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Synthesis of α-alkenyl-β-hydroxy adducts by α-addition of unprotected 4-bromocrotonic acid and amides with aldehydes and ketones by chromium(II)-mediated reactions

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The regioselective and diastereoselective chromium(II)-mediated reactions of 4-bromocrotonic acid or amides with aldehydes and ketones can proceed without the need to protect protic sites to generate the respective α-alkenyl-β-hydroxy adducts, i.e. formally the addition of the α-anion of a carboxylic acid or amide to an oxo-compound is featured.

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Keywords: allyl and enolate complexes; regio- and chemoselectivity; chromium; diastereoselectivity; Grignard-type reaction

Introduction

The application of chromium(II) reagents in organic chemistry has resulted in a wide variety of methods for coupling organic halides with aldehydes.[1] These reactions are characterized by mild conditions and an excellent chemoselectivity towards aldehydes in the presence of many other electrophilic functional groups. This has rendered them indispensable in many complex total syntheses such as the preparation of viridiofungin derivatives.[2] Particularly attractive methods are the chromium(II)-mediated Nozaki–Hiyama–Kishi and Reformatsky reactions which can be performed with polyfunctional substrates.[1,3] For instance, α-halo oxazolidones (Evans-type imides) result in high diasteroselectivity and enantioselectivity by chromium(II)-mediated Reformatsky reactions that allowed the development of an innovative method towards the total synthesis of tonantzitlolone and epothilones.[1,4] Also, α-halo ketones, esters, nitriles, *N,N'*-dialkylamides and 4-bromocrotonates can be coupled to aldehydes in excellent yields.[1,4] The Nozaki–Hiyama–Kishi reaction was recently used in the synthesis of enantioenriched α-exo-methylene γ-butyrolactones, in a two-step sequence, using chromium catalysis.[5]

4-Bromocrotonate derivatives are believed to react more readily through allylchromium(III) intermediates, instead of the thermodynamically favored chromium(III) dienolate (Scheme 1). Thus, the functional group attached to the allylchromium(III) species might be of secondary importance. Therefore, a carboxylic acid might produce allylchromium(III) in the course of the reaction which does not equilibrate fast with chromium(III) dienolate. Furthermore, the extraordinary stability of alkylchromium(III) complexes to hydrolysis enables carbon–carbon coupling in the presence of water,[1,6] suggesting a slow protonation of the allylchromium(III) adduct by inter- or intramolecular proton transfer in comparison with carbonyl electrophilic reactions.

Generally, aldol reactions of crotonate derivatives under Reformatsky conditions result in a mixture of α- and predominantly γ-substituted products. For example, preparation of zinc carboxylates by coupling of allylzinc bromide with several electrophiles gave the respective allylic alcohols in 21–81% yield with 12–100% γ-regioselectivity.[2] For the α-products, a mix of the *syn* and *anti* diastereoisomers was obtained.[2,7]

Alternatively, crotonic acids can be transformed into their dienolates by treatment with strong bases such as lithium naphthalide[8] or lithium diisopropylamide.[9] Subsequent reactions with aldehydes generate mainly the α-substituted alcohol (50–94%) in low to moderate yields (9–50%), but ketones still give predominantly γ-products.[6]

Hence, halo-crotonic acids must be transformed into their corresponding esters to favor *syn* allylic carbonyl compounds by α-addition.[2] This protection–deprotection strategy involves two extra steps if unprotected alkenyl-β-hydroxy acid or amide is desired.

