Direct Access to Mono-Protected Homoallylic 1,2-Diols via Dual Chromium/ Photoredox Catalysis

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Abstract: Herein, we present a dual catalytic strategy to efficiently obtain mono-protected homoallylic 1,2-diols by coupling abundant aldehydes with simple (silyl) enol ethers, thus providing direct access to this important motif without the (super)stoichiometric use of prefunctionalized metal-allyl species. The modularity of our approach is shown by the introduction of several silyl- and alkyl-based protecting groups, enabling a diverse protecting group strategy. To highlight functional group tolerance and chemoselectivity, we demonstrate the functionalization of a variety of aliphatic, aromatic and heteroaromatic aldehydes, even in presence of ketones and esters. The applicability was further supported by a large scale experiment and a robustness screening. Mechanistic studies support a radical mechanism, starting from the single electron oxidation of the silyl enol ether, facilitated by the *β*-silicon effect.

The 1,2-diol motif is of great interest for synthetic organic chemists, since it is incorporated in a multitude of bioactive compounds[1,2] and valuable intermediates.[3] Especially mono-protected homoallylic 1,2-diols have found widespread use as building blocks in the synthesis of carbohydrate frameworks[4] and other natural products[5–10] for two important reasons. Firstly, as one of the two alcohol moieties is protected, they are distinguishable and can be utilized independently, either for further functionalization or to selectively invert the stereocenter under Mitsunobu conditions.[2,11,12] This provides selective access to both the *syn* and the *anti* product. Secondly, the allyl moiety can serve as a synthetic linchpin, enabling a variety of subsequent established transformations, such as dihydroxylation,[13] epoxidation,[14] ozonolysis,[15] hydroboration[6,7,16] and many more[9,17] (**Figure 1A**).

While there are important reports to access this motif either via a *n*-BuLi initiated siloxy-[2,3] Wittig rearrangement[18] or the addition of acetals to aldehydes,[19] these methods were developed specifically for one type of protecting group and therefore lack generality. Thereby, state of the art for the synthesis of mono-protected, homoallylic 1,2-diol derivatives is still the stoichiometric use of prefunctionalized allyl-metal species. In this case, the protected alcohol is either already implemented in the allyl species, or another transient functional group is used, which can be subsequently cleaved to give the free alcohol (**Figure 1B**). This has been extensively studied using various metals, such as B,[6,20] Sn,[21] Zn,[22] In,[23] Al,[24] or Ti.[10] An excellent overview of the available methods and their respective applications in total synthesis was published by Lombardo and Trombini.[5] Although this strategy is very established, also in an enantioselective fashion,[25] it displays some major drawbacks. The allyl-metal species bearing the protected alcohol/ transient functional group must be expensively synthesized (typically by a hydroboration/ isomerization sequence or a protection/ lithiation/ transmetalation strategy)[5] and is then used in (super)stoichiometric amounts. This results in high costs and metal waste. Especially when one would like to evaluate different protecting groups, the elaborate synthesis of each respective starting material (SM) was reported to present a significant challenge.[11,26] Furthermore, owing to the high nucleophilicity of these allylation reagents, ketones, esters or imines are often not tolerated.[5]

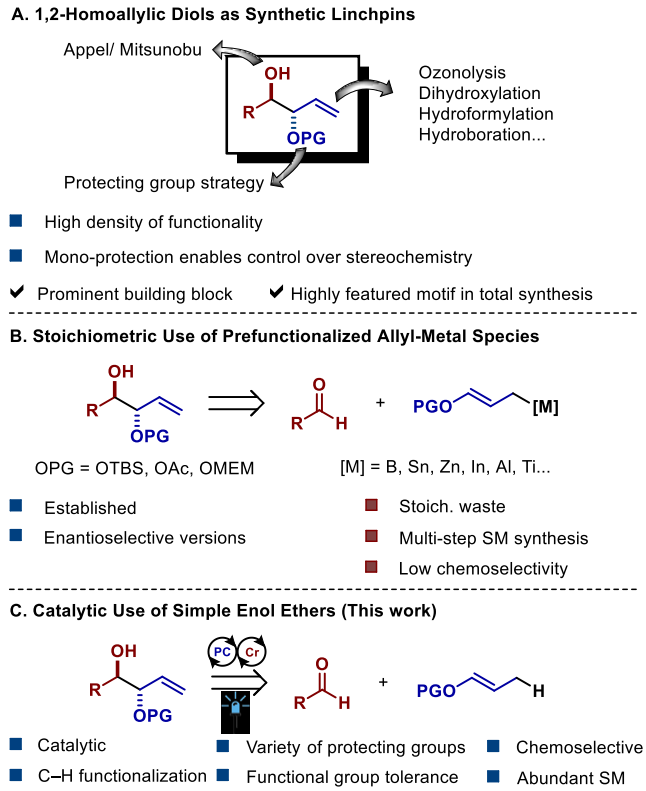


Figure 1. Utility of homoallylic 1,2-diol derivatives and retrosynthetic strategies. TBS = *tert*-butyldimethylsilyl , Ac = acetyl, MEM = 2-methoxyethoxymethyl.

