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Reaction of secondary and tertiary aliphatic halides with aromatic aldehydes mediated by chromium(II): a selective cross-coupling of alkyl and ketyl radicals

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Dedicated in memoriam to Martin W.G. de Bolster

Abstract

Takai–Utimoto reactions with secondary and tertiary aliphatic halides usually failed according to previous reports. Now, significant improvements could be achieved, and especially secondary aliphatic halides can be coupled to aromatic aldehydes in yields of up to >95%. A variety of processes are competing with the desired one, and thus conditions must be adapted to the nature of the aldehyde as well as the aliphatic halide used, as the outcome of these reactions is strongly affected by the putative radical intermediates.

Keywords: Organometallic catalysis; Chromium alkyls—secondary and tertiary; Catalysis—cobalt; Radical intermediates; Salt effect—lithium iodide; Barbier reaction—Grignard-type reaction

1. Introduction

Synthetic organic chemists have access to a huge variety of methods for aldol reactions.[1] A particularly attractive method is the chromium-Reformatsky reaction, which is mild, and can be performed with polyfunctional substrates.[2,3] However, research efforts toward the development of the homologous version, the 'homoaldol' reaction, are relatively scarce.[4–11] This might be explained by the following reasons (Fig. 1): the generation of the reactive oxo-alkylmetal intermediate requires the formation of a carbanion without the mesomeric stabilization of an electron-withdrawing carbonyl, as is present in aldol reactions, and stabilization of the carbanion is only possible by internal or through space complexation. As a further consequence, the carbonyl is prone to nucleophilic attack by the formed oxo-alkylmetal. In other words, a nucleophilic reagent must be generated in the presence of an electrophile. Furthermore, the initially

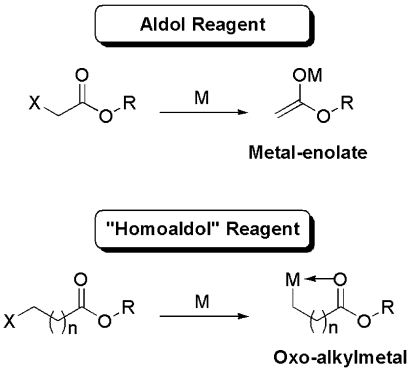

Figure 1. Aldol versus 'Homoaldol'.

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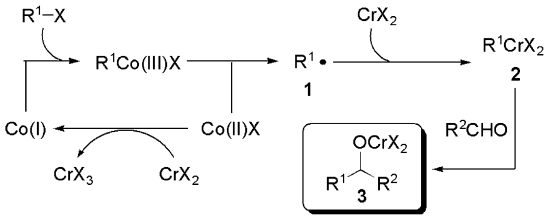
applied reagent and the formed organometallic species are not allowed to possess a strong basic character due to the presence of the acidic α-proton to avoid reprotonation to the thermodynamically more stable enolate isomeric form. Finally, it must react chemoselectively with a second carbonyl compound (usually an aldehyde) as reaction partner.

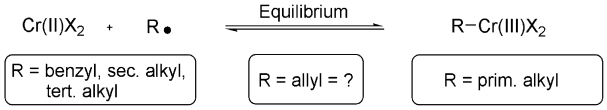
Masked carbonyl substrates were originally used for the synthesis of a 'homoaldol'.[4] Recently, the formation of oxo-alkylmetals was reported for a variety of metals, however, a disadvantage of most of them is that they are prepared by the silyloxycyclopropane route, which limits the scope of the reactions with respect to type (n=1) and substitution pattern,[5] or from methoxyallene, which suffers the same principal disadvantages.[6] The most important current class of reactive oxo-alkylmetals is that of the respective zincalkyls, generated, e.g., from alkenes by Knochel's method.[7] The possibility to generate oxo-alkylmetals by the reaction of a low-valent metal with a halogenated substrate would be generally applicable to a broad range of substrates, many of which are commercially available. Obviously, the high reactivity of organolithium and Grignard reagents do not fulfill the requirements for this reaction. Oxo-alkyllanthanides (La, Ce, Nd, and Sm) have been produced by the direct reaction of the lanthanide metal with ethyl 3-halopropionates.[8] Unfortunately, this method is limited to ketone electrophiles, and direct attack at the carbonyl is a common side reaction. Metallic zinc reacts with functionalized aliphatic iodides to the oxo-alkylzinc reagents. A disadvantage of zinc is its need to be activated, and the resulting oxo-alkylzinc has a low reactivity toward carbonyl electrophiles.[9] Transmetallation of these oxo-alkylzinc reagents into the corresponding zinc–copper couple promotes the coupling to aldehydes in the presence of a Lewis acid.[10] Oxo-alkylzinc reagents are also successfully applied in the transmetallation with titanium(IV) complexes, and the resulting oxo-alkyltitanium reagents couple selectively with aldehydes.[11]

