3$), 27.3 (C(CH$_3$)$_3$); FT-IR (film): 2968, 1726, 1480, 1284, 1153, 1032, 758, 699 cm^{-1} HRMS (ESI$^+$): m/z calculated for $C_{14}H_{21}O_3$ [M + H]$^+$: 237.1491.1451; found: 237.1501.

Compound ***4***. To a solution of the corresponding peracetylated substrate (185 mg, 0.51 mmol) and Cp_2ZrCl_2 (45 mg, 0.153 mmol) in dry THF (2.5 mL), DIBAL-H (1 M in THF, 2.5 mL, 2.5 mmol, 1.8 mmol/h) was added dropwise via a syringe pump at −20 °C. After the end of the addition, the reaction mixture was diluted with DCM (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 1:2) to give **4** (139 mg, 85%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.50 (t, J = 9.8 Hz, 1H, H$_3$), 4.98 (t, J = 9.8 Hz, 1H, H$_4$), 4.93 (d, J = 3.6 Hz, 1H, H$_1$), 4.83 (dd, J = 3.6, 9.8 Hz, 1H, H$_2$), 3.56 (m, 1H, H$_6$), 3.75 (ddd, J = 2.2, 3.6, 9.8 Hz, 1H, H$_5$), 3.68 (ddd, J = 2.2, 6.4, 12.6 Hz, 1H, H$_{6'}$), 3.38 (s, 3H, OCH$_3$), 2.31 (t, J = 6.4 Hz, 1H, OH), 2.04 (s, 3H, C(O)CH$_3$), 2.02 (s, 3H, C(O)CH$_3$), 1.98 (s, 3H, C(O)CH$_3$); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.6 (C(O)CH$_3$), 170.2 (C(O)CH$_3$), 170.0 (C(O)CH$_3$), 96.8 (C$_1$), 71.0 (C$_2$), 69.8 (C$_3$), 69.3 (C$_5$), 68.9 (C$_4$), 61.0 (C$_6$), 55.4 (OCH$_3$), 20.74 (C(O)CH$_3$), 20.72 (C(O)CH$_3$), 20.68 (C(O)CH$_3$); $[\alpha]_D$20 = +100 ($CHCl_3$, c = 0.1); mp +104−106 °C.

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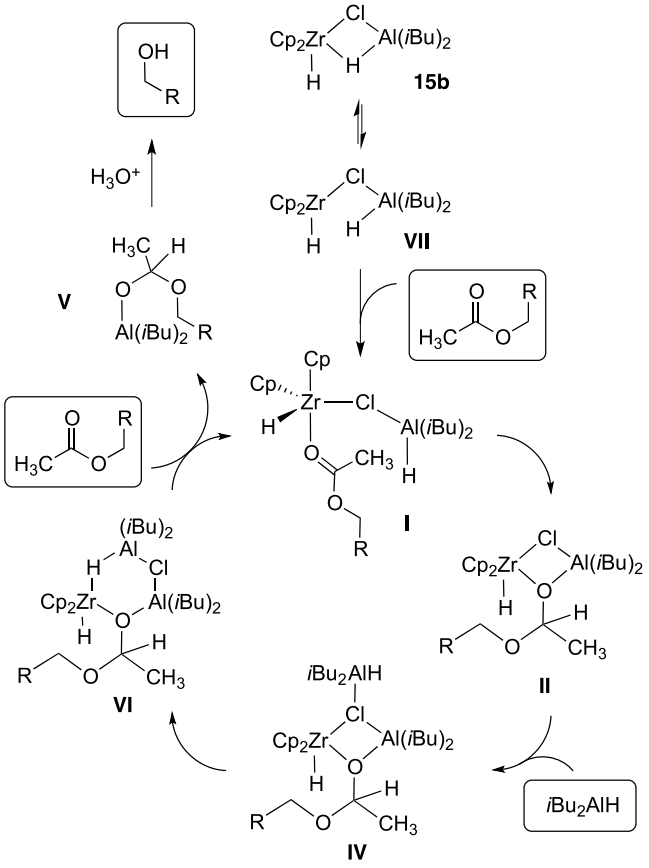
Scheme 6. Putative Catalytic Cycle for the Zirconium-Catalyzed Hydroalumination of C═O Bonds