Continuing our interest in the development of chemo- and diastereoselective methodologies based on chromium(II)/(III)

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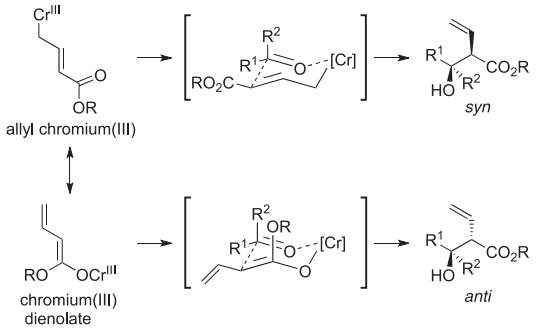


Scheme 1. Chromium(III) intermediates (R = H or alkyl)

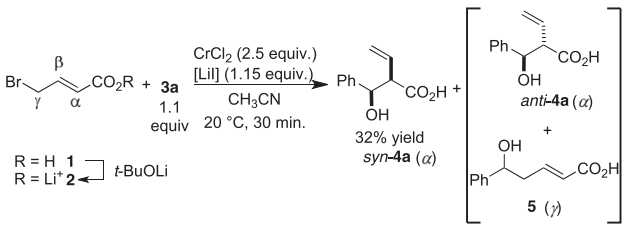
species,[10] we herein report the direct coupling of 4-bromocrotonic acid with aldehydes and ketones by chromium (II)-mediated Nozaki–Hiyama–Kishi reactions to give exclusively the *syn* α-alkenyl-β-hydroxy adducts, without the necessity of protection such as with a methyl- or silylester[1,11] or Zn salt.[12] Furthermore, Nozaki–Hiyama–Kishi and Reformatsky reactions of the corresponding primary and secondary amides are reported.

Results and discussion

Influenced by the literature, we initially assumed the requirement of decreasing the acidity of the substrate in the reaction medium in order to avoid protonation of any prospective allylchromium(III) intermediate and to favor α-addition. Therefore, we started our study by transforming 4-bromocrotonic acid (**1**) to its respective lithium salt (lithium 4-bromocrotonate, **2**). Treatment of **1** with lithium *t*-butoxide in *t*-butanol gave **2** in 99% yield.[13] This salt was then subjected to the chromium(II)-mediated Nozaki–Hiyama–Kishi reaction with benzaldehyde (**3a**) in acetonitrile to generate exclusively the α-*syn*-aldol product *syn*-**4a** in 32% yield after 0.5 h (Scheme 2). Apparently, the reaction follows an anionic path rather than a radical one via ketyl/allyl radical cross-coupling, since no typical radical byproducts were found, like dimers of the oxo-compound.[14]

It is postulated that the *trans*-allylchromium(III) species does not equilibrate with the chromium(III) dienolate and attacks the *si* benzaldehyde (**3a**) face in a Zimmerman–Traxler transition state (ZT-TS) model to generate the *syn*-aldol adduct exclusively (Scheme 1).

Neither the γ-alcohol **5** nor the *anti*-allylic carboxylic acid *anti*-**4a** were observed in the crude ^{1}H NMR spectrum. Despite the low isolated yield of the desired α-adduct *syn*-**4a**, the result is quite inspiring since this diastereoselectivity has not been accomplished with any other Nozaki–Hiyama–Kishi reaction. The low yield may be explained by the strong chelating character of the product as depicted in Fig. 1. Since chromium(III) is difficult to separate from



Scheme 2. Chromium(II)-mediated Nozaki–Hiyama–Kishi reaction of 4-bromocrotonate (**2**) with benzaldehyde (**3a**) to *syn*-**4a**. Isomers in brackets were not found (NMR) starting from lithium salt **2**

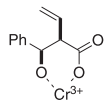
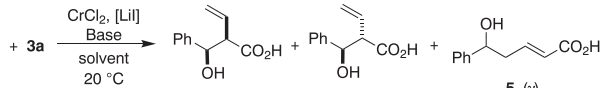


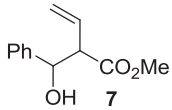
Figure 1. Dianionic Cr(III) chelate complex with the aldolate–carboxylate product

its ligands, the chelation might provoke considerable product loss during protonation and aqueous work-up.