Another attractive possibility to obtain 'homoaldol' products is the extension of the chromium(II)-Barbier or Takai–Utimoto reaction (not to confuse with the related Takai–Utimoto olefination) to oxo-substituted alkylhalides.[2a,3k,12] The chromium(III) oxo-alkyls are generated under cobalt catalysis and the generally accepted mechanism consists of the following steps (Scheme 1): (1) reduction of Co(III) to Co(I) by Cr(II); (2) oxidative addition of an alkyl halide to Co(I) to form the corresponding Co(III) alkyl; (3) homolytic cleavage of the C–Co(III) bond to yield an alkyl radical and Co(II); (4) reductive trapping of the alkyl radical by Cr(II) to generate the alkylchromium species, which then couples with an aldehyde; and (5) reduction of Co(II) to Co(I) by Cr(II) to close the catalytic cycle for Co(I). In principle, a different course, e.g., reduction of Co(III) alkyl by Cr(II) to Co(II) alkyl followed by disproportion to Co(I) and alkyl radical is possible too, and has been discussed previously.[2a,3k]



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

This method is characterized by its tolerance toward most of the common functional groups, and an excellent chemoselectivity for aldehydes. The obtained ester chromium alcoholates usually do not react further to the lactones,[†] which is not the case for most previously mentioned 'homoaldol' methods. The formation of α-methyl branched secondary alcohols is of great importance for the synthesis of polyketide natural products. A method suitable for complex substrates with many other functional groups appears feasible with the excellent chemoselectivity of chromium(II)-mediated reactions, would the use of secondary chromium alkyls become available. Until recently, secondary and tertiary aliphatic halides could not be coupled efficiently by this Barbier-type reaction,[3j] although secondary and even tertiary chromium(III) alkyls have been reported from metal–chromium(III) exchange reactions.[13] The reason for this might be the higher stability of the corresponding radicals. Also, instability of secondary and tertiary alkylchromium complexes toward β-hydride elimination was suspected, but appears unlikely to us as was argued earlier.[2a] However, according to a literature report, the one electron reduction of primary, and especially secondary and tertiary alkyl radicals with chromium(II) should be fast,[14] whereas others report no reactivity of allyl halides with chromium(II) if the oxo-compound as reaction partner is omitted.[15] In any case, only primary alkylchromium(III) was considered sufficiently stable as organometallic species to give useful reactions other than Wurtz-type homocouplings, whereas benzylic, secondary and tertiary alkylchromium(III) intermediates are considered to be in equilibrium with their homolytic cleavage products (Scheme 2).[16] For allylchromium, both preferences are discussed, and their application in Nozaki–Hiyama reactions is widely documented.[2,15] Also, Co(I) reactions to secondary and tertiary alkyl Co(III) complexes are well documented.[17] This supported us to study the behavior of unactivated secondary and tertiary aliphatic halides in the Takai–Utimoto reaction in more detail with the aim to extend the scope of this reaction to secondary and tertiary alkyls.[3j]



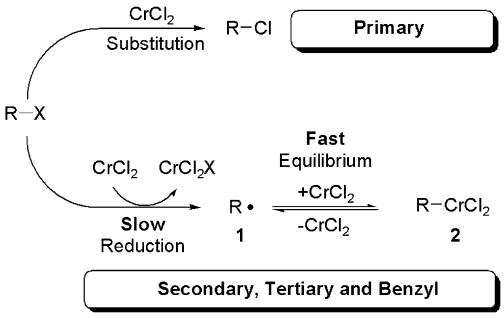
Scheme 2. Formation/homolytic cleavage equilibrium of chromium(III)organyls.

[†] Exceptions were observed by us in compounds exerting an exceptionally strong Thorpe–Ingold effect to close such a ring, which often results in five- or six-membered lactones. However, as in other instances this may also be a work-up artifact, and depending on work-up conditions different proportions of open and ring-closed esters can be found.

2. Results and discussion

The reaction of cyclododecyl iodide with benzaldehyde was presented in the original study of Takai.[12] Cyclododecane and cyclododecene were the only products reported, while the aldehyde remained unchanged. This is an indication that the Cr(II)-mediated reduction of a secondary aliphatic halide is working in principle, but fails in the C–C coupling. Based on our experience,[3] we know that well-stabilized chromium intermediates tend to react sluggishly, but this is strongly influenced by both steric effects and reaction conditions such as solvent or salt effects.[2a,3c]

Isopropyl iodide is the sterically least strained secondary halide and thus was chosen as starting point in a reaction with benzaldehyde. All reactions were performed under similar conditions (DMF, 55 °C, 16 h), using 2.5 equiv of chromium(II) chloride and 10 mol % lithium iodide. The beneficial effect of lithium iodide on many $CrCl_2$ reactions was discussed previously, and enabled, e.g., efficient chromium-Reformatsky processes.[2a,3c] The reaction temperature, cobalt catalyst, lithium iodide amount, and solvent were varied. The results are summarized in Table 1. The reduction potential of chromium(II) chloride is not sufficient to reduce primary aliphatic halides, and a substitution reaction with chloride takes place instead, thereby producing unreactive alkyl chloride (Scheme 3).[12] In contrast, secondary and tertiary aliphatic halides are readily reduced to form the intermediate radical, which is rapidly reduced in a second step by chromium(II) chloride to reversibly form the alkylchromium(III) species.[18] Performing the reaction in the absence of a cobalt catalyst and lithium iodide resulted in a moderate yield of alcohol **6a** (entry 1). The presence of catalytic or stoichiometric amounts of lithium iodide improved the yield, independent of the amount (entries 2 and 3). In the presence of lithium iodide an increased reactivity for chromium(II)-