Compound ***5***. To a solution of the corresponding peracetylated substrate (1.464 g, 4.044 mmol) and Cp_2ZrCl_2 (355 mg, 1.213 mmol) in dry THF (20 mL), DIBAL-H (1 M in THF, 16 mL, 16 mmol, 12 mL/h) was added dropwise via a syringe pump at −20 °C. After the end of the addition, the reaction mixture was diluted with DCM (50 mL), quenched with 1 M citric acid solution (30 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 30 mL). The organic phases were combined, washed with 1 M aq HCl solution (30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 1:2) to give **5** (1.062 g, 82%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.23 (t, J = 9.6 Hz, 1H, H_3), 5.01 (t, J = 9.6 Hz, 1H, H_4), 4.94 (dd, J = 8.1, 9.6 Hz, 1H, H_2), 4.43 (d, J = 8.1 Hz, 1H, H_1), 3.74 (ddd, J = 2.2, 8.4, 12.5 Hz, 1H, H_6), 3.59 (td, J = 5.2, 12.5 Hz, 1H, H_6), 3.47−3.51 (m, 1H, H_5), 3.49 (s, 3H, OCH_3), 2.21 (dd, J = 5.2, 8.4 Hz, 1H, OH), 2.03 (s, 6H, 2 × C(O)CH_3), 1.99 (s, 3H, C(O)CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.3 (C(O)CH_3), 170.2 (C(O)CH_3), 169.5 (C(O)CH_3), 101.6 (C_1), 74.0 (C_5), 72.7 (C_3), 71.4 (C_2), 68.7 (C_4), 61.3 (C_6), 57.1 (OCH_3), 20.73 (C(O)CH_3), 20.68 (C(O)CH_3), 20.66 (C(O)CH_3); $[\alpha]_D^{20}$ = −48 ($CHCl_3$, c = 0.1); mp +136−137 °C.

Compound ***6***. To a solution of the corresponding peracetylated substrate (179 mg, 0.495 mmol) and Cp_2ZrCl_2 (58 mg, 0.198 mmol) in dry THF (2.5 mL), DIBAL-H (1 M in THF, 2.5 mL, 2.5 mmol, 1.5 mL/h) was added dropwise via a syringe pump at −20 °C. After the end of the addition, the reaction mixture was diluted with DCM (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 1:2) to give **6** (130 mg, 80%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.37 (dd, J = 3.5, 10.0 Hz, 1H, H_3), 5.23 (dd, J = 1.6, 3.5 Hz, 1H, H_2), 5.22 (t, J = 10.0 Hz, 1H, H_4), 4.70 (d, J = 1.6 Hz, 1H, H_1), 3.74 (ddd, J = 2.3, 4.4, 10.0 Hz, 1H, H_5), 3.70 (ddd, J = 2.3, 8.5, 12.4 Hz, 1H, H_6), 3.61 (ddd, J = 4.4, 5.5, 12.4 Hz, 1H, H_6), 3.38 (s, 3H, OCH_3), 2.36 (dd, J = 5.5, 8.5 Hz, 1H, OH), 2.13 (s, 3H, C(O)CH_3), 2.06 (s, 3H, C(O)CH_3), 1.98 (s, 3H, C(O)CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.9 (C(O)CH_3), 170.1 (C(O)CH_3), 169.9 (C(O)CH_3), 98.7 (C_1), 70.5 (C_5), 69.6 (C_2), 68.8 (C_3), 66.5 (C_4), 61.3 (C_6), 55.3 (OCH_3), 20.9 (C(O)CH_3), 20.8 (C(O)CH_3), 20.7 (C(O)CH_3); $[\alpha]_D^{20}$ = +44 ($CHCl_3$, c = 0.13); mp +67−69 °C.

