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Positional chemoselectivity in the Zn(II)-mediated removal of phenol protecting groups

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ABSTRACT

A protocol was developed for the chemoselective *ortho*-deprotection of polyphenolic substrates using readily available $Zn^{II}X_2$ salts. This procedure provides exceptional positional selectivity for the deprotection of phenols that reside adjacent to directing carbonyl functionality in the presence of similar protecting groups at the *meta* and *para* positions. Good to excellent yields of the desired free phenols were obtained (⩽96%), and a wide assortment of protecting groups was readily removed under the reaction conditions.

The chemoselective removal of protecting groups in the synthesis of complex molecular targets continues to be a major challenge in organic chemistry.[1] As the complexity of a synthetic target increases, invariably the need for a protecting group strategy that enables the selective installation and mild removal of widely used protecting groups becomes crucial. A major challenge encountered in total synthesis is the selective removal of protecting groups that reside in similar stereoelectronic environments. In the context of our current synthetic efforts toward members of the calyxin family of natural products, a class of antitumor diarylheptanoid plant metabolites,[2] we encountered complications in the selective installation and removal of aryl ether protecting groups. The multitude of phenolic groups in the calyxins, as illustrated by blepharocalyxins A and B (Fig. 1),[2c] prompted us to explore a universal protection–deprotection strategy of this pervasive functional group.

Recently, Yadav et al. demonstrated the *ortho*-selective deprotection of methyl and allyl ethers using $CeCl_3$,[3] and Keith showed that I_2/MeOH would selectively remove MOM and PMB ethers.[4] Additionally, ultrasound sonication has proven effective at the selective desilylation of phenols,[5] whereas benzyl ethers are readily cleaved in the presence of a Brønsted acid (e.g., TFA).[6] During our work on phosphine-mediated, titanocene-catalyzed multicomponent couplings with aryl aldehydes, we required a general method that would enable the selective *ortho* deprotection of benzaldehyde derivatives **1** containing similar protecting groups at various positions around the benzene ring.[7] We speculated that a mild Lewis acid, such as a ZnX_2 salt, would participate in a directed *ortho*-deprotection through carbonyl oxygen chelation to provide phenols **2** (Scheme 1). Herein, we disclose the successful

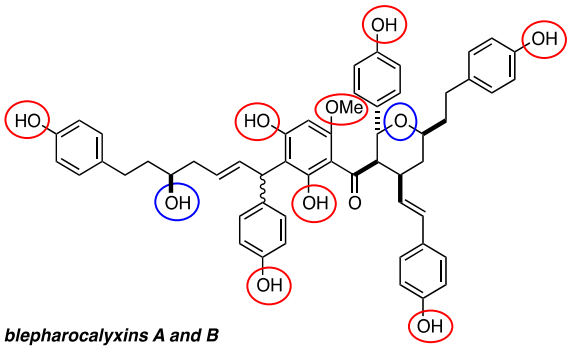
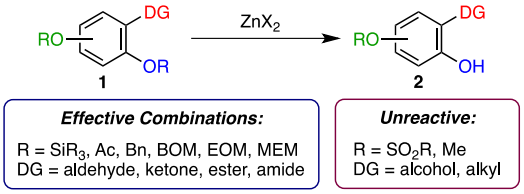


Figure 1. The blepharocalyxins.



Scheme 1. Selective *ortho*-deprotection.

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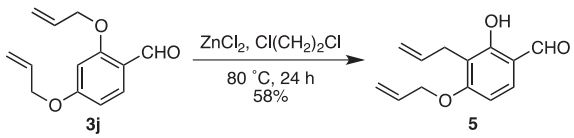
implementation of this approach as a general orthogonal deprotection strategy for a wide spectrum of phenolic protecting groups.