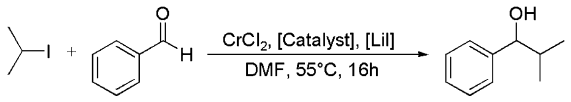
Scheme 3. Primary versus secondary and tertiary aliphatic halides reacting with $CrCl_2$ without cobalt catalyst.

mediated reactions is often observed, especially in THF.[2a,3c] This effect has been explained by the putative formation of better soluble, anionic chromate(II) species, e.g., $Li_2[CrX_4]$. Interestingly, this effect could neither be achieved to the same extent with iodide (NBu_4I) or lithium ($LiBF_4$) ions alone.[19] In DMF, $CrCl_2$ is quite well soluble, and the simple Lewis acid and/or to a minor extent iodide-exchange catalysis might be important too. However, as was shown in the context of our chromium-Reformatsky work, LiI in DMF is a mediocre catalyst at most to exchange chlorides or bromides into alkyliodides, and thus, if such an exchange is required, the addition of excess NaI or KI is significantly better to convert the less reactive halides (back) to iodides.[19]

Substitution of DMF by THF as solvent had a dramatic effect on the outcome of this reaction, as no product was obtained under these conditions (entry 4), most likely caused by the decreased reduction potential of chromium(II) chloride in the presence of THF.[20] Although a cobalt catalyst appears to be unnecessary in principle, we tested its possible influence, also in order to compare it to the original Takai–Utimoto procedure. The result was quite surprising. No additional positive effect was observed with cyanocobalamine (vitamin B_{12}) at standard conditions (55 °C, entry 5). However, alcohol **6a** was obtained in an excellent yield in the presence of cobalt tetramethoxyphenylporphyrin as a cheaper vitamin B_{12} alternative (entry 6).[3j] Surprisingly, at lower temperature both catalysts exerted an opposite effect (entries 7 and 8). Now, the reaction with cyanocobalamine (vitamin B_{12}) resulted in an excellent yield, and a strong decrease was observed for the cobalt tetramethoxyphenylporphyrin. At least two conclusions can be drawn from this: (1) the cobalt catalyst is at least partially involved in the reaction of secondary aliphatic halides and can have a limited beneficial effect; and (2) the cobalt dependent transformations (Scheme 1) of cyanocobalamine (vitamin B_{12}) and cobalt tetramethoxyphenylporphyrin are differently influenced by the reaction temperature. The reason may be found in differences in nucleophilicity, and in the reduction potentials of the various cobalt oxidation states, which are known to be important,[3i,12] obviously resulting in different kinetic temperature profiles, and maybe also in solubility.

The effect of the halide on the coupling of the isopropyl unit to benzaldehyde needed to be studied next. One might argue that the presence of lithium iodide in DMF will always,

Table 1
Reactivity of the secondary model substrate isopropyl iodide with benzaldehyde[a,b]

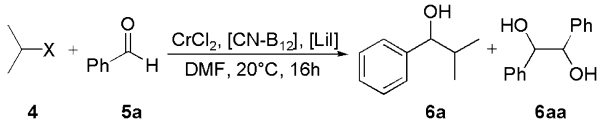


4a 5a 6a

Entry	Cobalt catalyst	Remark	Yield[c] (%)
1	None	No LiI	52
2	None	LiI (10 mol %)	72
3	None	LiI (250 mol %)	70
4	None	THF as solvent	0
5	Vitamin B_{12}[d]	55 °C	70
6	Co(porphin)[e]	55 °C	>95
7	Vitamin B_{12}[d]	20 °C	>95
8	Co(porphin)[e]	20 °C	52

[a] $CrCl_2$ (2.50 equiv), cobalt catalyst (5 mol %), LiI (10 mol %), benzaldehyde (1.00 equiv), and isopropyl iodide (1.10 equiv).
[b] Reaction without isopropyl iodide resulted in 68% pinacol coupling product **6aa** (presented in Table 2).
[c] Isolated yield based on benzaldehyde.
[d] Cyanocobalamine.
[e] Cobalt tetramethoxyphenylporphyrin.

Table 2
The influence of the halide on the reaction with benzaldehyde[a]