Compound ***7***. To a solution of the corresponding peracetylated substrate (165 mg, 0.569 mmol) and Cp_2ZrCl_2 (67 mg, 0.228 mmol) in dry THF (3 mL), DIBAL-H (1 M in THF, 2.9 mL, 2.9 mmol, 1.5 mL/h) was added dropwise via a syringe pump at −20 °C. After the end of the addition, the reaction mixture was diluted with DCM (6 mL), quenched with 1 M citric acid solution (5 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 6 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 1:2) to give **7** (84 mg, 59%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.35 (t, J = 5.7 Hz, 1H, H_3), 5.22 (d, J = 5.7 Hz, 1H, H_2), 4.90 (br s, 1H, H_1), 4.21 (td, J = 4.1, 5.7 Hz, 1H, H_4), 3.79 (td, J = 4.1, 11.3 Hz, 1H, H_5), 3.64 (ddd, J = 4.1, 8.2, 11.3 Hz, 1H, H_5), 3.41 (s, 3H, OCH_3), 2.21 (dd, J = 4.1, 8.2 Hz, 1H, OH), 2.10 (s, 3H, C(O)CH_3), 2.04 (s, 3H, C(O)CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.1 (C(O)CH_3), 169.7 (C(O)CH_3), 106.5 (C_1), 82.4 (C_3), 75.2 (C_2), 71.2 (C_4), 62.9 (C_5), 55.8 (OCH_3), 20.6 (2 × C(O)CH_3); $[\alpha]_D^{20}$ = −2 ($CHCl_3$, c = 1.4).

Compound ***8***. To a solution of the corresponding peracetylated substrate (231 mg, 0.525 mmol) and Cp_2ZrCl_2 (61 mg, 0.21 mmol) in dry THF (1 mL) and dry DCM (2 mL), DIBAL-H (1 M in THF, 1.7 mL, 1.7 mmol, 1.5 mL/h) was added dropwise via a syringe pump at −40 °C. After the end of the addition, the reaction mixture was diluted with DCM (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 2:1) to give **8** (142 mg, 68%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.45 (m, 2H, H_{Ar}), 7.28 (m, 3H, H_{Ar}), 5.49 (m, 2H, H_1, H_2), 5.35 (dd, J = 3.0, 10.1 Hz, 1H, H_3), 5.29 (t, J = 10.1 Hz, 1H, H_4), 4.26 (td, J = 3.2, 10.1 Hz, 1H, H_5), 3.64 (m, 2H, H_6, H_6), 2.26 (t, J = 6.4 Hz, 1H, OH), 2.12 (s, 3H, C(O)CH_3), 2.08 (s, 3H, C(O)CH_3), 2.00 (s, 3H, C(O)CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.8 (C(O)CH_3), 170.0 (C(O)CH_3), 169.8 (C(O)CH_3), 132.7 ($C_{Quat\ Arom.}$), 132.1 (2 × $CH_{Arom.}$), 129.3 (2 × $CH_{Arom.}$), 128.1 ($CH_{Arom.}$), 85.8 (C_1), 71.8 (C_5), 71.0 (C_2), 69.2 (C_3), 66.5 (C_4), 61.2 (C_6), 20.9 (C(O)CH_3), 20.8 (C(O)CH_3), 20.7 (C(O)CH_3); $[\alpha]_D^{20}$ = +74 ($CHCl_3$, c = 0.5).