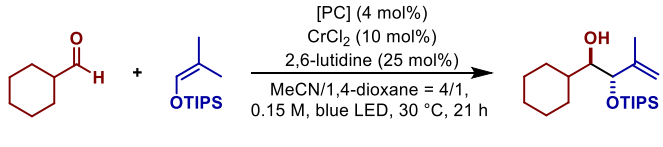
A general catalytic strategy to access these high value motifs from inexpensive and abundant starting materials in a redox-neutral fashion would therefore be highly desirable. Especially modularity

regarding different types of protecting groups and a broad functional group tolerance would be highly useful.

The utilization of chromium as an inexpensive (and contrary to common believe also rather low-toxic)[54] 3d transition metal to generate important carbon–carbon bonds has received great attention within the last decades, one example being the classical Nozaki-Hiyama-Kishi (NHK)-type allylation.[27] Still, the unique features of organochromium species render them of high interest as shown by reports from Shenvi[28] and Baran,[29] even using them in stoichiometric fashion.

Recently, our group as well as Kanai´s independently reported the ability of chromium to trap photochemically generated radicals,[30] starting from allyl amines/allyl arenes or unactivated alkenes respectively.[31,32] This dual catalytic approach was further established by our own work towards the synthesis of *α*-alkyl homoallylic alcohols[33] and the utilization of *α*-silyl amines to give 1,2-aminoalcohols.[34] In addition, the combination of this dual catalytic approach with hydrogen atom transfer (HAT)[35,36] was explored by Yahata and Kanai. Given our experience in this exciting field,[37] as well as the importance of the homoallylic 1,2-diol motif, we questioned, whether we could utilize simple enol ethers to enable direct access to these important structures (**Figure 1C**). Silyl enol ethers are less nucleophilic (more stable) than metal enolates,[38] easily prepared in one simple step from the respective aldehyde and would thus be an ideal allyl radical precursor. In addition to the general advantages of this catalytic approach (mild conditions, less waste, C–H-functionalization), the high chemoselectivity of organochromium species[39] would also enable the selective conversion of aldehydes in presence of other carbonyls. Indeed, literature precedence showed, that the single-electron oxidation of silyl enol ethers by commercial iridium based photocatalysts is possible.[40] Moreover, the addition of *γ*-silyloxyallylchromium species to aldehydes has been shown in chromium-mediated pinacol couplings.[41–43]

Table 1. Reaction conditions, deviation table and control reactions.[a]



1a 1b 3a

Entry	Deviation from Standard Conditions	Yield (%)
1	**None**	**94**
2	No light	-
3	No chromium	-
4	No base	5
5	No photocatalyst	-
6	**2 mol% PC**	**81**
7	**$CrCl_3$**	**82**
8	1.5 equiv. of 1b	78

[a] Reaction conditions: [PC] = [Ir(dFCF$_3$ppy)$_2$-(5,5'-dCF$_3$bpy)]PF$_6$, **1a** (0.1 mmol), **1b** (0.3 mmol), reaction time: 21 h. Yields were determined via ^{1}H NMR spectroscopy with mesitylene as an internal standard. Diastereomeric ratio in all cases = 78:22.

Given this initial idea, we started our investigation with the coupling of aldehyde **1a** and silyl enol ether **1b**. However neither our previously reported conditions for the oxidation of allyl arenes,[31] nor Kanai´s conditions utilizing an acridinium catalyst to oxidize unactivated alkenes[32] afforded any detectable amounts of the 1,2-diol product **3a**. After extensive optimization, (see SI) we were pleased to obtain product **3a** in 94% yield (**Table 1**, entry **1**) using [Ir(dFCF$_3$ppy)$_2$-(5,5'-dCF$_3$bpy)]PF$_6$ as photocatalyst instead, with $CrCl_2$ as chromium source and 2,6-lutidine as a base in a MeCN/1,4-dioxane mixture. Control experiments proved, that the reaction does not proceed without photocatalyst, chromium or light (entries **2,3,5**). It is noteworthy that air stable $CrCl_3$ could be used as an alternative chromium source (entry **7**) and reduction of the photocatalyst loading to 2 mol% (entry **6**) or lowering the enol ether equivalents to 1.5 equiv. (entry **8**) led to only slightly diminished yields.