In an effort to establish the optimized conditions necessary for the *ortho* deprotection of benzaldehyde derivatives, we began by ascertaining the optimal Zn(II) salt in the deprotection of bis-TBS ether **1a** (Table 1). Although, ZnI_2 proved ineffective, the addition of $ZnBr_2$ or $ZnCl_2$ in CH_2Cl_2 at room temperature for 6 h provided *ortho*-desilylated phenol **2a** in 78% and 77% yields, respectively (entries 1–3). Continuing our optimization studies with $ZnCl_2$, we found that ethereal solvents failed to yield phenol **2a** in greater than trace quantities (entries 4–6). In contrast to CH_2Cl_2, $CHCl_3$ proved ineffective, whereas $Cl(CH_2)_2Cl$ showed comparable reactivity, providing phenol **2a** in 83% yield (entries 7 and 8). Increasing the reaction temperature to 80 °C in $Cl(CH_2)_2Cl$ led to a further improvement in the yield of **2a** (entry 9). Attempts to reduce the amount of $ZnCl_2$ from 2 equiv to 1.5 and 1.05 equiv led to a modest reduction in the yield of **2a** (entries 10 and 11). Performing the reaction at 80 °C with 1.05 equiv of $ZnCl_2$ failed to improve upon this result (entry 12). Employing $ZnBr_2$ and ZnI_2 in $Cl(CH_2)_2Cl$ gave similar results obtained with CH_2Cl_2 as the solvent (entries 13 and 14). Given the relative overall ease of handling $ZnCl_2$, we settled on the use of this readily available Zn(II) salt for the continuation of our study.

With optimized conditions in hand, we next examined the scope of *ortho*-selectivity observed in the desilylation of poly-TBS ether substituted benzaldehydes **1** (Table 2). In general, good yields of 2-hydroxy benzaldehydes **2** were obtained upon treatment of **1** with $ZnCl_2$ in $Cl(CH_2)_2Cl$ regardless of the aryl substitution pattern. Benzaldehydes **1b** and **1c** bearing TBS-ethers in the *meta* position remained intact leading to 2-hydroxy benzaldehydes **2b** and **2c** in 61% and 78% yields, respectively (entries 1 and 2). Additionally, 2,3,4-tris-silyl ether **1d** underwent smooth *ortho* selective desilylation to provide benzaldehyde **2d** in 67% yield (entry 3). Interestingly, 2,4,6-tris-silyloxy benzaldehyde **1e** underwent mono-*ortho* deprotection in 82% yield even in the presence of excess $ZnCl_2$ (entry 4).

We next turned our attention toward determining the generality of this method for the selective *ortho* deprotection of other commonly employed phenol protecting groups (Table 3). Removal of the *ortho*-TIPS group in benzaldehyde **3a** occurred readily to provide phenol **4a** in 71% yield (entry 1). Deacylation of *ortho*-acetate groups also proved effective (entry 2). With exception of the methoxyethoxymethyl (MEM) group, which provided an optimal yield of 26% under our standard conditions, the selective *ortho* deprotection of methoxy ether derived protecting groups generally performed better in ether than chlorinated solvents (entries 3–5). Interestingly, treatment of 2-benzyloxy benzaldehyde **3f** with $ZnCl_2$ in DCE for 24 h at 80 °C provided the expected *ortho*-phenol **4f** in 72% yield (entry 6), whereas the 2,4-dimethoxy benzaldehyde **3g** proved unreactive (entry 7). Likewise, sulfonates **3h** and **3i** also failed to undergo desulfonylation, resulting in nearly quantitative yields of the starting benzaldehyde derivatives (entries 8 and 9). These composite results not only demonstrate the positional selectivity in the *ortho* deprotection of silyl, acetyl, methoxy, and benzyl groups, but also the chemoselectivity for these groups over sulfonyl and methyl groups.