Compound ***9***. To a solution of the corresponding peracetylated substrate (198 mg, 0.508 mmol) and Cp_2ZrCl_2 (59 mg, 0.203 mmol) in dry THF (2.5 mL), DIBAL-H (1 M in THF, 2.0 mL, 2.0 mmol, 1.5 mL/h) was added dropwise via a syringe pump at −40 °C. After the end of the addition, the reaction mixture was diluted with DCM (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 1:2) to give **9** (153 mg, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 6.20 (d, J = 3.8 Hz, 0.95H, H_{1A}), 5.61 (d, J = 7.6 Hz, 0.05H, H_{1B}), 5.35 (t, J = 10.4 Hz, 0.95H, H_{3A}), 5.15 (d, J = 9.3 Hz, 0.05H, H_{3B}), 5.02 (t, J = 10.4 Hz, 0.95H, H_{4A}), 5.01 (m, 0.10H, H_{2B}, H_{4B}), 4.97 (dd, J = 3.8, 10.4 Hz, 0.95H, H_{2A}), 4.19 (m, 1H, 0.05H, H_{6B}),

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4.16 (dd, J = 4.1, 12.8 Hz, 0.95H, H_{6A}), 4.01 (ddd, J = 2.3, 4.1, 10.4 Hz, 0.95H, H_{5A}), 3.98 (m, 0.05H, H_{6B}), 3.97 (dd, J = 2.3, 12.8 Hz, 0.95H, H_{6A}), 3.75 (ddd, J = 2.1, 4.4, 10.1 Hz, 0.05H, H_{5B}), 2.06−1.91 (m, 13H, C(O)CH_3, OH); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.5 (C(O)CH_{3B}), 170.1 (C(O)CH_{3A}), 169.9 (C(O)CH_{3A}), 169.5 (C(O)CH_{3A}), 169.3 (C(O)CH_{3B}), 169.1 (C(O)CH_{3A}), 168.8 (C(O)CH_{3B}), 168.6 (C(O)CH_{3B}), 91.6 (C_{1B}), 88.9 (C_{1A}), 72.63 (C_{3B}), 72.56 (C_{5B}), 70.1 (C_{2B}), 69.7 (C_{3A}, C_{5A}), 69.1 (C_{2A}, C_{6B}), 67.8 (C_{4A}), 67.6 (C_{4B}), 61.4 (C_{6B}), 20.8−20.3 (C(O)CH_3).

Compounds ***10/10′***. To a solution of the corresponding peracetylated substrate (143 mg, 0.526 mmol) and Cp_2ZrCl_2 (46 mg, 0.158 mmol) in dry THF (2.5 mL), DIBAL-H (1 M in THF, 2.1 mL, 2.1 mmol, 1.5 mL/h) was added dropwise via a syringe pump at −40 °C. After the end of the addition, the reaction mixture was diluted with DCM (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 1:1) to give **10/10′** (83 mg, 69%) as an inseparable mixture. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 6.45 (dd, J = 1.3, 6.0 Hz, 0.92H, H_{1A}), 6.37 (dd, J = 0.9, 6.1 Hz, 0.08H, H_{1B}), 5.41 (ddd, J = 1.3, 2.4, 6.2 Hz, 0.92H, H_{3A}), 5.18 (dd, J = 6.2, 8.9 Hz, 0.92H, H_{4A}), 4.95 (dd, J = 5.8, 8.8 Hz, 0.08H, H_{4B}), 4.83 (dd, J = 2.8, 6.1 Hz, 0.08H, H_{2B}), 4.77 (dd, J = 2.4, 6.0 Hz, 0.92H, H_{2A}), 4.38 (dd, J = 5.4, 12.2 Hz, 0.08H, H_{6B}), 4.28 (ddd, J = 0.9, 2.8, 5.8 Hz, 0.08H, H_{3B}), 4.21 (dd, J = 2.5, 12.2 Hz, 0.08H, H_{6B}), 4.10 (ddd, J = 2.5, 5.4, 8.8 Hz, 0.08H, H_{5B}), 3.99 (ddd, J = 3.0, 4.6, 8.9 Hz, 0.92H, H_{5A}), 3.76 (dd, J = 3.0, 12.8 Hz, 0.92H, H_{6A}), 3.69 (dd, J = 4.6, 12.8 Hz, 0.92H, H_{6A}), 2.59 (br s, 0.08H, OH_B), 2.38 (br s, 0.92H, OH_A), 2.11 (s, 0.24H, C(O)CH_{3B}), 2.09 (s, 2.76H, C(O)CH_{3A}), 2.07 (s, 0.24H, C(O)CH_{3B}), 2.03 (s, 2.76H, C(O)CH_{3A}); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ (ppm) 171.0 (2 × C(O)CH_{3B}), 170.6 (2 × C(O)CH_{3A}), 145.8 (C_{1A}), 144.0 (C_{1B}), 102.9 (C_{2B}), 99.1 (C_{2A}), 76.6 (C_{5A}), 74.0 (C_{5B}), 71.6 (C_{4B}), 68.4 (C_{3A}), 67.8 (C_{4A}), 67.1 (C_{3B}), 61.9 (C_{6B}), 60.6 (C_{6B}), 21.1 (C(O)CH_{3A}), 21.0 (C(O)CH_{3A}), 20.9 (C(O)CH_{3A}), 20.8 (C(O)CH_{3B}).