4 5a 6a 6aa

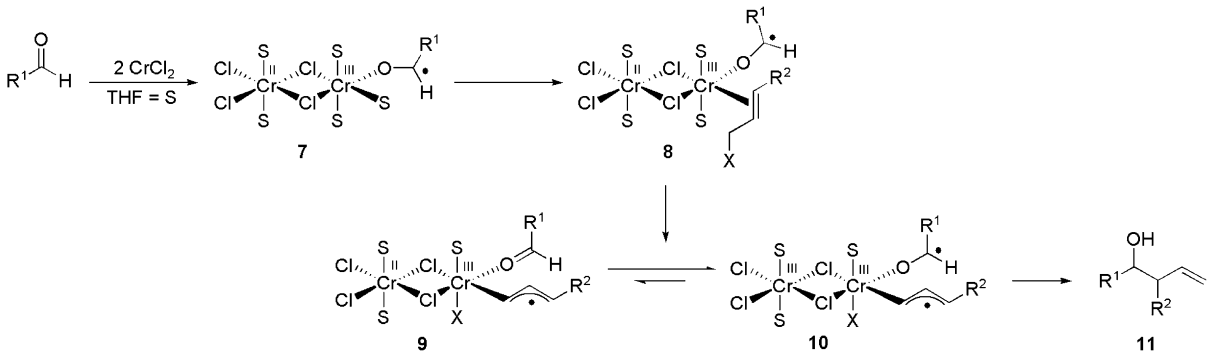
Entry	X	Yield[b] (%)
1	I (**4a**)	>95
2	Br (**4b**)	44
3	Cl (**4c**)	0[c]

[a] $CrCl_2$ (2.50 equiv), cyanocobalamine (vitamin B_{12})=CN-B_{12} (5 mol %), LiI (10 mol %), benzaldehyde (1.00 equiv), and isopropyl halide (1.10 equiv).
[b] Isolated yield based on benzaldehyde.
[c] Side product: 52% pinacol coupling product **6aa**.

via nucleophilic substitution catalysis, deliver isopropyl iodides (and/or chlorides from $CrCl_2$). But this process, although fast with higher alkalihalides (NaI, KI), is very slow with LiI. Only minimal exchange is observed if secondary halides are reacted with lithium iodide in DMF, in contrast to NaI. The reactions were performed under identical conditions (DMF, 55 °C, 16 h), using 2.5 equiv chromium(II) chloride, 5 mol % cyanocobalamine (vitamin B_{12}), and 10 mol % lithium iodide. The results are summarized in Table 2. Importantly, the Takai–Utimoto reaction is highly sensitive to the rate at which the alkylchromium species is generated.[12] The yield of alcohol **6a** was strongly reduced in the case of the bromide (entry 2), and no product **6a** was obtained when isopropyl chloride was applied (entry 3). The reaction with chloride **4c** exclusively resulted in the formation of pinacol coupling product **6aa**.

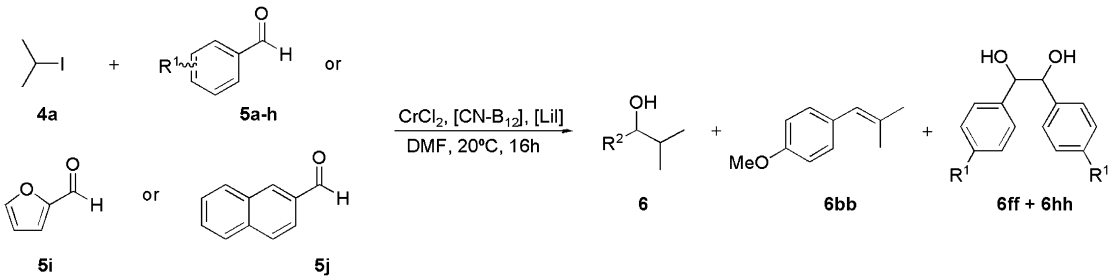
To place these results in a broader perspective, it is useful to discuss the mechanistic background of chromium(II)-mediated reactions. Most researchers relate their results to the principle of the mechanisms presented in Schemes 1 and 2. The initially formed radical **1** is reduced in a second step by chromium(II) chloride to generate the organochromium species **2**, which contains an alkyl group of carbanionic nature. A consecutive nucleophilic attack on the aldehyde affords chromium alcoholate **3**.[21] An alternative mechanism (Scheme 4) was proposed by Mulzer for the Nozaki–Hiyama reaction, the addition of allyl halides to aldehydes, using rather special, oxygen-rich substrates, which may exert a special behavior.[15] Mulzer proposed a single electron transfer to the aldehyde under formation of ketyl radical **7**, which transfers its unpaired electron to the coordinated allyl halide in intermediate **8**. A second single electron transfer by chromium(II) to the aldehyde affords diradical **10**, which couples to the desired product **11**. Questionable is the formation of ketyl radical **7**, as this should give pinacol coupling byproduct, which is not commonly observed in Nozaki–Hiyama reactions to any noteworthy extend. Also does it contradict the very low reactivity of ketones in Nozaki–Hiyama reactions. Evenmore, allyl intermediate **9** is also formed in the absence of aldehyde, and this approach has been used in Wurtz-type dimerization reactions,[22] whereas Mulzer reports instances where the omission of aldehydes prevents reaction.[15] Unfortunately, there is no conclusive experimental proof available for any of these suggested mechanisms to date, and indeed several mechanisms may apply dependent on the nature of the alkyl halide, the chromium salt and its ligands (incl. solvent), and maybe also of the oxo-compound. The principle difference is the nature of the intermediate organochromium(III) species, which may be anionic or radical, depending on the type of organic halide used. The radical character of alkylchromium(III) complexes is supported by the addition reactions to stabilized alkenes,[14,23] whereas anion stabilization as in Reformatsky reactions favors anionic behavior.[2a,3] Furthermore, the likelihood of a radical based mechanism for benzyl, secondary and tertiary alkyl halides is higher than for primary alkyl and allyl halides as allyl radicals are more effectively trapped by chromium(II) chloride.[18]

