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Letter

Chromium-Catalyzed Linear-Selective Alkylation of Aldehydes with Alkenes

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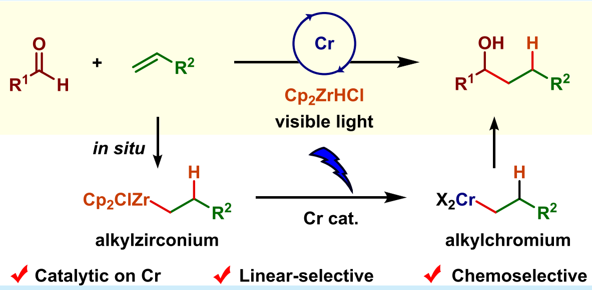
ABSTRACT: We developed a chromium-catalyzed, photochemical, and linear-selective alkylation of aldehydes with alkylzirconium species generated *in situ* from a wide range of alkenes and Schwartz's reagent. Photochemical homolysis of the C−Zr bond afforded alkyl radicals, which were then trapped by a chromium complex catalyst to generate the alkylchromium(III) species for polar addition to aldehydes. The reaction proceeded with high functional group tolerance at ambient temperature under visible-light irradiation.



Nucleophilic alkylation of carbonyl compounds with organometallics is a fundamental process in organic synthesis. Despite the high utility of organolithium and -magnesium reagents, their excessive reactivity and basicity often make them incompatible with functionalized substrates. Therefore, improving the chemoselectivity and utility of nucleophilic organometallic reagents is a very important research topic.[1] Among nucleophilic and chemoselective organometallics for the alkylation of aldehydes, alkylchromium(III) reagents are versatile for the synthesis of multifunctional molecules.[2] Alkyl halides (in most cases, alkyl iodides) are traditionally used as precursors of alkylchromium(III) reagents (Figure 1a).[3] Recently, Shenvi[4] and Baran[5] developed elegant methods for accessing alkylchromium(III) reagents that allowed for chemoselective alkylation of aldehydes with feedstock starting materials such as alkenes or activated carboxylic acids (Figure 1a). Specifically, in Shenvi's reaction, branched addition products were obtained due to the regioselectivity of Co-catalyzed hydrosilylation followed by Co/Cr exchange through a secondary alkyl radical. Yahata reported the nucleophilic addition of hydrocarbon alkanes to aldehydes by combined use of a chromium salt and photoredox catalyst, which also produced branched products (Figure 1a).[6] Those methods significantly expanded the scope of Cr-mediated carbonyl alkylation, but stoichiometric amounts of Cr salts are required. Although catalytic processes for generating alkylchromium species have been reported, the substrate scope remains to be improved.[7,8] Here, we developed Cr-catalyzed, linear-selective alkylation of aldehydes by alkylzirconium species generated in situ from alkenes and Schwartz's reagent (Figure 1b). Due to the mild reaction conditions, various multifunctional substrates are compatible.

Our working hypothesis for Cr-catalyzed alkylation of aldehydes is shown in Figure 2. Alkylzirconium **2** is regioselectively prepared from alkene **1** and Schwartz's reagent under mild conditions.[9] Photoactivation of **2** by visible-light

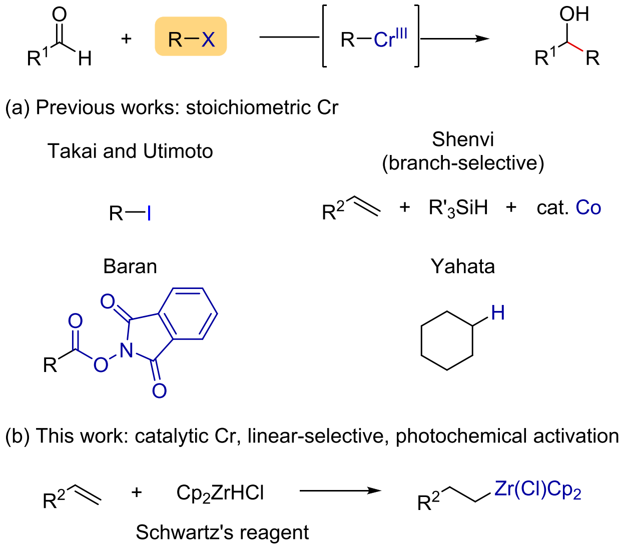


Figure 1. Precursors (R−X) of alkylchromium(III) species in alkylation of aldehydes. (a) For previously reported Cr-mediated reactions. (b) This work: alkylzirconium species as a precursor for alkylchromium(III) species.

