Chromium(II)-Mediated Reformatsky Reactions of Carboxylic Esters with Aldehydes

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Introduction

The Reformatsky reaction,[1,2] like other aldol-type reactions, may be regarded as a two-step process with (ester) enolate formation as the first step followed by the actual aldol reaction with a keto component. The value of the Reformatsky variation is threefold: The enolate can be formed at an invariably predetermined site, under neutral conditions and in the presence of many functional groups.[3] The position thus activated may differ from those accessible by thermodynamically or kinetically controlled base-induced enolizations.

The major disadvantage of the classical procedure with zinc was low reactivity, low reproducibility, and access to thermodynamic products only. The more recent introduction of highly activated metals[4] led to a renaissance of the Reformatsky reaction but requires at least one additional step for the preparation of the reagents. Many problems, however, could not be addressed by these modifcations. Microscale preparations are difficult to perform with the often pyrophoric materials, and selectivity is sacrificed for reactivity in many instances. Other limitations originate from the still heterogeneous reaction conditions, e.g. in applications with polymer supported substrates. Problems associated with the nature of the metal, usually zinc, include low stereo-, regio-, and chemoselectivity. Thus with propionate and most aldehydes a <2:1 ratio in favor of the more common *syn* isomer is achieved thermodynamically, whereas low-temperature methods with activated metals give 1:1 mixtures kinetically.

We envisaged that a metal salt with a suitable reduction potential for selective reactivity should be a better reagent. As such, it might be (partly) soluble, allowing for homogeneous reaction conditions, which in addition might be controllable by the ligands (solvent). Chromium(II) lent itself toward this purpose. Apart from excellent chemoselectivity in the enolate forming step,[5] we expected further advantages in the C−C coupling, because the related Nozaki−Hiyama reaction of allyl compounds[6,7] gives excellent chemo- and simple diastereoselectivity toward aldehydes and *anti* products, respectively.[6,8−10] In addition only kinetic products would be expected for reasons discussed elsewhere.[11−13]

Table 1. Reaction of Symmetrical α-$R^{1/2}$-α-bromoacetates with Chromium Dichloride[a]/ Catalytic Lithium Iodide and Aldehydes (R^4-CHO) in THF (R^{1-4}: cf. Scheme 1)

entry no.	$R^1 = R^2$	R^3	R^4	*T* (°C)	*t* (h)	yield (%)
1	H	Me	Ph	55	1.0	89[b]
2	H	Et	Ph	55	1.0	72[b,c]
3	H	*t*-Bu	Ph	55	1.0	63[b,c]
4	Me	Me	Et	20	0.5	81[c,d]
5	Me	Me	*i*-Pr	55	4.0	93
6	Me	Me	Ph	55	4.0	90
7	Me	Me	Ph-CH_{2-}	20	1.0	98

[a] $CrCl_2$, 99.9% Strem Chemicals Inc. if not stated otherwise. [b] $CrCl_2$, ca. 90%, Merck-Schuchardt. [c] Reaction time and workup are not optimized. [d] In DMF.

Results and Discussion

The chromium dichloride mediated reaction of α-bromo esters is run in a Barbier-type fashion.[2] The reaction proved to be highly reproducible with easy handling even on a micromolar scale. Unexpectedly it appeared to be somewhat slow at room temperature in most solvents in comparison to the much more reactive ketones or vinylogous esters.[3,11−15] However, addition of lithium iodide, especially in tetrahydrofuran, and slightly elevated temperatures result in clean formation of the aldol products in a few hours in good to excellent yields (Tables 1 and 2, Scheme 1). The effect of lithium iodide certainly includes general lewis acid[16] and nucleophilic iodide catalysis: in some cases traces of α-iodo esters could be detected as intermediates. The main influence, however, seems to be the salts visible ability to solubilize and modify chromium dichloride. Whether $Li_2[CrX_4L_2]$ or a similar complex species is involved in this process is speculation at this time.

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(16) Chromium dichloride of >99.9% purity purchased from Strem Chemicals was used to avoid catalytically active contaminations. Less reactive esters sometimes give increased yields if either freshly prepared $CrCl_2$ × 2THF complex[26] (which may contain residual aluminum or lithium chloride) or a preformed mixture of 99.9% purity $CrCl_2$ with 10 mol % $AlCl_3$ is used.

