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Takai–Utimoto reactions of oxoalkylhalides catalytic in chromium and cobalt

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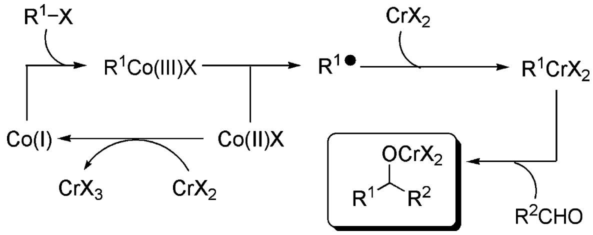
Abstract—The scope of chromium(II)/cobalt(I)-catalyzed Takai–Utimoto reactions was extended to substrates with unprotected reactive functional groups. In the presence of a higher chlorosilane and manganese the first chromium(II)/cobalt(I)-catalyzed version for the coupling of oxoalkylhalides with aldehydes resulted.

The application of chromium(II) reagents in organic chemistry has resulted in a wide variety of methods for the coupling of organic halides with aldehydes.[1,2] These reactions are characterized by mild conditions and an excellent chemoselectivity toward aldehydes in the presence of many other electrophilic functional groups. This has rendered them indispensible in many complex total syntheses. Especially, the 'simple' generation of alkylchromium(III) reagents under cobalt catalysis from unactivated aliphatic halides, the chromium-Barbier-type reaction known as the Takai–Utimoto reaction (Scheme 1),[3] has several advantages over other known methods, for example, for the generation of oxo-alkylorganometallics, that is, 'homoenolates' in a more general meaning, and their subsequent reaction with a carbonyl electrophile (La,[4] Ce,[4] Nd,[4] Sm,[4] Zn,[5] Zn–Cu,[6] Zn–Ti[7]). However, some unfavorable restrictions still persist. So far a version catalytic in chromium was not available for functionalized substrates.



Scheme 1. Putative mechanism for the Takai–Utimoto reaction.

Still the Takai–Utimoto reaction is one of the most efficient, versatile, and mild methods to generate primary homoenolates.[1,3] The chromium(II) reagents do not need to be activated like zinc, and allow the presence of ketones, carboxylic esters, nitriles, and other reactive functional groups.[1] For example, ester chromium alcoholates resulting from 3- or 4-haloalkanoates do not react further with the lactones if worked up carefully, which is not the case for most other methods. A severe drawback of this reaction is its need for stoichiometric quantities of chromium(II) chloride. For the development of diastereo- and enantioselective Takai–Utimoto reactions a version catalytic in both chromium and cobalt is highly desirable. An approach that triggered the development of chromium-catalyzed reactions is based on the application of manganese in combination with scavengers like chlorotrialkylsilanes (Scheme 2).[8] The selectivity profile of the stoichiometric reactions is preserved in this set-up, and resulted in both racemic and enantioselective chromium-catalyzed Nozaki–Hiyama and Nozaki–Hiyama–Kishi reactions.[9] This prompted us to investigate the possibility to adapt this chromium-catalyzed strategy for the synthesis of oxo-functionalized, homoenolate-type units.

Keywords: Catalysis; Alkylchromium; Cobalt; Homoaldol.

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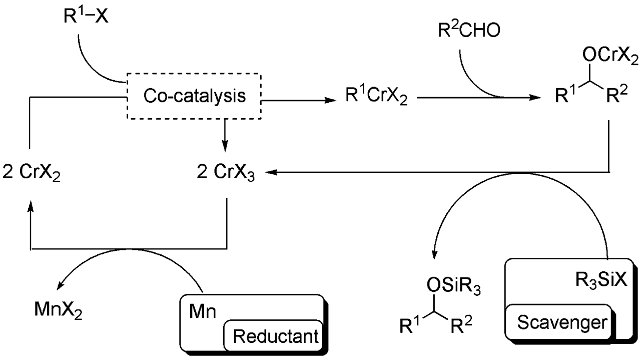


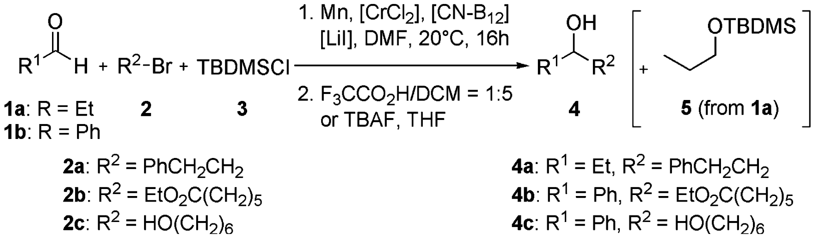
Scheme 2. Putative mechanism for the chromium-catalyzed Takai–Utimoto reaction (the additional cobalt-catalytic cycle—cf. Scheme 1—which takes place in the dotted box is omitted for clarity).