With these mechanistic implications in mind, we started to study the role of the aldehyde in the reaction with isopropyl iodide, and the results are summarized in Table 3. Substituents on the aromatic ring of benzaldehyde exerted a dramatic effect on the yield of alcohol **6**. Good yields of alcohols **6b** and **6c** were obtained with *p*-methoxy benzaldehyde and *m*-methoxy benzaldehyde, respectively (entries 2 and 3). The moderate yield with *o*-methoxy benzaldehyde **5d** implies that the reaction is highly sensitive toward steric interactions, a common observation in Cr(II)-mediated reactions (entry 4).[2] Surprisingly, a substituent that is expected to affect the electrophilicity of the aldehyde only to a minor extent, like a methyl, resulted in a strongly reduced yield (entry 5). Electron-withdrawing substituents like a bromo or a fluoro or a trifluoromethyl favor, in different degrees, the formation of pinacol coupling products (entries



Scheme 4. Alternative mechanism for $CrCl_2$-mediated reactions.

Table 3
The reaction of isopropyl iodide with aromatic aldehydes[a,b]



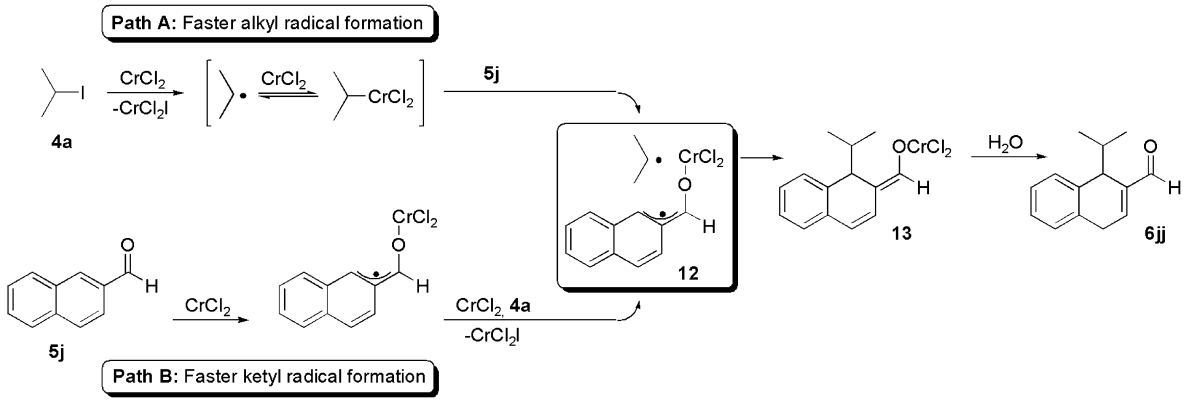
Entry	R^1	Product	Yield[c] (%)
1	H (**5a**)	**6a**	>95
2	4-OMe (**5b**)	**6b**	70[d]
3	3-OMe (**5c**)	**6c**	63
4	2-OMe (**5d**)	**6d**	37
5	4-Me (**5e**)	**6e**	55
6	4-Br (**5f**)	**6f**	17[e]
7	4-F (**5g**)	**6g**	51[f]
8	4-CF_3 (**5h**)	**6h**	0[g]
9	Furan-2-yl (**5i**)	**6i**	39
10	2-Naphthaldehyde (**5j**)	**6j**	37+11[h]
11[i]	2-Naphthaldehyde (**5j**)	**6j**	29+36[j]

[a] $CrCl_2$ (2.50 equiv), cyanocobalamine (vitamin B_{12})=CN-B_{12} (5 mol %), LiI (10 mol %), aldehyde (1.00 equiv), and isopropyl iodide (1.10 equiv).
[b] Reactions of other substrate combinations than isopropyl iodide/benzaldehyde were not optimized for yield.
[c] Isolated yield based on aldehyde.
[d] Isolation of 5% **6bb**, dehydrated **6b**.
[e] Isolation of 31% pinacol coupling product **6ff**.
[f] Pinacol coupling product detected by GC–MS of the crude product, but not isolated.
[g] Isolation of 61% pinacol coupling product **6hh**.
[h] Isolation of 11% **6jj** (presented in Scheme 5).
[i] $CrCl_2$(TMEDA) instead of $CrCl_2$.
[j] Isolation of 36% **6jj** (presented in Scheme 5).

6–8). Unfortunately, aliphatic aldehydes were completely unreactive under these reaction conditions. Furan-2-yl **5i** was coupled in moderate yield (entry 9). Obviously, the aldehyde partner needs to have the proper redox or radical stabilizing potential in order to allow good yield, e.g., through conjugation to an aromatic system.