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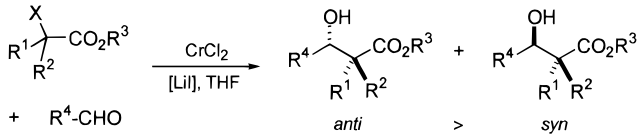
Table 2. Reaction of Asymmetrical α-$R^{1/2}$-α-bromoacetates and Aldehydes (R^4-CHO) with Chromium Dichloride[a]/Catalytic Lithium Iodide in THF

entry no.	R^1	R^2	R^3	R^4	T (°C)	t (h)	*anti:syn*[b]	yield (%)
8	H	Me	Me	*i*-Pr	55	3.0	71:29	72[c,d,e]
9	H	Me	Me	*i*-Pr	20	1.0	77:23	84
10	H	Me	Me	*i*-Pr	55	1.0	60:40	86
11	H	Me	*t*-Bu	Ph	20	2.0	70:30	95
12	H	Me	Me	Ph	20	2.0	78:22	81
13	H	Me	Me	Ph	55	2.0	60:40	88
14	H	Et	Me	Ph	55	3.0	74:26	82[f]
15	H	*i*-Pr	Me	Ph	55	2.0	30:70[g]	85[c]
16	H	Ph	Me	Ph	55	2.0	79:21	84[d]
17	H	$-CH_2-CH_2-$		Ph	20	2.0	>95:<5[g]	81[f,c]
18	Me	Ph	Me	*i*-Pr	20	1.0	68:32[g]	86
19	Me	Me	Me	PhCH(CH_3)	20	3.0	76:24[g]	84[e]

[a] $CrCl_2$, 99.9%, Strem Chemicals Inc. if not stated otherwise. [b] Determined from crude product (Celite- or silica-filtered when necessary). [c] $CrCl_2$, ca. 90%, Merck-Schuchardt. [d] X = Cl. [e] The reaction time is not optimized. [f] $CrCl_2 \times 2THF$.[28] [g] Assignment uncertain, based on coupling constants and models.

Scheme 1



$R^1 < R^2$ ($R^{1\text{-}4}$: see tables); X = Cl, Br, (I)

α-Chloro esters give similar results, but react more slowly (cf. entry 8). With aromatic aldehydes, diol coupling can become a competing side reaction with chlorides. Nonactivated halogenides in the reactants or in the solvent (e.g. methylene chloride) are not effected.

Two substituent effects can be observed: Larger ester groups can give lower yields (R^3: Me > Et > *t*-Bu, entries 1−3) or require longer reaction times, probably due to increased hindrance around the sterically sensitive chromium(III) ion.[17] Ester groups even larger then *t*-Bu still seem to allow the reaction with chromium(II) but not the subsequent attack of the electrophile. Accordingly, increased amounts of dehalogenated starting material from proton quenching during workup are observed.[18] In contrast to these observations, increased substitution at the α-carbon results in equal or even better yields in most cases. Quarternary centers are generated with ease (entries 4−7, 18, and 19).[12] Sterically this contradicts the first observation. The obvious argument of increased stability of either an enolate or especially a radical intermediate (as proposed for the Hiyama−Nozaki reaction) is not necessarily conclusive considering the similar yields observed with α,α-disubstituted acetates and phenylacetates (entries 16 and 18).

A significant influence on yields through the steric effect of aldehydes was not observed (cf. entries 4−7). However, in contrast to the Hiyama−Nozaki reaction, aliphatic aldehydes often give slightly better results than aromatic benzaldehyde which tends to form stronger chromium complexes in its products. Transenolization, a frequent problem in reactions under basic conditions or in those prone to retro-aldolization, was never observed despite temperatures of 55 °C and several hours reaction

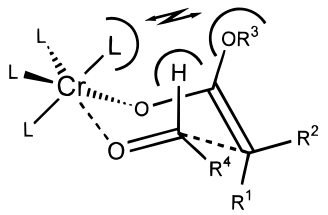


Figure 1.

time. This is exemplified by the successful reaction of phenylacetaldehyde as electrophile (entry 7) which otherwise dimerizes easily. In contrast to the literature on allyl chromium reagents,[19] we found aldimines—activated or not—and iminium salts to be unsuitable electrophiles.

Anti products are formed preferentially (Table 2), which is in sharp contrast to the *syn* selectivity obtained with ester enolates of other metal ions (Li, Zn, etc.)[1,20] or those reported for ketones.[14] Following the assignments made in the literature, increased bulk of the α-substituent leads to a reversal of stereochemistry in favor of *syn* products (entry 15 and footnote *g*), again in contrast to the *anti* preference induced by other counterions. Interestingly α-bromo lactones (entry 17), which must form the *E*-enolate, also give the *anti (threo)* product preferentially.