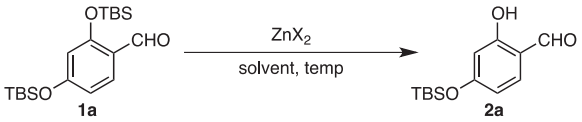
Given the synthetic utility of allyl ether protecting groups, we chose to examine the 2,4-bisallyloxy benzaldehyde **3j** using our optimized conditions (Eq. 1). Interestingly, the expected *ortho*-deprotection product was not observed, but instead provided the 3-allyl arylation adduct **5** in 58% yield. The reaction likely proceeds through an aromatic Claisen rearrangement mediated by the Zn^{II} Lewis acid.[9] Exploitation of this unexpected reactivity for the mild *ortho* functionalization of allyl aryl ethers would enable the site-selective allylation of benzoyl derivatives, and is under current investigation.



(1)

To determine the extent to which Lewis basic functionality other than that of aldehydes is capable of directing the *ortho* selective deprotection of phenolic ethers, we next examined 2,4-bissilyloxy

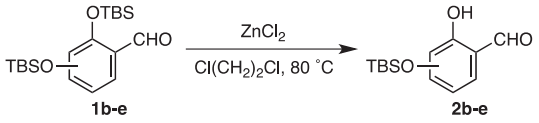
Table 1
Optimization of bis-silyloxy *ortho*-deprotection[a]

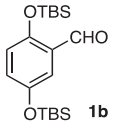
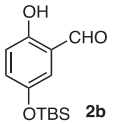
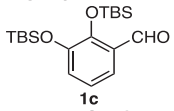
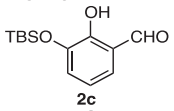
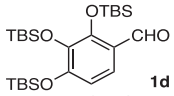
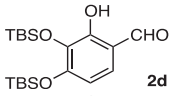
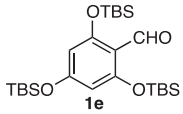
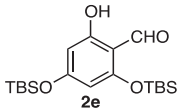


Entry	X	Solvent	Temp (°C)	Yield[b] (%)
1	I	CH_2Cl_2	25	NR
2	Br	CH_2Cl_2	25	78
3	Cl	CH_2Cl_2	25	77
4	Cl	Et_2O	25	<5
5	Cl	1,4-Dioxane	25	<5
6	Cl	THF	25	<5
7	Cl	$CHCl_3$	25	<5
8	Cl	$Cl(CH_2)_2Cl$	25	83
9	*Cl*	*$Cl(CH_2)_2Cl$*	*80*	*91*
10	Cl (1.5 equiv)	$Cl(CH_2)_2Cl$	25	85
11	*Cl (1.05 equiv)*	*$Cl(CH_2)_2Cl$*	*25*	*88*
12	*Cl (1.05 equiv)*	*$Cl(CH_2)_2Cl$*	*80*	*87*
13	Br	$Cl(CH_2)_2Cl$	25	79
14	I	$Cl(CH_2)_2Cl$	25	NR

[a] Reactions conducted on a 0.5 mmol scale using 2 equiv of ZnX_2 at 0.1 M (see Supplementary data for details).
[b] Isolated yield after chromatographic purification.

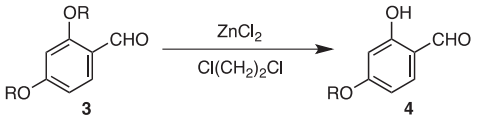
Table 2
Temperature and additive effect on metallation[a]

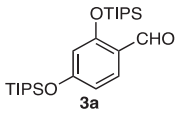
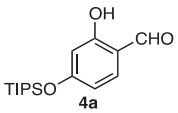
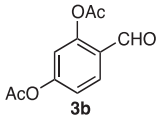
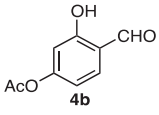
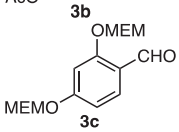
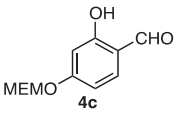
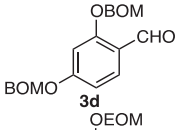
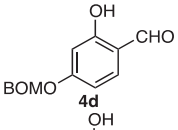
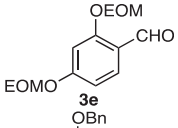
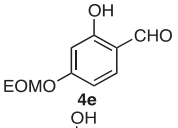
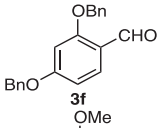
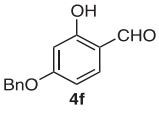
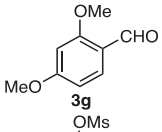
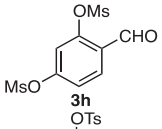
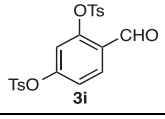