Compound ***11***. To a solution of the corresponding peracetylated substrate (176 mg, 0.510 mmol) and Cp_2ZrCl_2 (45 mg, 0.153 mmol) in dry THF (2.5 mL), DIBAL-H (1 M in THF, 1.75 mL, 1.75 mmol, 1.5 mL/h) was added dropwise via a syringe pump at −20 °C. After the end of the addition, the reaction mixture was diluted with DCM (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 1:1) to give **11** (122 mg, 79%). ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.46 (dd, J = 9.4, 8.9 Hz, 0.66H, H_{3A}), 4.85−4.78 (m, 1H, H_{3B}, H_{1A}), 4.49−4.43 (m, 1H, H_{1B}, H_{4A}), 4.38−4.25 (m, 1.30H, H_{6A}, H_{5B}, H_{4B}), 3.83 (ddd, J = 9.6, 4.7, 2.0 Hz, 0.66H, H_{5A}), 3.58 (s, 1H, OMe_B), 3.56−3.45 (m, 1H,, H_{2A}, H_{6B}), 3.44 (s, 2H, OMe_A), 3.43−3.28 (m, 1.3H, H_{6B}, H_{2B}, H_{6A}), 3.09 (d, J =3.4 Hz, 0.66H, OH_A), 3.00 (d, J =5.3 Hz, 0.34H, OH_B), 2.08−1.93 (m, 6H, C(O)CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.7 (C(O)CH_3), 170.4 (C(O)CH_3), 170.3 (C(O)CH_3), 170.0 (C(O)CH_3), 102.8 (C_1), 98.8 (C_1), 73.9 (C_2), 72.3 (C_5), 70.1 (C_2), 69.5 (C_5), 68.9 (C_4), 68.6 (C_4), 63.8 (C_3), 61.1 (C_3), 61.0 (C_6), 60.8 (C_6), 57.4 (OCH_3), 55.5 (OCH_3), 20.7 + 20.6 + 20.6 (4 × C(O)CH_3).

Compound ***12***. To a solution of the corresponding peracetylated substrate (187 mg, 0.518 mmol) and Cp_2ZrCl_2 (45 mg, 0.155 mmol) in dry THF (2.5 mL), DIBAL-H (1 M in THF, 1.55 mL, 1.55 mmol, 1.5 mL/h) was added dropwise via a syringe pump at −20 °C. After the end of the addition, the reaction mixture was diluted with DCM (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (EtOAc/MeOH, 95:5) to give **12** (78 mg, 47%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.77 (d, J = 8.9 Hz, 1H, H_1), 5.30 (dd, J = 10.6, 9.5 Hz, 1H, H_3), 5.03 (t, J = 9.5 Hz, 1H, H_4), 4.59 (d, J = 9.5 Hz, 1H, H_2), 3.90 (m, 1H, H_5), 3.75 (dd, J = 12.5, 3.5 Hz, 1H, H_6), 3.65−3.47 (m, 6H, OCH_3, H_6, NH, OH), 2.05 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 1.95 (s, 3H, $CH_3C(O)NH$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ (ppm) 171.1 (NHC(O)CH_3), 170.5 (C(O)CH_3), 170.2 (C(O)CH_3), 101.7 (C_1), 74.0 (C_2), 72.3, (C_5) 68.9 (C_4), 61.3 (C_3), 56.8 (C_6), 54.5 (OCH_3), 23.3 (C(O)CH_3), 20.8 (C(O)CH_3), 20.7 (C(O)CH_3).