These observations are in accordance with the reaction of an *E*-enolate and a Zimmermann−Traxler transition state model as presented in Figure 1. The related crotylchromium reagents are well-known for their ability to give *anti* products from both (*E*)- and (*Z*)-crotyl halides.[6,8] The extraordinary tendency of crotylchromium intermediates to react exclusively as the *E*-isomer via a similar transition state is widely accepted[8,10,21] and thus may be adapted to the heteroequivalent discussed here as well. An alternative boat transition state should favor (*E*)-enolates even more in order to avoid 1,4-interaction of the axial chromium ligand and R^1.[22] The *anti* preference, nevertheless, seems to be less strong quantitatively in the Reformatsky -aldol. This may be caused by allylic strain from the additional axial alkoxy substituent (OR^3)[21] or by a heteroatom effect. Independent of enolate stereochemistry, the small ionic radius of chromium(III)[17] combined with an octahedral coordination and its enhanced steric influence through the superaxial ligand should force the aldehyde into the proper relative orientation with the R^4 group equatorial. In this respect chromium-centered transition states may best be compared to those of titanium(IV).[22]

Accordingly the diastereomeric excess in most cases is slightly better with chromium(III) than with other metal counterions in identical systems (Zn, Li, etc.),[1,20] but is still unsatisfactory. *Anti:syn* ratios are usually in the range of 60:40 to 80:20, depending mainly on the reaction temperature (cf. entries 9 + 10, 12 + 13). However, future improvements can be expected. These may be achieved either by lower temperatures paired with more reactive chromium salts or rather by solvent effects

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(ligand effects). Both approaches are under current investigation, and the latter has already proven partly successful for vinylogous systems.[3,15]

In the reaction of chromium Reformatsky reagents with 2-phenylpropanal the simple diastereofacial selectivity is quantitatively similar to that of most other enolates[23] giving a 3:1 ratio (at room temperature!, entry 19). Again the less usual β,γ *anti* product (*anti-Cram*) seems to form preferentially, in contrast to reactions of other enolates and allyl chromium reagents.[21,23,24] Chemical yields with chromium(II) are much better than those reported with zinc (84% vs 35%, respectively).[25]

In summary we presented a variation of the Reformatsky reaction which offers excellent reproducibility even on a microscale, convenient handling without activation, excellent chemo- and improved simple diastereoselectivity, the latter being inverse to that of more common approaches, i.e. *anti* selective.

Experimental Section

General. Anhydrous chromium dichloride (99.9%) was purchased from Strem Chemicals Inc. or from Merck-Schuchardt (90%) or prepared according to the literature.[26] Aldehydes were freshly distilled (Kugelrohr). THF was dried over K/benzophenone; dry DMF was purchased from Aldrich. Petroleum ether (<70 °C) and ethyl acetate were distilled. For chromatography silica 60 F_{254} (TLC) and 40−63 μm at ca. 1.3 bar (LC) from E. Merck was used. Detection was achieved by iodine vapor followed by ethanolic molybdato phosphate solution and/or UV fluorescence.

NMR spectra were recorded in $CDCl_3$/TMS on a Bruker ARX 300, mass spectra on a Finnigan MAT 90 and 95Q, and IR spectra on a Perkin-Elmer 1420.

Syn:*anti* ratios were determined by ^{1}H-NMR from crude products, filtered as described below if residual paramagnetic chromium(III) had to be removed. Yields are of isolated products. If diastereomers were not separated, their distribution may slightly deviate from the ratio in crude material.

General Procedure. Approximately 2.5 equiv of anhydrous chromium dichloride and 0.1 equiv of dry lithium iodide are suspended in dry THF (ca. 1.5 mL/mmol of $CrCl_2$) under an argon atmosphere. If more dissolved chromium dichloride or a faster reaction is required, THF may be substituted by DMF (entry 4) or DMA. To the light gray-green suspension are added via syringe 1.0 equiv of aldehyde and 1.1 equiv of α-halo ester (the ratio maybe inversed with valuable α-halo esters). After completion of the reaction, usually 1−6 h at room temperature or up to 60 °C, it is quenched with brine and vigorously stirred for 15 min. The organic layer is separated, and the aqueous phase is extracted three times with ether. The combined organic layers are washed with ion-exchanged water to remove traces of chromium(III) residues, dried over $MgSO_4$, filtered, and concentrated *in vacuo* by rotary evaporation. In single cases filtration through Celite or silica to remove residual chromium complex is necessary. Diastereomers can be separated by column chromatography on silica preferentially with petroleum ether/ethyl acetate.