Surprisingly, the *syn*-**4a** aldol adduct was isolated in similar yields switching from salt **2** to its original acid **1**. This result was achieved by slowly adding solid acid **1** to an aldehyde/chromium(II) chloride suspension in aprotic solvent, thus keeping the proton concentration in the medium low. It is also noted that acetonitrile gives slightly better yield than tetrahydrofuran (THF) (Table 1, entries 1 and 2), together with total regioselectivity. Based on these preliminary results, instead of transforming **1** into its respective lithium salt **2**, simply adding a removable organic base might further improve the result. Hence, **1** was reacted with **3a** in the presence

Table 1. Chromium(II)-mediated Nozaki–Hiyama–Kishi reaction of 4-bromocrotonic acid (**1**) with benzaldehyde (**3a**) in the presence of tertiary amines[a]



Entry	Base	Solvent	Time (h)	Ratio α:γ	Ratio α_{syn}:α_{anti}	Yield (%)[b]
1	—	**CH_3CN**	**2.00**	**100:0**	**95:5**	**42**
2	—	THF	2.00	95:5	>97:3	31
3	**DIPEA**	**THF**	**1.00**	**>97:3**	**>97:3**	**62**
4	DIPEA	CH_3CN	1.00	>95:5	>95:5	56
5	DIPEA	DMF	1.00	—[c]	—[c]	32[d]
6	DIPEA	CH_2Cl_2	1.00	85:15	>95:5	27
7	DIPEA	Et_2O	1.00	—[c]	—[c]	11
8	Et_3N	THF	0.50	59:41	85:15	24
9	TMEDA	THF	0.50	—	—	49
10	DBU	THF	0.50	—[e]	—[e]	—[e]
11	(−)-quinidine	THF	1.00	94:6	96:4	64
12	(−)-sparteine	THF	1.00	>98:2	95:5	67
13	(−)-sparteine	CH_3CN	1.00	96:4	96:4	59
14[f]	—	CH_3CN	0.50	 > 97:3	92:8	78[f]

[a]For specific details and exact amounts refer to the experimental section. Product distributions are based on crude product (hydrolysis and filtered through silica to remove paramagnetic chromium)

[b]Isolated yield of isomeric mixture based on minor component

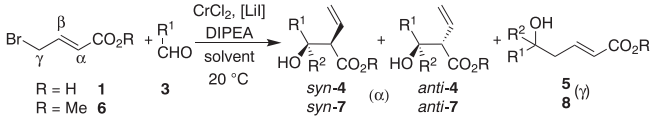
[c]Chromium(III) traces in the crude product caused line broadening in the ^{1}H NMR spectrum not allowing determination of the product distribution

[d]Work-up resulted in product loss

[e]Decomposition of **1**

[f]Reference reaction of methyl 4-bromocrotonate (**6**) to main product **7** (Table 2) according to Schrekker *et al*[10]

Table 2. Chromium(II)-mediated Nozaki–Hiyama–Kishi reaction of 4-bromocrotonic acid (**1**) with aldehydes and ketones (**3a–e**) in the presence of DIPEA. Comparison with methyl ester **6** as starting material[a]



Entry	3	R^1	R^2	Products	R	Solvent	Time (h)	α:γ	α_{syn}:α_{anti}	Yield (%)[b]
1	**a**	Ph	H	**4, 5**	H	THF	0.5	>97:3	>97:3	62
2	**b**	Et	H	**4, 5**	H	THF	1.0	>99:1	>99:1	88
3[c]	**b**	Et	H	**7, 8**	Me	CH_3CN	2.0	89:11	82:18	64
4	**c**	*i*-Pr	H	**4, 5**	H	THF	0.5	100:0	>99:1	73
5[c]	**c**	*i*-Pr	H	**7, 8**	Me	*i*-PrCN	3.0	91:9	90:10	56
6	**d**	Et	Me	**4, 5**	H	THF	2.0	100:0	60:40[d]	68
7	**d**	Et	Me	**4, 5**	H	CH_3CN	2.0	100:0	60:40[d]	44
8[c]	**d**	Et	Me	**7, 8**	Me	Butanone	1.0	95:5	60:40	95
9	**e**	Ph	Me	**4, 5**	H	THF	2.0	100:0	50:50[d]	7
10	**e**	Ph	Me	**4,5**	H	CH_3CN	1.0	100:0	85:15[d]	32
11[c]	**e**	Ph	Me	**7, 8**	Me	CH_3CN	1.0	95:5	65:35	46