Entry	Substrate	Product	Yield (%)[b]
1			61
2			78
3			67
4[c]			82

[a] Reactions conducted on a 0.2 mmol scale using 1.05 equiv of $ZnCl_2$ at 0.1 M (see Supplementary data for details).
[b] Isolated yield after chromatographic purification.
[c] Reaction was conducted at 25 °C for 9 h.

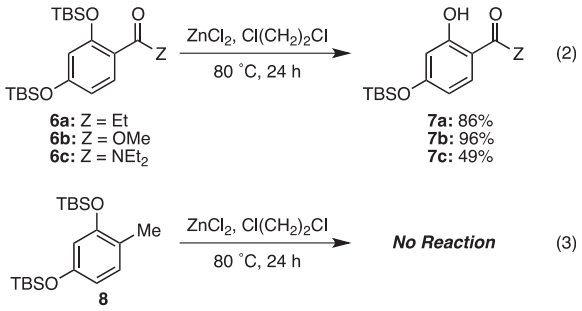
Table 3
Protecting group versatility[a]



Entry	Substrate	Product	Temp (°C)	Yield[b] (%)
1	 **3a**	 **4a**	25 80	12 71
2	 **3b**	 **4b**	25 80 130	NR <5 59[c]
3	 **3c**	 **4c**	25	26
4[d]	 **3d**	 **4d**	25	71
5[d]	 **3e**	 **4e**	25	55
6	 **3f**	 **4f**	80	72
7	 **3g**	—	80	NR
8	 **3h**	—	80	NR
9	 **3i**	—	80	NR

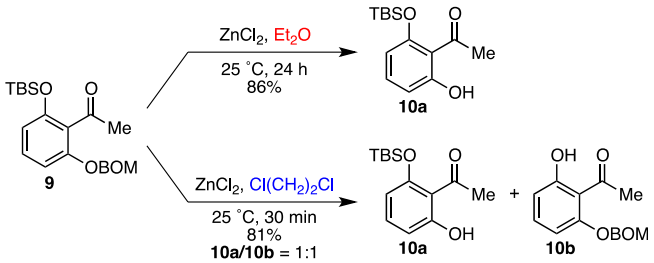
[a] Reactions conducted on a 0.15 mmol scale using 1.05 equiv of $ZnCl_2$ at 0.1 M (see Supplementary data for details).
[b] Isolated yield after chromatographic purification.
[c] Reaction conducted in PhCl.
[d] Et_2O used as solvent.

benzyl ketone **6a** and benzoate **6b** under our optimized reaction conditions (Eq. 2). Upon treatment with $ZnCl_2$, the corresponding 2-hydroxy benzoyl derivatives **6a** and **7b** were obtained in 86% and 96% yields, respectively. Although ketones and esters underwent *ortho*-selective desilylations in excellent yields, amide **6c** provided phenol **7c** in diminished yield, and benzyl alcohols proved ineffective at directing the deprotection reaction, resulting in complete recovery of the starting benzyl alcohol. The Lewis basic benzoyl group adjacent to the site of deprotection is crucial to the observed reactivity, as demonstrated by the observation that 2,4-silyloxy toluene **8** failed to provide any products resulting from desilylation, giving only a quantitative recovery of the starting material (Eq. 3).