Typical Procedures: Methyl 2,2-Dimethyl-3-hydroxy-4-phenylbutyrate (entry 7). To a suspension of $CrCl_2$ (251 mg, 2.05 mmol) and dry LiI (11 mg, 0.08 mmol) in dry THF (3.2 mL) were added via syringe phenylacetaldehyde (86 μL, 0.738 mmol) and methyl 2-bromoisobutyrate (102 μL, 0.820 mmol). The resulting suspension was stirred for 60 min at room temperature. After usual workup the resulting residue was purified by flash chromatography on silica with 4:1 petroleum ether:ethyl acetate to afford 160 mg (98%) of butyrate (R_f = 0.42): ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 1.27 (s, 3 H), 1.28 (s, 3 H), 2.24 (d, ^3J = 5.3 Hz, 1 H), 2.54 (dd, ^2J = 13.4 Hz, ^3J = 10.3 Hz, 1 H), 2.81 (dd, ^2J = 13.4 Hz, ^3J = 2.1 Hz, 1 H), 3.69 (s, 3 H), 3.92 (ddd, ^3J = 10.3 Hz, ^3J = 5.3 Hz, ^3J = 2.1 Hz, 1 H), 7.19−7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ 20.7, 21.8, 38.4, 47.2, 52.0, 126.4, 128.5, 129.3, 129.7, 139.1, 177.7.

Methyl 2,4-Dimethyl-3-hydroxypentanoates (entry 18). To a suspension of $CrCl_2$ (843 mg, 6.86 mmol) and dry LiI (36 mg, 0.27 mmol) in dry THF (11 mL) were added via syringe 2-methylpropanal (274 μL, 3.02 mmol) and methyl 2-bromo-2-phenylpropionate (660 mg, 2.74 mmol, as solution in dry THF). The resulting suspension was stirred for 60 min at room temperature. The usual workup afforded 640 mg of crude product. A 322 mg portion was subjected to flash chromatography with 10:1 hexanes:ethyl acetate to afford a total of 278 mg (86%) methyl 2,4-dimethyl-2-phenyl-3-hydroxypentanoates separated in two diastereomers of 90 mg (**18-I:** 32 relative %, R_f = 0.40) and 188 mg (**18-II:** 68 relative %, R_f = 0.18), presumably the *syn* and *anti* isomers, respectively.

18-I (syn ?): ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 0.77 (d, ^3J = 6.6 Hz, 3 H), 0.92 (d, ^3J = 6.6 Hz, 3H), 1.62 (s, 3 H), 1.73−1.80 (m, 1 H), 2.02 (d, ^3J = 4.3 Hz, 1 H, OH), 3.65 (s, 3 H), 4.06 (dd, ^3J = 4.9 Hz, ^3J = 4.3 Hz, 1 H), 7.25−7.49 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ 16.9, 18.5, 21.6, 30.4, 52.1, 54.8, 80.3, 126.6, 126.8, 127.2, 127.3, 128.5, 140.4, 176.3; IR (film) ν [cm^{-1}] 3600−3300, 3030, 2940, 2860, 1740, 1595, 1575, 1490, 1460, 1439, 1425; MS (*m*/*z*, CI: *i*-BuH) 237 (0.4, [M + H]$^+$), 219 (8.6 [237 − H_2O]), 164 (12.3, [237 − C_4H_9O]$^+$). Anal. Calcd for $C_{14}H_{20}O_3$ (236.3): C, 71.2; H, 8.5. Found: C, 71.2; H, 8.4.

18-II (anti ?): ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 0.69 (d, ^3J = 6.9 Hz, 3 H), 0.90 (d, ^3J = 6.9 Hz, 3 H), 1.64 (s, 3 H), 3.14 (d, ^3J = 6.0 Hz, 1 H, OH), 3.66 (s, 3 H), 4.17 (dd, ^3J = 6.0 Hz, ^3J = 4.0 Hz, 1 H), 7.24−7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ 19.3, 20.0, 25.0, 31.5, 54.8, 58.1, 82.3, 128.9, 129.5, 130.9, 143.6, 179.8; IR (film) ν [cm^{-1}] 3600−3300, 3030, 2940, 2860, 1740, 1595, 1575, 1490, 1460, 1439, 1425; MS (*m*/*z*, CI: *i*-BuH) 237 (3.35, [M + H]$^+$), 220 (7.36, [237 − OH]$^+$), 219 (53.78, [237 − H_2O]), 164 (16.94, [237 − C_4H_9O]$^+$). Anal. Calcd for $C_{14}H_{20}O_3$ (236.3): C, 71.2; H, 8.5. Found: C, 71.3; H, 8.3.

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Supporting Information Available: Tables of ^{1}H NMR, ^{13}C NMR, IR, and MS data and elementary analyses (or HRMS spectra) for new compounds; literature references for known compounds; and selected additional spectral data (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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