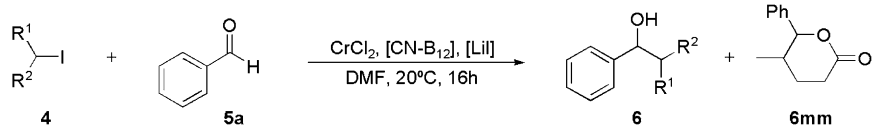
This extreme sensitivity of the reaction toward small changes in the aldehydes' electron density and/or radical stabilization properties implies the involvement of a radical intermediate. The outcome of the reaction appears to depend on the rate at which the ketyl radical is formed. A slow generation might favor a competitive homo-Wurtz-coupling reaction of the halide alone, and a fast generation favors the homo-pinacol coupling reaction of the aldehyde only. Probably, benzaldehyde **5a** provides the optimum kinetics for the hetero-cross-coupling under the standard conditions used for this study (entry 1).

Disappointing was the yield with 2-naphthaldehyde. However, this is caused by the competing generation of the mechanistically highly interesting side product **6jj** (Scheme 5). TMEDA and other electron-donating amine ligands are known to increase the reduction potential of chromium(II) chloride.[20]



Scheme 5. Proposed mechanism for the formation of aldehyde **6jj**.

Table 4
The reaction of secondary aliphatic iodides with benzaldehyde[a,b]



Entry	R^1	R^2	Product	Yield[c] (%)
1	Me	Me (**4a**)	**6a**	>95
2	Et	Me (**4d**)	**6k**	44
3	$-(CH_2)_5-$ (**4e**)		**6l**	58
4	$(CH_2)_2CO_2Me$	Me (**4f–Br**)[d]	**6m**[e]	10[d]

[a] $CrCl_2$ (2.50 equiv), cyanocobalamine-vitamin B_{12}=CN-B_{12} (5 mol %), LiI (10 mol %), benzaldehyde (1.00 equiv), and aliphatic iodide (1.10 equiv).
[b] Reactions of other substrate combinations than isopropyl iodide/benzaldehyde were not optimized for yield.
[c] Isolated yield based on benzaldehyde.
[d] Bromide used instead of iodide.
[e] Alcohol **6m** is easily transformed to lactone **6mm** with *p*-TsOH in benzene.

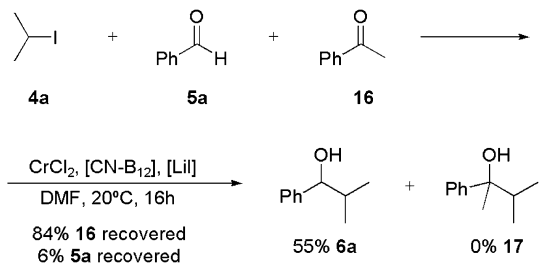
Using $CrCl_2$(TMEDA) instead of $CrCl_2$ resulted in an improved yield of 36% of aldehyde **6jj** (entries 10 and 11). A direct nucleophilic attack to the naphthyl core rather than to the aldehyde position can be considered highly unlikely for any isopropylanion based species, although an 'ene-type' reaction to **13** is feasable too. Considering a radical mechanism similar to those of Mulzer[15] and Takai,[18] or as proposed for Sm(II) reactions,[24] one might speculate that product **6jj** is formed through diradical intermediate **12**. This generalized mechanism can also explain the formation of homocoupling products and why the outcome of these radical reactions is extremely sensitive to the structure of both substrates. In addition to the mechanistic insight, this reaction also has synthetic implications, as all other organometallic reagents will react with the aldehyde exclusively, and not by breaking up the aromatic systems.

The results with sterically more demanding secondary aliphatic iodides are summarized in Table 4. Application of *sec*-butyl iodide or cyclohexyl iodide both resulted in moderate yields of alcohols **6k** and **6l**, respectively (entries 2 and 3). It is known that the stability of alkylchromium species decreases with an increasing chain-length of the alkyl group.[13b] Thus the persistence of aldehyde after incomplete reaction with bulkier iodides instead of pinacol coupling might be explained by a faster generation or greater stability of the alkyl radical compared to the ketyl radical, and as a consequence this undergoes radical homocoupling reactions like the Wurtz-type dimerization. The effect of a sterically more demanding secondary aliphatic iodide is the same as that obtained by rendering the aldehyde less reactive (cf. Table 3, entry 4). The biggest synthetic value of the Takai–Utimoto reaction is its tolerance to a wide variety of functional groups, including esters (homoenolates). Thus, bromide ester substrate **4f–Br** was tested, but resulted in a poor yield of hydroxy ester **6m** (entry 4), which was even lower when the iodide of **4f** was applied. Hydroxy ester **6m** could be isolated, but spontaneously reacted further to lactone **6mm** if kept at room temperature or if subjected to acidic (work-up) conditions.

The reaction of *tert*-butyl halides with benzaldehyde was studied as well (Scheme 6). The reaction with Cr(II) should generate quite stable, sterically demanding, and thus unreactive radicals. This should be seen in the outcome of these reactions. Indeed, low yields were obtained with iodide **14a** (7%) and bromide **14b** (19%), and application of chloride **14c** did not result in the formation of alcohol **15**. Instead competing pinacol coupling of benzaldehyde to product **6aa** occurred in high yield (up to 73% yield). Obviously, the side reactions dominate when the organochromium species is unable to react further because the radical is too stabilized or sterically hindered to participate in cross-coupling or Wurtz-homocoupling.