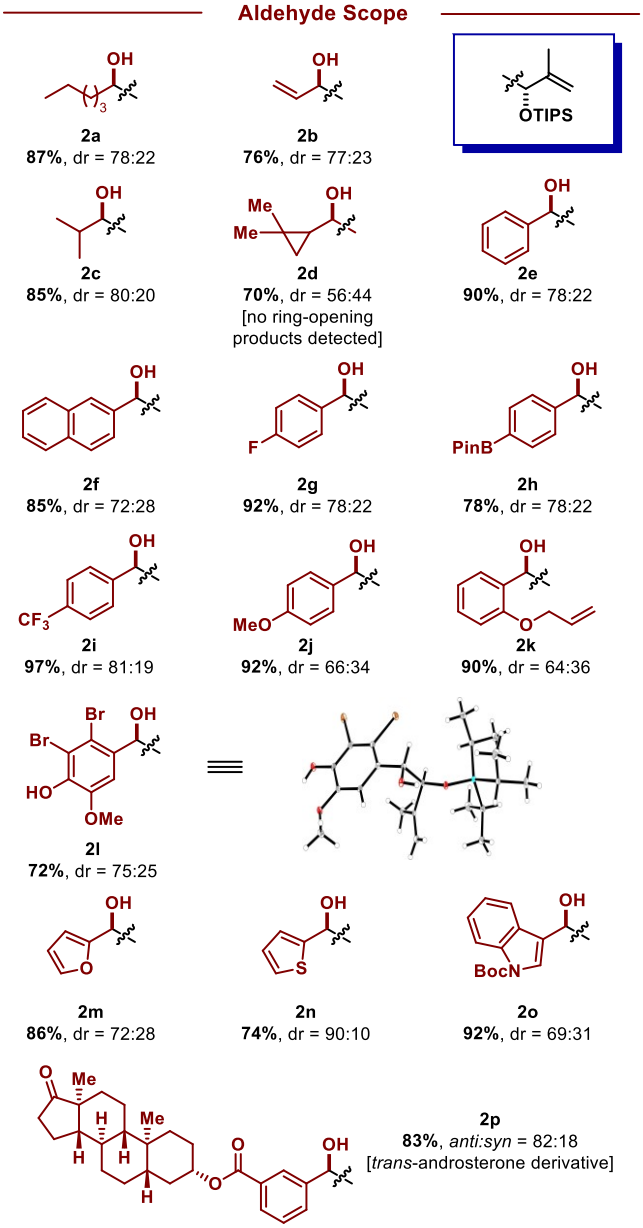


Figure 2. Use of different aldehydes in the catalytic hydroxyallylation. 0.2 mmol scale, for reaction conditions see table 1, reaction time: 40 h.

Next, we examined the substrate scope, focusing on the aldehydes first (**Figure 2**). A variety of aldehydes was shown to be excellent coupling partners. Primary and secondary aliphatic aldehydes were equally reactive (entries **2a–d**). Similar to previous reports,[31,33] tertiary aldehydes did not show reactivity

presumably due to steric hindrance. A diversity of aromatic aldehydes could be efficiently converted to the respective products. Electron-neutral (entries **2e–f**), electron-poor (entries **2g–i**) and electron-rich (entries **2j–k**) benzaldehydes all showed excellent reactivity, tolerating high level of substitution and acidic free alcohol groups (entry **2l**). Bis(pinacolato)diboron (Bpin) was also shown to be well tolerated (entry **2h**). To our delight, also heteroaromatic aldehydes could be cleanly functionalized (indole, furane or thiophene derivatives **2m–o**). Allylic positions (entry **2k**) were tolerated and pleasingly also acrolein could be efficiently functionalized giving exclusively the 1,2-addition product **2b**, bearing two alkenes as synthetic linchpins. The conversion of a *trans*-androsterone derivative **2p** highlights the excellent chemoselectivity of our protocol, since even in presence of an ester and a ketone moiety, only the aldehyde was selectively functionalized.