Crucial was the choice of the chlorotrialkylsilane, as the course of the reaction was dramatically influenced by this. TMSCl directed the reaction mainly toward pinacolization[10] instead of the desired product. In contrast, the sterically more demanding TBDMSCl resulted in good yields of the desired product, and largely suppressed pinacolization. The development of the chromium(II)-catalyzed Takai–Utimoto reaction was performed with TBDMSCl, and an aliphatic aldehyde as this combination is less sensitive toward pinacolization.[10] The results are summarized in Table 1. The reaction with an excess of alkyl bromide **2a** afforded alcohol **4a** in 28% yield (entry 1). In spite of the low yield, this result proved that the reaction can be performed catalytic in chromium because the theoretical maximum of 7.5% yield for a stoichiometric process was clearly surpassed. Responsible for the reduced yield compared to the use of stoichiometric amounts of Cr(II) is the formation of TBDMS–ether **5** as a result of a reduction of propanal.[2j,10,11] The application of propanal in a twofold excess versus (2-bromoethyl)benzene resulted only in a small increase in yield (entry 2). To our surprise, (2-bromoethyl)benzene was not fully consumed. Possible explanations might be a thwarted formation of the alkylchromium species or hindered regeneration of chromium(II). The moderate yield is obviously also the consequence of another side reaction, of the aliphatic halide, which was further confirmed when propanal was added slowly (entry 3). In this case bromide **2a** was fully converted, which indicates that TBDMSCl promotes a side reaction. Addition of TBDMSCl over a period of 15 h improved the catalytic reaction significantly and resulted in a complete consumption of (2-bromoethyl)benzene (entry 4).

A Takai–Utimoto reaction of oxo-functionalized alkyl halides, that is, a homoaldol type reaction catalytic in chromium was the ultimate goal believed to be amenable if the chemoselectivity of chromium(III) reactions was also preserved in the catalyzed version. Indeed, carboxylic ester **2b** can be coupled with benzaldehyde to afford alcohol **4b** in a good yield (entry 6). Even an alcohol like in **2c** that normally needs to be protected, can be converted to the desired alcohol **4c** without protection. In the stoichiometric Takai–Utimoto reaction this is quite efficient (entry 7).[2i] However, under the slower catalytic conditions (entry 8) a much lower yield is obtained, probably because 1 equiv of the silylchloride is used up by reaction with the alcohol thereby producing detrimental HCl. Additionally, the high concentration of the alcohol versus chromium(II) chloride might cause problems. During our studies, Kishi reported a similar chromium-catalyzed coupling of aliphatic halides with aldehydes.[9b,g,h] High yields were obtained with a chromium-catalyst loading of 1.0 mol %, however, sensitive functional groups like intramolecular carbonyls were not included in his study.

In conclusion, a Takai–Utimoto reaction catalytic in both chromium and cobalt has been developed, using manganese as bulk reductant, and the chlorotrialkyl-

Table 1. The chromium-catalyzed Takai–Utimoto reaction for the synthesis of homoaldol units[a]



Entry	1	2	1:2:3	Remark	Yield[b] (%)
1	**1a**	**2a**	1.0:1.8:2.4	None	28 (**4a**)
2	**1a**	**2a**	2.0:1.0:2.0	None	37 (**4a**)
3	**1a**	**2a**	2.0:1.0:2.0	Slow addition of **1a**	18 (**4a**)
4	**1a**	**2a**	2.0:1.0:2.0	Slow addition of **3**	56 (**4a**)
5	**1b**	**2b**	Stoichiometric in Cr(II)		>90 (**4b**)
6	**1b**	**2b**	2.0:1.0:2.0	None	59 (**4b**)
7	**1b**	**2c**	Stoichiometric in Cr(II)		60 (**4c**)
8	**1b**	**2c**	2.0:1.0:2.0	None	24 (**4c**)

[a] 15.0 mol % Cr(II); see experimental part for detailed reaction conditions, CN–B_{12} = cyanocobalamine (vitamin B_{12}).

[b] Isolated yield based on minor component.

silane TBDMSCl as scavenger. This reaction set-up afforded the first chromium-catalyzed procedure for the conversion of oxo-functionalized primary aliphatic halides.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.119.

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