[a]For specific details and exact amounts refer to the experimental section

[b]Yield of isomeric mixture based on minor component

[c]Reference reaction of methyl 4-bromocrotonate (**6**) to main product **7** according to Wessjohann and Scheid[1]

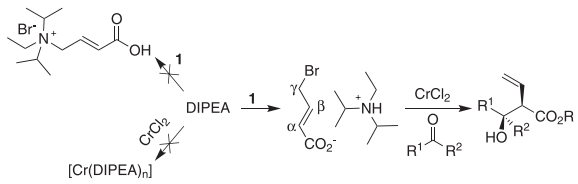
[d]Assignment of diastereomers is based on chemical shifts and coupling constants reported for the analogous ester[10]

of tertiary amines, chromium(II) chloride and aprotic solvents at 20 °C (Table 1).

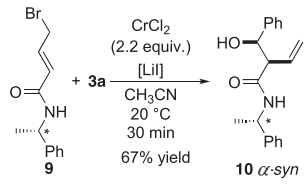
Amines have a considerable influence on the reaction yield and regioselectivity, but have little effect on the diastereoselectivity. When applying *N,N*-diisopropylethylamine (DIPEA; Hünig's base) as base, polar aprotic solvents such as THF and acetonitrile are best for this C-C coupling as has been reported previously for methyl crotonates.[1,10] Dimethylformamide (DMF; Table 1, entry 5) as a highly polar solvent can improve the solubility of $Cr(II)Cl_2$, and consequently can result in higher yields, as sometimes does dichloromethane (for unknown reasons). Ethyl ether turns out to be not a suitable alternative solvent because traces of paramagnetic Cr(III) present in the crude product result in the necessity of performing further purification, which causes significant product loss (Table 1, entry 7). Also, triethylamine is not effective yielding an almost equimolar mixture of α and γ products in just 24% yield (Table 1, entry 8). Thus, steric hindrance seems to be important considering that Et_3N and DIPEA have similar pK_a values. Hence, the highly hindered base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was also tested. The solution turned dark immediately after the addition of this amine and no further reaction was noticed (Table 1, entry 10). The reason behind this observation was not pursued, but it is likely that, because of its higher basicity, DBU decomposes the starting material **1** into unknown compounds. The weaker diamino base *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) is suitable but clearly less efficient than DIPEA (Table 1, entry 9). Consequently, DIPEA is identified as the best additive in this reference reaction. The regio- and diastereoselectivity are comparable to the results obtained with the corresponding methyl ester as starting material; yields are only a little lower (Table 1, entries 3, 4, 11, 12 versus 14). Possibly, the DIPEA efficiency is threefold: efficient deprotonation of **1** without deactivation of the chromium species through complexation or participation in the decomposition of the substrate via nucleophilic attack at C_γ (Scheme 3).

Due to the positive influence of tertiary bases in the previous reaction, it was decided to check if optically active amines such as (−)-quinidine and (−)-sparteine would affect the diastereomeric ratio of the allylic products.[15,16] Both bases afford aldol products **4a** with slightly improved yields (Table 1, entries 11–13), but no considerable effect on the selectivities is observed.