The typical chemoselectivity of Takai–Utimoto reactions toward aldehydes in the presence of a ketone was also observed for the reaction with secondary aliphatic halides. Only alcohol **6a** was obtained from the reaction of isopropyl iodide with benzaldehyde in a competition experiment with acetophenone (Scheme 7). However, the yield of alcohol **6a** is lower when compared to an experiment without acetophenone (Table 2, entry 1). A possible explanation might be found in the competitive formation of the acetophenone ketyl and benzaldehyde ketyl radicals. The isopropylchromium reagent cannot react fast with the bulky acetophenone or the derived radical, and this might decrease the amount of either reduction equivalents or

Scheme 6. Takai–Utimoto reactions with tertiary aliphatic halides.



Scheme 7. Competition experiment between benzaldehyde (1.00 equiv) and acetophenone (1.00 equiv) in the Cr(II)-mediated reaction with isopropyl iodide (1.10 equiv).

benzaldehyde ketyl radical, respectively. This might enhance side reactions of the isopropyl radical.

3. Conclusion

In conclusion, the Takai–Utimoto reaction can be used to couple secondary and to some extent tertiary aliphatic halides with aromatic aldehydes. Ketones and aliphatic aldehydes are not reactive. The outcome of the reactions are, however, very sensitive toward small changes in the alkyl halide as well as in the aldehyde and the conditions, which need to be optimized for each system. This behavior can be explained by a mechanism in which an alkyl radical and a ketyl radical selectively cross-couple to afford the product. A better stabilized radical at either end results in a shift from cross-coupling to homocoupling, i.e., with electron-rich aldehydes' reactivity leans toward reactions of the alkyl radical, like the Wurtz coupling, whereas with either an alkyl halide that generates a less reactive alkyl radical or an electron poor aldehyde the pinacol coupling reaction is favored. This version of the Takai–Utimoto reaction principally allows the synthesis of secondary 'homoaldols', and is chemoselective toward aldehydes, important features for polyketide synthesis applications, but conditions need to be optimized to allow useful yields. These observations might result in a better understanding of the chromium(II)-mediated reactions of radical stabilizing alkylchromium species like secondary, tertiary, allylic, or benzylic ones, in general.

4. Experimental

4.1. General remarks

All reactions were carried out under an argon atmosphere in flame-dried glassware using standard syringe and septa techniques. The commercial reagents **4a–e**, **5b–j**, **14a–c**, **16**, cyanocobalamine (vitamin B_{12}), cobalt tetramethoxyphenylporphyrin, lithium iodide, chromium(II) fluoride, TMEDA, and chromium(II) chloride (99.9% from Strem Chemicals) were used as purchased. Substrate **4f** was synthesized according to a literature procedure, and its purity was determined by ^{1}H NMR.[25] THF was distilled from potassium/benzophenone. Absolute DMF was purchased from Fluka. Benzaldehyde **5a** was distilled from potassium hydride. Spectral data of the known compounds **6a**,[26] **6aa**,[27] **6b**,[28] **6bb**,[29] **6e**,[30] **6ff**,[31] **6hh**,[32] **6i**,[33] **6j**,[34] **6k**,[35] **6l**,[36] **6mm**,[37] and **15**[38] were in accordance with the literature data. Thin-layer chromatography was carried out on Merck silica 60/F-254 aluminum-backed plates. Flash chromatography was performed using Merck silica gel 60 (40–60 μm). NMR spectra were recorded in $CDCl_3$. Chemical shifts δ are quoted in parts per million (ppm), and coupling constants J are given in hertz (Hz).

4.2. Syntheses

4.2.1. General procedure for the reaction of secondary and tertiary aliphatic halides with chromium(II) chloride and aldehydes/ketones

To chromium(II) chloride (200 mg, 1.63 mmol, 2.50 equiv), cyanocobalamine (vitamin B_{12}) (44 mg, 33 μmol, 0.05 equiv), and LiI (8.7 mg, 65 μmol, 0.10 equiv) was added 2.5 ml DMF under vigorous stirring. After a few minutes, the aldehyde/ketone (0.65 mmol, 1.00 equiv) and aliphatic halide (0.72 mmol, 1.10 equiv) were added in this order. The resulting mixture was stirred for 16 h at 20 °C, and the reaction was quenched with 2.5 ml water. The water layer was extracted with diethyl ether, and the combined organic fractions were washed with H_2O and aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography, usually with a hexane/diethyl ether mixture as eluent.

4.2.2. 1-(3-Methoxy-phenyl)-2-methyl-propan-1-ol (*6c*)

Flash chromatography afforded **6c** as a colorless oil in 63% yield. R_f=0.24 (hexane/diethyl ether=80:20); ^{1}H NMR (400 MHz) δ 7.25 (dd, J=8.2, 8.2, 1H), 6.90–6.87 (m, 2H), 6.81 (m, 1H), 4.33 (d, J=7.0, 1H), 3.81 (s, 3H), 1.95 (m, 1H), 1.85 (br s, 1H), 1.00 (d, J=7.0, 3H), 0.81 (d, J=6.6, 3H); ^{13}C NMR (100 MHz) δ 159.5 (C), 145.4 (C), 129.1 (CH), 118.9 (CH), 112.8 (CH), 112.0 (CH), 79.9 (CH), 55.2 (CH_3), 35.2 (CH), 19.1 (CH_3), 18.2 (CH_3); IR (neat): 3430 (w), 2958 (w), 789 (w), 702 (w) cm^{-1}; HRMS-EI (70 eV) *m/z* calcd for $C_{11}H_{16}O_2$ (M^+) 180.1150, found 180.1158. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.10; H, 8.54.