Compound ***13***. To a solution of the corresponding peracetylated substrate (164 mg, 0.541 mmol) and Cp_2ZrCl_2 (48 mg, 0.162 mmol) in dry THF (2.5 mL), DIBAL-H (1 M in THF, 1.6 mL, 1.6 mmol, 1.5 mL/h) was added dropwise via a syringe pump at −20 °C. After the end of the addition, the reaction mixture was diluted with DCM (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (petroleum ether/EtOAc 4:1) to give **13** (124 mg, 88%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.47 (bs, 1H), 4.24 (bs, 1H), 3.89 (dd, J = 4.0 Hz, J = 6.1 Hz, 2H), 2.73 (d, J = 4.8 Hz, 1H), 1.48 (s, 9H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ (ppm) 169.8, 155.8, 82.5, 80.1, 63.9, 56.3, 28.3, 27.9; $[\alpha]_D^{20}$ = −23 ($CHCl_3$, c = 0.5).

Compound ***14***. To a solution of the corresponding peracetylated substrate (198 mg, 0.376 mmol) and Cp_2ZrCl_2 (33 mg, 0.112 mmol) in dry THF (2 mL), DIBAL-H (1 M in THF, 1.1 mL, 1.1 mmol, 1.5 mL/h) was added dropwise via a syringe pump at −20 °C. After the end of the addition, the reaction mixture was diluted with DCM (5 mL), quenched with 1 M citric acid solution (4 mL), and stirred for few seconds until a clear biphasic mixture is obtained. The aqueous phase was extracted with DCM (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (petroleum ether/EtOAc 95:5) to give **14** (130 mg, 71%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 4.60 (s, 1H), 4.51 (s, 1H), 4.40 (dd, J = 9.6, 6.6 Hz, 1H), 3.72 (d, J = 10.9 Hz, 1H), 3.25 (d, J = 10.9 Hz, 1H), 2.39.2.25 (m, 1H), 1.97 (s, 3H), 1.93−1.72 (m, 3H), 1.65−0.86 (m, 32H), 0.80−0.73 (m, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ (ppm) 171.2, 150.6, 109.9, 81.1, 60.7, 55.5, 50.5, 48.9, 47.95, 47.93, 42.9, 41.1, 38.5, 37.9, 37.4, 37.2, 34.3, 34.1, 29.9, 29.3, 28.1, 27.2, 25.3, 23.8, 21.5, 21.0, 19.2, 18.3, 16.6, 16.3, 16.1, 14.9.

Site-Selective De-*O*-acetylation of 3 in Toluene. A mixture of Cp_2ZrCl_2 (163 mg, 0.56 mmol) and of a 1.5 M solution of DIBAL-H in toluene (1.5 mL, 2.24 mmol) in dry toluene (2 mL) was stirred at −20 °C for 10 min. After addition of a solution of **3** (185 mg, 0.51 mmol) in dry toluene (1 mL), the reaction mixture was stirred for 30 min at this temperature. CH_2Cl_2 (5 mL) and a 1 M citric acid solution (4 mL) were then added. After vigorous stirring for a few minutes, a clear biphasic mixture was obtained. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined, washed with 1 M aq HCl solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by chromatography over silica gel (cyclohexane/EtOAc 1:2) to give **4** (87 mg, 73%) as a white solid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00060.

Detailed DFT calculations and ^1H and $^{13}C\{^1H\}$ NMR spectra of compounds **2** and **4**−**14** (PDF)

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Notes

The authors declare no competing financial interest.

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