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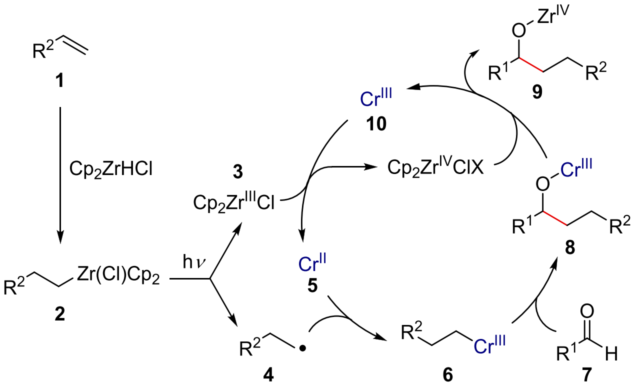


Figure 2. Proposed catalytic cycle.

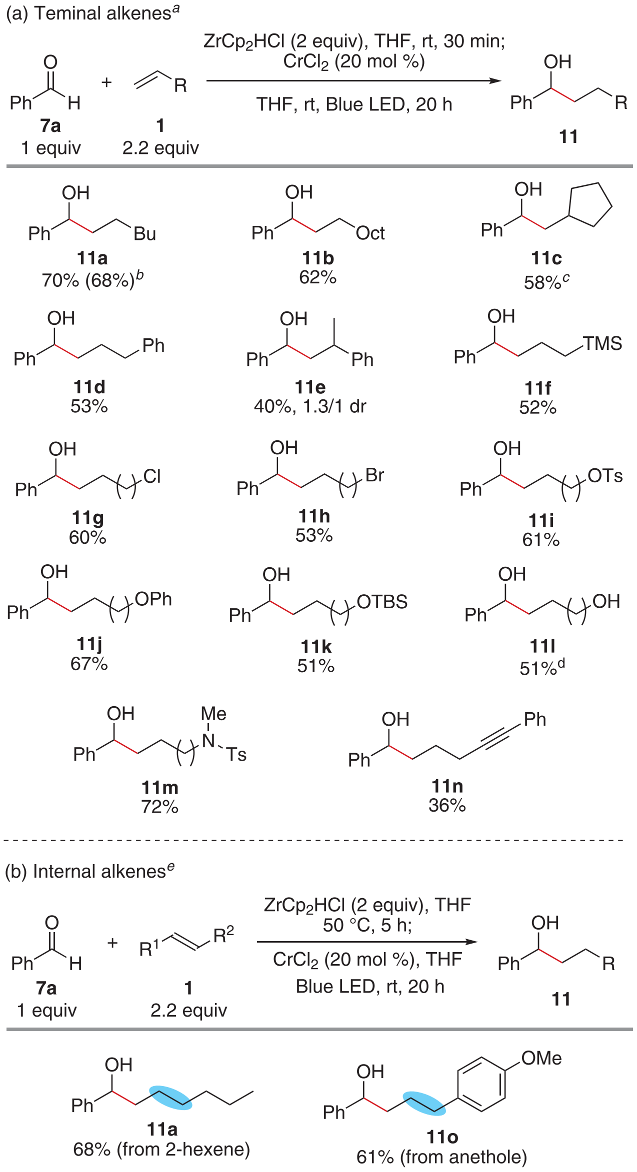
irradiation produces reduced Zr(III) species **3** and alkyl radical **4** through homolysis of the C−Zr bond,[10] the latter of which is oxidatively intercepted by Cr(II) complex **5** to afford alkylchromium(III) **6**.[4−8,11] Then, **6** reacts with aldehydes **7** to produce Cr(III) alkoxide **8**. Ligand exchange between **8** and Zr(IV) species affords Zr(IV) alkoxide **9** and Cr(III) salt **10**.[7a] Finally, single-electron reduction of **10** by Zr(III) species **3** regenerates **5** and closes the catalytic cycle.[12] We envisioned catalytic turnover in Cr and linear selectivity due to the high oxophilicity of Zr(IV) salts (**8** to **9**) and the regioselectivity in hydrozirconation (**1** to **2**).