To determine the scope and limitations of the almost exclusive formation of the α-addition products, the method was expanded to aliphatic aldehydes and ketones in the presence of DIPEA (Table 2). The regioselectivities, diasteroselectivities and yields obtained from reactions of 4-bromocrotonic acid with aliphatic aldehydes surprisingly are superior even to those obtained with the corresponding methyl ester **6** (Table 2, entries 2 versus 3 and entries 4 versus 5). Also, the coupling of **1** with ketones in the

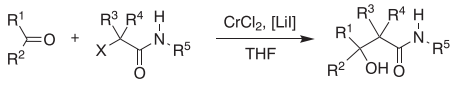


Scheme 3. Role of DIPEA in the Cr-mediated reaction of 4-bromocrotonic acid with aldehydes and ketones



Scheme 4. Chromium(II)-mediated Nozaki–Hiyama–Kishi reaction of the chiral secondary amide **9** with benzaldehyde (**3a**)

Table 3. Chromium(II)-mediated Reformatsky reaction of primary and secondary α-halo-amides **11a–d** with aldehydes and acetophenone (**3e**)[a]



3 11 12

Entry	3	R^1	R^2	11	X	R^3	R^4	R^5	Time (h)	12	Yield (%)[b]
1	**a**	Ph	H	**a**	Br	Et	Et	H	2.5	**a**	93
2	**e**	Ph	Me	**a**	Br	Et	Et	H	1.0	**b**	25
3	**a**	Ph	H	**b**[c]	Br	H	Me	Ph(Me)CH	1.0	**c**[d]	79
4	**a**	Ph	H	**c**[c]	Br	H	H	Ph(Me)CH	1.0	**d**	71
5	**a**	Ph	H	**d**	I	H	H	H	0.5	**e**	15[e]
6	**f**	(*S*)-Ph(Me)CH	H	**d**	I	H	H	H	1.2	**f**	22[e]
7	**c**	*i*-Pr	H	**d**	I	H	H	H	0.5	**g**	16[e,f]

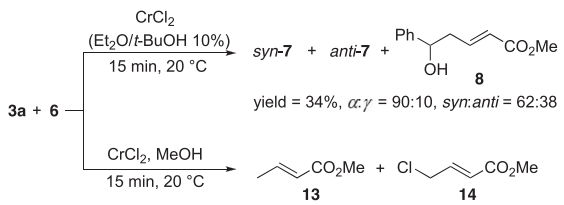
[a]For specific details and exact amounts refer to the experimental section.
[b]Isolated yield based on minor component
[c]No asymmetric induction with (*S*)-phenylethylamide
[d]*Syn*/*anti* ratio = 64:36
[e]Reduced yields due to high water solubility of the products
[f]Without lithium iodide

presence of DIPEA results exclusively in the α-alkenyl-β-hydroxy acids, albeit in slightly lower yields than those accomplished with methyl ester **6** (Table 2, entries 6 versus 8, 10 versus 11).

Noteworthy is the superior diasteroselectivity of the free acid **1** achieved with phenyl methyl ketone **3e** when compared to the reaction of ester **6** (Table 2, entries 10 versus 11).

The effective utilization of **1** and its *in situ* generated ammonium salts in chromium(II)-mediated Reformatsky reactions prompted us to extend the method to the coupling of amides. As a start, the reaction of enantiomerically pure 4-bromocrotonyl *N*-phenylethylamide (**9**) with **3a** was chosen (Scheme 4). This reaction is 100% regio- and diasteroselective, and the α-*syn* isomer is the only product. The (*S*)-(−)-α-methylbenzylamine unit of substrate **9** does not promote preference between the two possible *syn* isomers, which results in the isolation of the purified α-*syn*-**10** isomers in 34 and 33% yield.

The exclusive α-addition observed in the formation of *syn*-**10** instigated us to extend our studies to the chromium-mediated Reformatsky reaction of simpler, non-vinylogous primary and secondary α-halo-amides with aldehydes (**3a**, **c**, **f**) and acetophenone (**3e**) (Table 3). Seemingly, the α-addition of the amides **11** proceeds through a chromium(III) enolate intermediate, in contrast to the carboxylates **1** and **2** (with an allylchromium intermediate proposed). The coupling of the primary bromocarboxamide **11a** with



Scheme 5. Chromium(II)-mediated Nozaki–Hiyama–Kishi reaction of methyl 4-bromocrotonate (**6**) with benzaldehyde (**3a**) in the presence of protic solvents