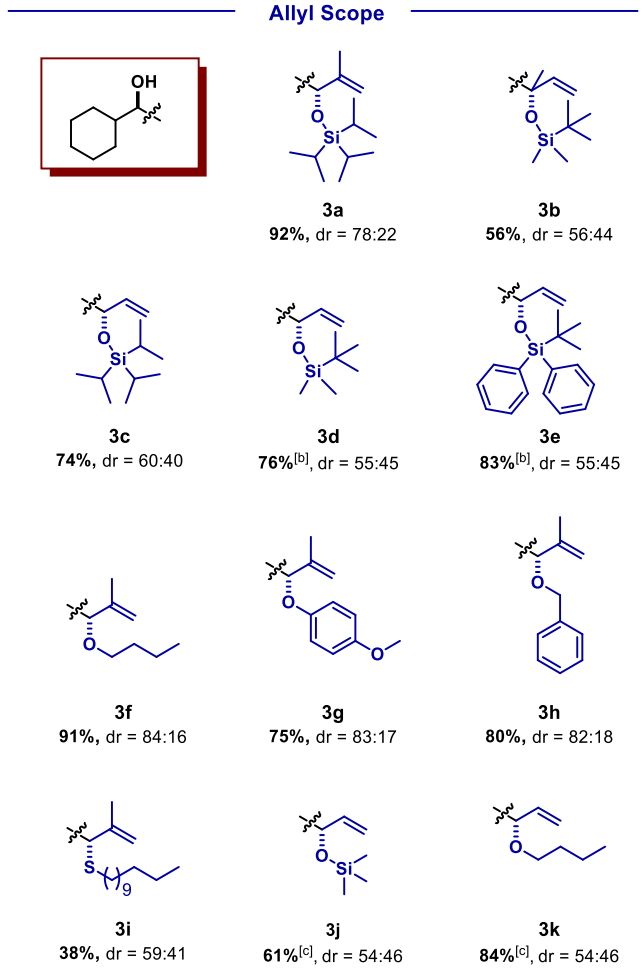


Figure 3. Use of different enol ethers in the catalytic hydroxyallylation. 0.2 mmol scale, for reaction conditions see table 1, reaction time: 40 h. [b] 7 mol% photocatalyst loading. [c] reaction conditions: $[Ir(dtbbpy)(ppy)_2]PF_6$ (2 mol%), $CrCl_2$ (2.5 mol%), K_2HPO_4 (1 equiv.), triisopropylsilanethiol (35 mol%), DMA/1,4-dioxane = 3/2, 0.2 M, blue LED, 30 °C, 18 h.

Next, we examined the allyl scope focusing on the introduction of different established protecting groups as well as the influence of substitution (**Figure 3**). The most prominent silyl protecting groups such as *tert*-butyldimethylsilyl (TBS), triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) gave the respective products (entries **3c–e**) in good to excellent yields. The introduction of a substituent in the *β*-position gave the respective product (entry **3a**) in excellent yield, while substitution of the *α*-position (entry **3b**) gave access to a quarternary stereocenter. Besides silyl enol ethers, substituted aliphatic enol ethers showed excellent reactivity, enabling access to other common protecting groups such as benzyl (Bn) (entry **3h**), aliphatic or aromatic ethers (entries **3f–g**). Moreover it was shown that aliphatic thioethers could be converted, albeit with diminished yield (entry **3i**). In summary, while silyl enol ethers showed great reactivity (independent from their substitution pattern, due to their lower oxidation potential), aliphatic enol ethers were only reactive if they were substituted. To solve this limitation, as well as the problem that the trimethylsilyl (TMS) group was found to be instable under our reaction conditions, we also developed a second catalytic system as a workaround. In this case, we combined our dual catalytic approach with a thiol based HAT catalyst. While during the preparation of this manuscript, Kanai reported very elegant complementary work on the use of a thiophosporic imide HAT catalyst[44] focusing on the activation of unactivated alkenes,[36] we found that the combination of $[Ir(dtbbpy)(ppy)_2]PF_6$ (2 mol%), $CrCl_2$ (2.5 mol%) and commercial triisopropylsilanethiol[45] (35 mol%) (see figure **3** or SI) enabled both, the introduction of the TMS protecting group (entry **3j**) and the conversion of unsubstituted aliphatic ethers (entry **3k**), thereby solving the previous limitations of our method.