According to this hypothesis, we optimized the reaction conditions using benzaldehyde (**7a**) and 1-hexene (**1a**). Hexylzirconocene was prepared *in situ* by mixing alkene **1a** and Schwartz's reagent in THF for 30 min. Alkylation product **11a** was obtained in 70% yield in the presence of 20 mol % of $CrCl_2$ under visible-light irradiation. A linear product was predominantly observed. Control experiments revealed that $CrCl_2$ and light irradiation were both essential for efficient reaction progress.[13]

We next studied the substrate scope under the optimized conditions. First, the scope of alkenes was investigated (Scheme 1a). The reaction with terminal alkenes afforded linear alkylated products in up to 70% yield (**11a**−**11e**).[14] A silyl group, alkyl halides, and alkyl tosylate were all tolerated (**11f**−**11i**). Ether-containing alkenes gave the target product in an acceptable yield (**11j**, **11k**). Free alcohol did not interfere with the reaction (**11l**). The reactivity of the present chromium catalysis using 5-hexen-1-ol as an alkene substrate was compared with the previously reported catalytic alkylation of aldehydes, silver perchlolate-[15a] or zinc bromide-catalyzed[15b] reactions. A higher yield was obtained when using the chromium catalysis, demonstrating the utility of the present conditions.[13] Alkenes containing a protected amine afforded an amino alcohol derivative (**11m**). Hydrozirconation proceeded chemoselectively at a C═C double bond in the presence of a C≡C triple bond, and the alkylation reaction proceeded at the alkene moiety of the substrate (**11n**).[16] Increasing the reaction scale to 1.0 mmol did not affect the results (68%, **11a**). When 1,5-hexadiene was used, **11c** was obtained as a major product (28%), suggesting the presence of a radical intermediate. This result was consistent with the proposed reaction mechanism shown in Figure 2.[13]

When internal alkenes were used, terminal alkylzirconocenes were generated under thermodynamic conditions.[17] Based on this chain walking strategy,[18] we tested internal alkenes as an alkyl group source (Scheme 1b). 2-Hexene afforded linear alkylated product **11a** with bond formation at the terminal carbon in 68% yield. *trans*-Anethole gave **11o** in 61% yield.

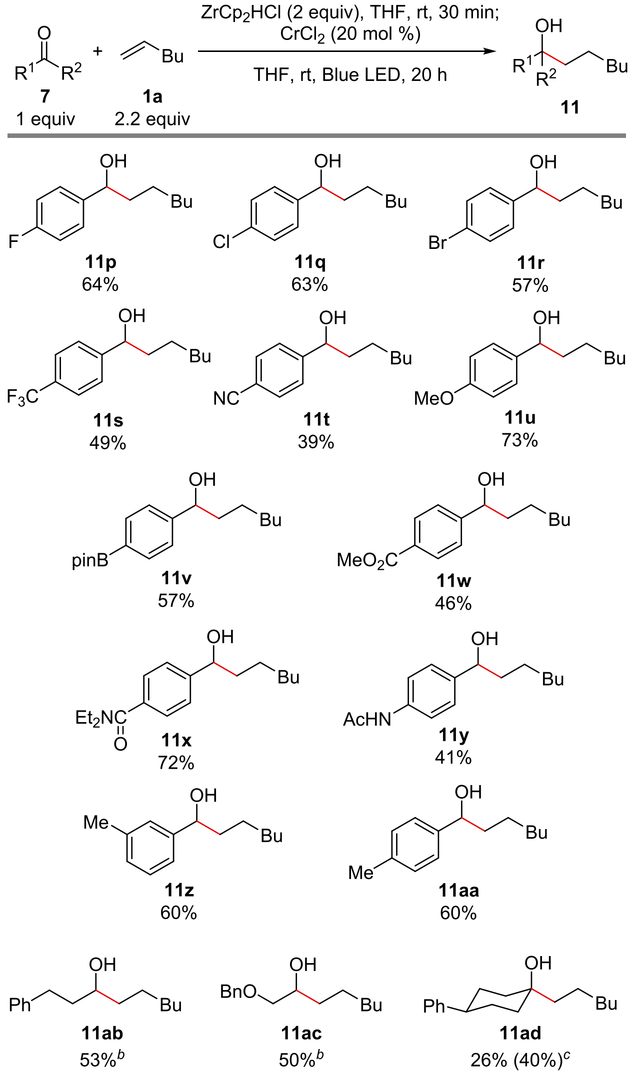
Scheme 1. Substrate Scope of Alkenes[a]