3a results in the β-hydroxycarboxamide **12a** in 98% yield after 2.5 h at 55 °C (Table 3, entry 1). It was expected that the reaction of iodocarboxamide **11d** with **3a** would give the respective α-addition product in high yield. Although TLC indicated the sole formation of **12e**, only 15% of the expected secondary amide could be isolated. This can be explained by the high water solubility and better chromium ion complexation of the product, implying that most of product **12e** is lost during the aqueous work-up. Similar behavior is noted after the reaction of the primary amide **11d** with 2-phenylpropanal (**12f**, 22%) and isobutyraldehyde (**12 g**, 16%). Hence, the α-adduct must be sufficiently apolar to allow its separation from chromium salt by extraction into the organic phase during work-up. This can be accomplished by the presence of alkyl substituents such as in **11a** (R^3 and R^4 = ethyl) or through a lipophilic amine portion like in (*S*)-(−)-α-methylbenzylamides **11b** and **11c**.

The chiral amides **11c** and **11d** do not influence the enantioselectivity of the reaction towards the β-hydroxycarboxamides **12c** and **12d** (Table 3, entries 3 and 4). Expectedly, **3e**, when reacted with the primary amide **11a**, gives a lower yield of the β-hydroxycarboxamide **12b**. However, if one considers the steric bulk around the adjacent quarternary centers formed in aldol-type reactions, the yield is very good.[1]

In contrast to the carboxamides and 4-bromocrotonic acid, α-halocarboxylic acids are unsuitable Reformatsky substrates. All attempts to react them in chromium-mediated Reformatsky reactions almost exclusively afforded the corresponding dehalogenated carboxylic acid products.

Influence of proton concentration and mobility

In order to study the influence of free protons in a more general way, methyl bromocrotonate (**6**) was reacted with **3a** in the presence of protic solvents, namely either methanol or *t*-butanol (10%) as extremes in ether (Scheme 5). *t*-Butanol is highly hindered and 100 times less acidic than methanol. The reaction in *t*-butanol (10 vol.% in ether) gives a 9:1 mixture of α-**7**:γ-**8** in 34% yield and a diastereoselectivity of 90:10 of *syn* versus *anti* isomers. When methanol is used, methyl crotonate **13** and minor amounts of chloromethyl crotonate **14** are formed; the latter by nucleophilic substitution with chloride, but no coupling product is isolated. Thus, protons do not easily interfere in the chromium-mediated Nozaki–Hyama–Kishi reaction unless they are very mobile (acidic). The same behavior is expected to occur for the Reformatsky reaction.

Conclusions

Unprotected protic vinylogous halo acids and amides react in chromium(II)-mediated Nozaki–Hiyama–Kishi reactions with aldehydes in good to excellent yields to result in α-alkenyl-β-hydroxy adducts, if proton mobility and acidity are controlled, e.g. by using DIPEA as base. The Reformatsky reaction of simple primary and secondary α-halo carbox amides with aldehydes (or ketones to give sterically highly congested molecules) in the presence of chromium(II) chloride expands the scope of these Cr(II)-mediated reactions. Especially in reactions of complex natural products, be it in total or semi synthesis or for derivatization, it is important to have a portfolio of methods that do not require protection–deprotection strategies. The method herein described certainly can contribute to this

portfolio, since several biomolecules contain β-hydroxy-α-alkenoic acid or amide moieties, e.g. viridiofungin derivatives.