While our developed reaction protocol typically gave the respective products in very good to excellent yields, the observed diastereomeric ratio is rather moderate, depending on the substitution pattern. NOE-studies after cyclization[42] of deprotected product **3d** (see SI), as well as the obtained crystal structure[53] (**Figure 2**, entry **2l**) confirmed the *anti*-diastereomer to be formed dominantly. Allyl-chromium species have been reported to react via a Zimmerman-Traxler type transition state,[46] leading to excellent diastereoselectivites. However, the observation of only moderate selectivities when using *γ*-silyloxyallylchromium species has also been made in studies on similar intermediates in chromium catalyzed pinacol couplings.[41–43] Here it was reasoned that the stereochemical outcome reflects the conformational equilibrium of the *γ*-silyloxyallylchromium species, as intramolecular coordination between oxygen and chromium leads to a stable five-membered ring (**Figure 4**).

Nevertheless, as the diastereomers are perfectly separable via column chromatography, we believe that this only displays a minor drawback for the application of our method, keeping in mind its simplicity and efficiency. In addition, as mentioned in the introduction (opposite to the unprotected 1,2-diol products obtained by pinacol couplings) the high-yielding Mitsunobu stereoinversion of mono-protected 1,2-diols is very established, therefore after separation, each diastereomer can be independently stereoinverted, enabling selective access to both, the *syn* and the *anti* product.

Our mechanistic proposal is depicted in **Figure 4**. The electron donation from the oxygen lone pair renders the alkene electron-rich enough to be oxidized by the exited state of the photocatalyst $[Ir(dFCF_3ppy)_2(5,5'\text{-}dCF_3bpy)]PF_6$ (E_{Ox} = +1.68 V versus SCE in MeCN).[47] Subsequent deprotonation leads to an allyl radical which is trapped by Cr^{II} to give a *γ*-silyloxyallylchromium species, which would add to the aldehyde, giving the respective *anti* or *syn* product depending on its conformation. The formed alkoxide is then hydrolyzed to liberate the product and Cr^{III}. Both catalysts

are regenerated by reduction of Cr^{III} with Ir^{II}. To support this proposal, several mechanistic experiments were conducted.

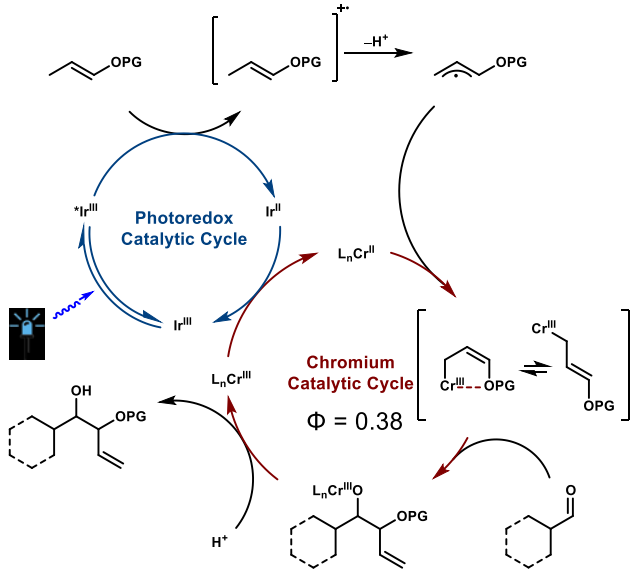


Figure 4. Mechanistic proposal and quantum yield.

As a radical-probe experiment,[48] dimethylcyclopropylaldehyde was cleanly converted to cyclic product **2d** without any ring-opened products being detected, hinting towards a chromium-mediated mechanism and not a radical-radical coupling. This is in agreement with the control experiment without chromium catalyst not yielding any detectable products. The quantum yield was determined to be Φ = 0.38 by ferrioxalate actinometry,[49] thus indicating a truly photocatalytic pathway, although an unefficient radical chain cannot be excluded. Linear scan voltammetry studies (**Figure 5A**) revealed the oxidation potential of **1b** to be E_{Ox} = +1.64 V (hyperconjugation and *β*-silicon effect)[50], while the potential of the unsubstituted silyl enol ether (only *β*-silicon effect, E_{Ox} = +1.96 V, see SI), is at the limit of the oxidative capability of the photocatalyst. This explains the observed slower reaction of unsubstituted silyl enol ethers and why unsubstituted alkyl enol ethers (neither *β*-silicon effect nor hyperconjugation) cannot be directly oxidized and thus had to be activated via a HAT approach. Stern-Volmer Quenching studies (**Figure 5B**) revealed a similar relation. Substituted silyl enol ether **1b** directly quenches the excited state of $[Ir(dFCF_3ppy)_2\text{-}(5,5'\text{-}dCF_3bpy)]PF_6$, while unsubstituted alkyl enol ethers did not show quenching. However the HAT catalyst triisopropylsilanethiol was shown to interact with the photocatalyst (see SI).