[a] General reaction conditions: **1** (0.44 mmol) and $ZrCp_2HCl$ (0.4 mmol) were reacted in THF (0.5 mL) at room temperature. After 30 min, the resulting solution was added to a solution of **7a** (0.2 mmol) and $CrCl_2$ (0.04 mmol) in THF (1.5 mL). The mixture was stirred at room temperature under blue LED irradiation for 20 h. Yield was isolated yield. [b] 1.0 mmol scale. [c] Methylenecyclopentane was used as the alkene substrate. [d] **1** (0.4 mmol) and $ZrCp_2HCl$ (0.8 mmol) were used. [e] General reaction conditions: **1** (0.44 mmol) and $ZrCp_2HCl$ (0.4 mmol) were reacted in THF (0.5 mL) at 50 °C. After 5 h, the resulting solution was added to a solution of **7a** (0.2 mmol) and $CrCl_2$ (0.04 mmol). The mixture was stirred at room temperature under blue LED irradiation for 20 h. Yield was isolated yield.

We next investigated the scope of aldehydes (Scheme 2). A series of aromatic aldehydes bearing halogens (**11p**−**11r**), electron-withdrawing groups (**11s**, **11t**), an electron-donating group (**11u**), and pinacol boron ester (**11v**) reacted with 1-hexene (**1a**), affording the corresponding products. The reaction chemoselectively proceeded with the aldehyde moiety in the presence of an ester or amide group (**11w**−**11y**). The

Scheme 2. Substrate Scope of Aldehydes[a]