Experimental

All reactions were carried out under an argon atmosphere in flame-dried glassware using standard syringe and septa techniques. The commercial reagents **6**, **11a**, **11d**, lithium *t*-butoxide, crotonic acid, *N*-bromosuccinimide, 2,2′-azobis(2-methylpropionitrile) (AIBN), oxalyl chloride, 2-bromopropionyl bromide, (*S*)-(−)-α-methylbenzylamine, bromoacetyl bromide, (−)-quinidine, (−)-sparteine, DBU, TMEDA, triethylamine, DIPEA, lithium iodide and chromium(II) chloride (99.9% from Strem Chemicals) were used as purchased. Diazomethane was synthesized according to a literature procedure.[17] THF and diethylether were distilled from potassium/benzophenone. Absolute DMF and *t*-butanol were purchased from Fluka. Acetonitrile was distilled from Sicapent (Merck) and flushed with argon. Dichloromethane and carbon tetrachloride were filtered through basic aluminium oxide. Aldehydes **3a**–**c**, **3f** and ketones **3d** and **3e** were distilled from calcium chloride under an argon atmosphere and stored over a 0.4 nm molecular sieve. Spectral data of known compounds were either in accordance with those of the literature (**1**,[18] *syn*-**4a**,[13] *anti*-**4a**,[13] *syn*-**4b**,[19] *syn*-**4c**,[11] **5**,[13] *syn*-**7**,[10] *anti*-**7**,[10] **8**,[20] **12e**[21] and **14**[22]) or the commercial substance (**13**). TLC was carried out with Merck silica 60/F-254 aluminium-backed plates. Flash chromatography was performed using Merck silica gel 60 (40–60 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD, and tetramethylsilane was used as internal standard. Chemical shifts are quoted in ppm, and coupling constants *J* are given in Hz.

General procedure for chromium(II)-mediated reaction

To chromium(II) chloride (2.2–3.2 equiv.) and lithium iodide (0.10–0.19 equiv. (1.15 equiv. in the reaction with **2**)) was added solvent (1.5 ml/mmol $CrCl_2$) under vigorous stirring at 20 °C. After 10 min, aldehyde (1.0–1.1 equiv. (2.0–5.0 equiv. in the reaction with 2-iodoacetamide)) or ketone (10 equiv.) and alkyl halide (1.0–1.1 equiv.) (2-iodoacetamide was added as a solution in the solvent used) were added in this order. The resulting mixture was stirred for the time indicated at 20 °C. The reaction was quenched with oxygen-free brine. The water layer was extracted three times with 80% diethyl ether–pentane. The combined organic fractions were washed with $NH_4Cl_{(sat.)}$ and brine (extra two times with H_2O to DMF, *t*-BuOH, or MeOH as solvent). The organic layer was dried over $MgSO_4$, filtered through a short silica column to remove further paramagnetic Cr(III) and concentrated under vacuum. ^{1}H NMR analysis of the crude product after being filtered through silica determined yield and isomer distribution. Further purification was accomplished by column chromatography on silica or recrystallization. Solvents are indicated.

General procedure for chromium(II)-mediated reactions of carboxylic acid halo substrates

The general procedure for the chromium(II)-mediated reactions was modified as follows. The reaction was quenched with oxygen-free and saturated aqueous NaCl with 20% citric acid. Ethyl acetate was added, and the mixture was stirred for 30 min at 20 °C. The organic layer was separated, and the water layer was extracted three times with ethyl acetate. For stronger acids or strongly retained Cr(III), prior treatment with a phosphate solution or diazomethane esterification was applied.[9,22] The combined organic extracts were dried on sodium or magnesium sulfate, filtered and the solvent removed using a rotary evaporator. The crude product was used to determine the product distribution, usually by NMR, and eventually purified by column chromatography on silica.

General procedure for chromium(II)-mediated Nozaki–Hiyama–Kishi reaction of 4-bromocrotonic acid in presence of amines

To chromium(II) chloride (2.3–2.5 equiv.) and lithium iodide (0.10–0.42 equiv.) was added solvent (1.5–8 ml) under vigorous stirring at 20 °C. After 5 min, aldehyde (1.5–5.1 equiv.)/ketone (9.2–13 equiv.) and a solution formed of **1** (145–220 mg, 0.88–1.33 mmol, 1.0 equiv.), amine (1.04–1.10 equiv.) and solvent (1.5–4.0 ml) were added to the reaction flask. Work-up, if required after addition of phosphoric instead of citric acid, is stated as above or described individually.

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