As highlighted in the introduction, the strength of our protocol lies within its simplicity, modularity regarding different protecting groups as well as applicability due to its high functional group tolerance. While halides, esters, ketones, Bpin or allylic positions have already been covered within the substrate scope, we also wanted to investigate the tolerance of external additives (robustness screen) as well as condition-based parameter changes (sensitivity assessment). The results of the respective screens can be seen in **Figure 5**. The robustness screen[51] (**Figure 5C**, for further information see SI) showed that our method tolerated 12 out of 14 external additives, including acidic and electrophilic ones. The results of the sensitivity assessment[52] are depicted in **Figure 5D**. It was shown, that the only crucial reaction parameter is the amount of water, while temperature, concentration, oxygen and light intensity only showed little impact on the reaction outcome. To show the scalability, the screening included a 2 mmol reaction, giving the product in almost quantitative yield (98%). This shows the general robustness and insensitivity of our developed catalytic conditions.

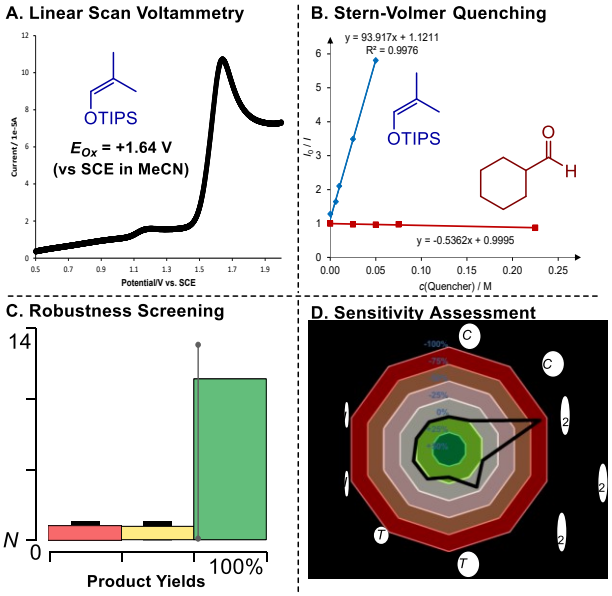


Figure 5. [A] Linear scan voltammetry. **[B]** Stern-Volmer quenching study. **[C]** Robustness screening. **[D]** Sensitivity Assessment.

In summary, we developed a simple catalytic protocol to couple abundant aldehydes with silyl or alkyl enol ethers to give high value, mono-protected homoallylic 1,2-diol products. A variety of common protecting groups as well as a broad applicability towards aliphatic, aromatic and heteroaromatic aldehydes bearing different functional groups and substitution patterns was shown. The limitation of unsubstituted aliphatic enol ethers not being reactive was solved by elaboration of a second catalytic system, utilizing a commercial HAT catalyst. Mechanistic experiments support a classical dual catalytic pathway, initiated by single electron oxidation of the enol ether, enabled by a combination of +M and *β*-silicon effect. A robustness screen and a sensitivity assessment highlighted the functional group tolerance and scalability. We hope that this protocol will help to overcome the drawbacks of using prefunctionalized, stoichiometric metal-allyl species in the synthesis of complex organic molecules and building blocks. Further studies to apply this strategy to introduce other functional groups as well as the development of an enantioselective version are ongoing in our laboratory.

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Keywords: Photoredox • Chromium • Dual Catalysis • Diols • Hydroxallylation

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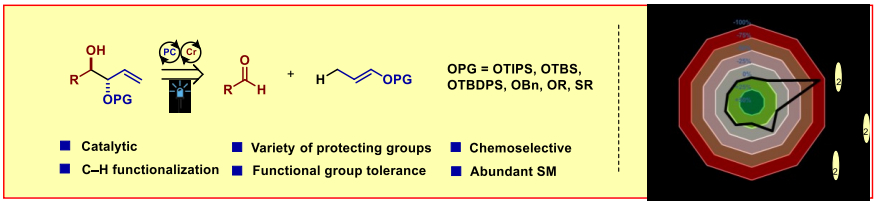
TOC Graphic


OH
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OPG = OTIPS, OTBS,
OTBDPS, OBn, OR, SR
Catalytic
C–H functionalization
Variety of protecting groups
Functional group tolerance
Chemoselective
Abundant SM