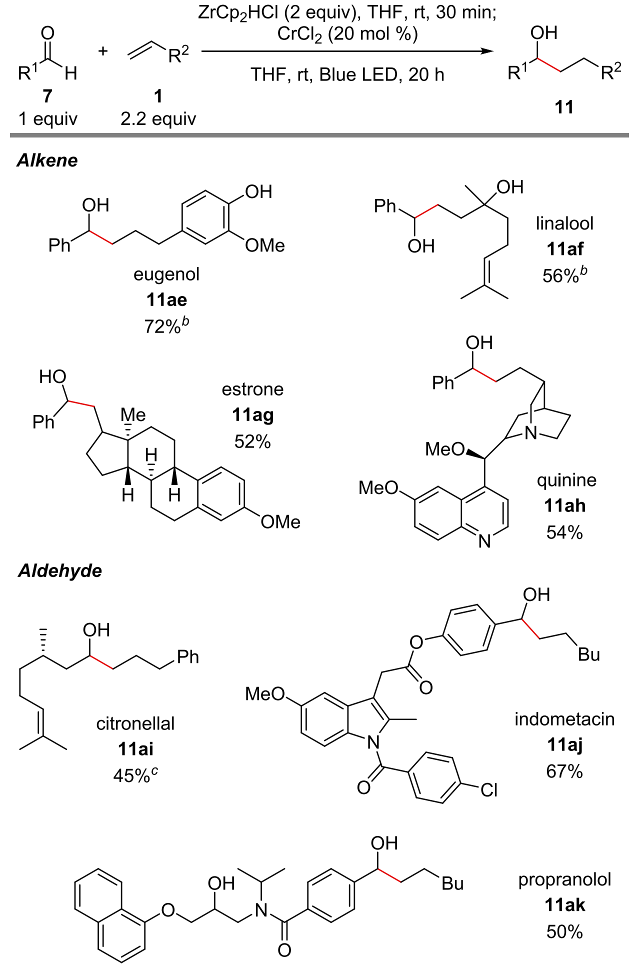


[a] General reaction conditions: **1a** (0.44 mmol) and ZrCp$_2$HCl (0.4 mmol) were reacted in THF (0.5 mL) at room temperature. After 30 min, the resulting solution was added to a solution of **7** (0.2 mmol) and CrCl$_2$ (0.04 mmol) in THF (1.5 mL). The mixture was stirred at room temperature under blue LED irradiation for 20 h. Yield was isolated yield. [b] CrCl$_2$ (0.06 mmol) was used. [c] NMR yield.

introduction of a methyl substituent at a *meta-* or *para-*position did not affect the results (**11z**, **11aa**). The reaction of aliphatic aldehydes also proceeded in the presence of 30 mol % of CrCl$_2$ (**11ab**, **11ac**). The reaction conditions were applicable to a ketone substrate (**11ad**), although the yield was low.

We then studied functionalized substrates to assess the functional group tolerance (Scheme 3). Alkenes from natural products, eugenol, linalool, estrone, and quinine were competent substrates (**11ae**−**11ah**). The reaction proceeded in the presence of phenol, tertiary alcohol, tertiary amine, and pyridine moieties. Hydrozirconation selectively proceeded at a terminal C═C double bond in the presence of a sterically hindered trisubstituted C═C double bond (**11af**). Citronellal reacted with allylbenzene to afford the product **11ai** in 45% yield. Drug-conjugated aldehydes provided the corresponding products in 67% and 50% yield (**11aj**, **11ak**), respectively. These results demonstrated the high functional group compatibility and chemoselectivity of this method.

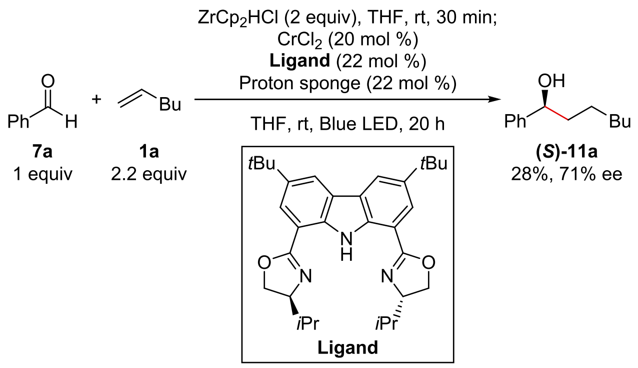
Scheme 3. Application to Functionalized Substrate[a]



[a] General reaction conditions: **1** (0.44 mmol) and ZrCp$_2$HCl (0.4 mmol) were reacted in THF (0.5 mL) at room temperature. After 30 min, the resulting solution was added to a solution of **7** (0.2 mmol) and CrCl$_2$ (0.04 mmol) in THF (1.5 mL). The mixture was stirred at room temperature under blue LED irradiation for 20 h. Yield was isolated yield. [b] **1** (0.4 mmol) and ZrCp$_2$HCl (0.8 mmol) were used. [c] CrCl$_2$ (0.06 mmol) was used.

Finally, we demonstrated the applicability of this method to an enantioselective variant (Scheme 4). When the carbazole-based bisoxazoline ligand[7b,19] was evaluated for the reaction between **7a** and **1a**, product **11a** was obtained in 71% ee.[13] This preliminary result demonstrated, at least in principle, the

Scheme 4. Preliminary Result of Asymmetric Reaction



feasibility of an enantioselective protocol based on this method. Further improvement of the reaction efficiency is ongoing.

In conclusion, we developed a linear-selective alkylation of aldehydes using a chromium catalyst and alkylzirconium reagents generated in situ through the hydrozirconation of alkenes. The reaction proceeded under mild conditions at ambient temperature and visible-light irradiation. Linear-alkylated products were selectively obtained from both terminal and internal alkenes. The high chemoselectivity of this reaction makes it applicable to functionalized substrates, including nonprotected hydroxy groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03180.

> Experimental procedures, characterization data for all new compounds, results of optimization and mechanistic studies, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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