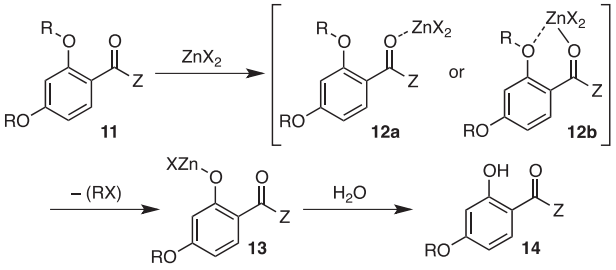


Based on the observed influence of solvent and temperature on *ortho* deprotection efficiency, it is noteworthy that selective removal of orthogonal *ortho* protecting groups is possible through a judicious selection of reaction conditions. For instance, *ortho*-TBS groups (DCE, 25 °C: 88%; Table 1, entry 11) are readily cleaved in the presence of *ortho*-TIPS groups (DCE, 25 °C: 12%; Table 3, entry 1). Additionally, *ortho*-silyl ethers in general are reliably cleaved in the presence of *ortho*-acetates, which require elevated temperatures and long reaction times (PhCl, 130 °C: 59%; Table 3, entry 2).[8] The observation that the removal of methoxy ether derivatives occurs more readily in Et_2O led us to speculate that exploitation of this reactivity would enable orthogonal deprotection in the presence of other phenolic ethers (Scheme 2). Thus, treatment of ketone **9** with $ZnCl_2$ in Et_2O at 25 °C led to dealkylation of the BOM group to provide phenol **10a** in 86% yield. However, attempts to orthogonally deprotect the TBS group in **9** led to a 1:1 mixture of phenols **10a** and **10b** resulting from the independent removal of both the TBS and BOM groups. As observed with aldehyde **1e**, only removal of one protecting group was observed under the reaction conditions.

The results described herein indicate a mechanism that likely involves coordination of the Lewis acidic ZnX_2 with the directing carbonyl functionality. This effectively activates the *ortho*-protected phenol for deprotection and appears highly dependent on



Scheme 2. Orthogonal *ortho*-deprotection.



Scheme 3. Proposed mechanism.

the nature of the protecting group.[3–5,9] A likely mechanism involves formation of intermediates **12a** and **12b** resulting from ZnX_2 coordination to the carbonyl group as either a monodentate Lewis acid, or chelation to the adjacent phenolic oxygen in a bidentate fashion[10] respectively upon exposure to benzoyl derivative **11** (Scheme 3). The presence of bulky *ortho* ethers (e.g., TBSOAr) likely prevents bidentate chelation,[11] whereas less sterically demanding groups, such as the methoxy methyl derivatives and benzyl, enable the formation of intermediate **12b**.[12] Regardless of whether ZnX_2 behaves as a monodentate or bidentate Lewis acid, the enhanced electrophilicity of the *ortho* ether in **12a** and **12b** and increased stability of the resulting phenoxide lead to the observed chemoselectivity. Addition of exogenous halide from the Zn(II) salt at the more electrophilic ether leads to liberation of the 2-hydroxy group and formation of zinc phenoxide **13**. Experiments were performed using anhydrous $ZnCl_2$ weighed in a glove box for accuracy and reproducibility. However, it is noteworthy that comparable results were obtained with $ZnCl_2$ exposed to air without the strict exclusion of water or oxygen. These observations suggest that although adventitious water may aid in cleavage of the *ortho* protecting group, a more likely mechanism involves phenol displacement by residual halogen. Subsequent protonation of zinc phenoxide **13** upon aqueous workup provides the observed phenol **14**.

In conclusion, the method described herein enables the selective *ortho*-deprotection of phenol derivatives in the presence of other hydroxy groups bearing the same protecting group. This method requires only the use of inexpensive and readily available $ZnCl_2$ or $ZnBr_2$, and avoids the more conventional harshly Brønsted or Lewis acidic conditions used in the *ortho*-deprotection of phenols.[1,13] Given the prevalence of polyhydroxylated benzene derivatives in biologically active natural products, this method will find broad utility in the context of total synthesis.[14] Further exploration of the directing effects of carbonyl groups for the deprotection of neighboring protecting groups, as well as additional mechanistic studies, is underway and will be reported in due course.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.103.

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