4.2.3. 1-(2-Methoxy-phenyl)-2-methyl-propan-1-ol (*6d*)

Flash chromatography afforded **6d** as a colorless oil in 37% yield. R_f=0.20 (hexane/diethyl ether=85:15); ^{1}H NMR (400 MHz) δ 7.26–7.21 (m, 2H), 6.94 (dd, J=7.4, J=7.4, 1H), 6.88 (d, J=8.2, 1H), 4.49 (d, J=7.4, 1H), 3.84 (s, 3H), 2.38 (br s, 1H), 2.06 (m, 1H), 1.03 (d, J=6.6, 3H), 0.79 (d, J=7.0, 3H); ^{13}C NMR (100 MHz) δ 156.6 (C), 131.5 (C), 128.2 (CH), 128.1 (CH), 120.5 (CH), 110.5 (CH), 77.2 (CH), 55.2 (CH_3), 34.1 (CH), 19.6 (CH_3), 18.5 (CH_3); IR (neat): 3433 (w), 2958 (m), 1237 (s), 754 (s) cm^{-1}; HRMS-EI (70 eV) *m/z* calcd for $C_{11}H_{16}O_2$ (M^+) 180.1150, found 180.1159.

4.2.4. 1-(4-Bromo-phenyl)-2-methyl-propan-1-ol (*6f*)

Flash chromatography afforded **6f** as a colorless oil in 17% yield. R_f=0.13 (hexane/diethyl ether=85:15); ^{1}H NMR (400 MHz) δ 7.46 (d, J=8.2, 2H), 7.19 (d, J=8.2, 2H), 4.35

(d, J=6.6, 1H), 1.91 (m, 1H), 1.80 (br s, 1H), 0.97 (d, J=6.6, 3H), 0.80 (d, J=6.6, 3H); ^{13}C NMR (100 MHz) δ 142.5 (C), 131.21 (CH), 128.3 (CH), 121.1 (C), 79.2 (CH), 35.2 (CH), 18.8 (CH_3), 18.0 (CH_3); IR (neat): 3396 (w), 2959 (m), 908 (w), 826 (w), 782 (w), 734 (m) cm^{-1}; HRMS-EI (70 eV) *m/z* calcd for $C_{10}H_{13}BrO$ (M^+) 228.0150, found 228.0145.

*4.2.5. 1-(4-Fluoro-phenyl)-2-methyl-propan-1-ol (**6g**)*

Flash chromatography afforded **6g** as a colorless oil in 51% yield. R_f=0.15 (hexane/diethyl ether=85:15); ^{1}H NMR (300 MHz) δ 7.27 (dd, J=8.6, J=5.5, 2H), 7.02 (dd, J=8.6, 8.6, 2H), 4.35 (d, J=6.8, 1H), 1.92 (m, 1H), 1.80 (br s, 1H), 0.99 (d, J=6.6, 3H), 0.78 (d, J=6.8, 3H); ^{13}C NMR (75.50 MHz) δ 161.9 (d, J=244, C), 139.1 (d, J=3.0, C), 128.0 (d, J=8.3, CH), 114.9 (d, J=21.1, CH), 79.3 (CH), 35.4 (CH), 19.0 (CH_3), 18.3 (CH_3); IR (neat): 3420 (w), 2960 (w), 1604 (w), 1510 (m), 842 (w), 776 (w) cm^{-1}; MS-EI *m/z*: 168.1 (5%, M^+), 125.0 (100%, $M^+-C_3H_7$).

*4.2.6. 1-Isopropyl-1,4-dihydro-naphthalene-2-carbaldehyde (**6jj**)*

Flash chromatography afforded **6jj** as a colorless oil in 36% yield. R_f=0.28 (hexane/diethyl ether=90:10); ^{1}H NMR (400 MHz) δ 9.60 (s, 1H), 7.22–7.18 (m, 4H), 7.14 (dd, J=2.3, 5.9, 1H), 3.86 (m, 1H), 3.73 (m, 1H), 3.59 (m, 1H), 1.96 (m, 1H), 0.91 (d, J=7.0, 3H), 0.66 (d, J=6.6, 3H); ^{13}C NMR (100 MHz) δ 192.6 (CH), 149.7 (CH), 144.4 (C), 136.5 (C), 134.1 (C), 129.6 (CH), 127.7 (CH), 126.2 (CH), 126.1 (CH), 43.4 (CH), 35.0 (CH), 32.6 (CH_2), 20.7 (CH_3), 18.7 (CH_3); IR (neat): 2960 (m), 1685 (s), 791 (w), 740 (m) cm^{-1}; MS-EI *m/z*: 198.1 (100%, M^+-H_2).

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Supplementary data

Supplementary data and representative spectra associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.12.039.

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