Excellent Aldehyde and Ketone Selectivity in Chromium(II)-Mediated Reformatsky Reactions

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Abstract: The chromium Reformatsky reaction allows the highly chemoselective addition of ester enolates to aldehydes or methyl ketones at room temperature. Aldehyde selectivities of ≥ 50 : 1 *vs.* methyl ketones and ≥ 200 : 1 *vs.* larger ketones and other electrophiles can be achieved in most cases. Methyl ketones are preferred with similar effectivity against higher ketones. Effects of solvents, lithium iodide and substituents are discussed.

Chromium(II) mediated reactions of activated halides, especially the Hiyama-Nozaki reaction, are frequently applied in complex total syntheses because of their extraordinary chemo- and stereoselectivity, reliability and ease of handling.[1-4] The corresponding Reformatsky reaction of α-haloesters with chromium(II) is much less investigated.[5-10] Recently, we have demonstrated that chromium-Reformatsky reactions exhibit a considerable number of advantages over conventional Reformatsky systems, including excellent reproducibility without activation, irreversibility and exclusive kinetic product formation, and inverse diastereoselectivity.[6-9]

The aldehyde selectivity of nucleophiles generated in Reformatsky-fashion from bromo esters with chromium(II) was studied in competition experiments.[11] Typical results of intermolecular competition experiments employing a tenfold excess of a reactive methyl ketone similar to the reacting aldehyde are compiled in the Table. With the exception of quarternary α-bromo ester **3**, aldehyde selectivities against methyl ketones exceed 97% (*ca.* 30:1), and often can be improved to 99% (≥ 90:1) with a more appropriate solvent. Against higher ketones or in intramolecular competitions, only the aldehyde derived products were detected (> 200 : 1, *cf.* also Scheme 1).

A Zimmerman-Traxler transition state model (Figure 1) similar to the one proposed for the allyl case is suitable to explain the results.[12] Although the behaviour of the reactive species of the Reformatsky reaction, i. e. the oxa-allyl or enolate species of chromium(III), differs considerably from the the allyl species in many aspects, we still believe that this model allows a good explanation for the observed selectivity. Thus strong 1,3-interactions of the *endo*-axial chromium ligand with the pseudoaxially oriented R^2 group in the electrophile would greatly encourage reactions of electrophiles with a small R^2 group, i. e. aldehydes (R^2 = H) would be preferred to ketones, methyl ketones to larger ketones.

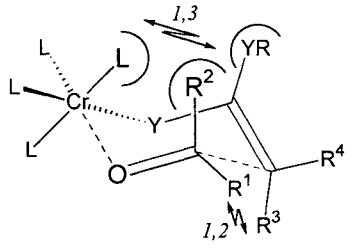
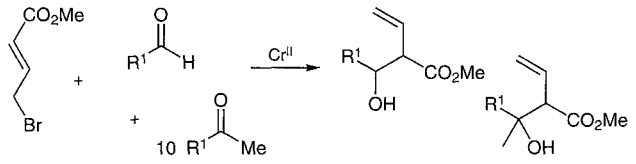


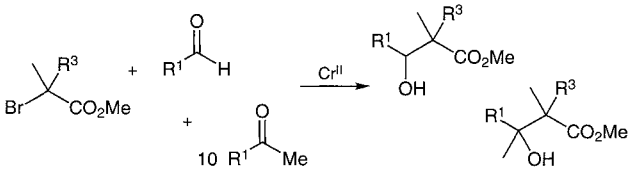
Figure 1. Y = CH_2, O

However, this is true qualitatively for all metals favoring such a transition state. The improved quantitative differences expected for chromium(III) [and titanium(IV)[13]] are governed by three factors which sterically tighten the transition state depicted in Figure 1 to allow unusually strong interactions: (1) the ideal octahedral coordination preferred by Cr^{III} which pushes the *endo*-axial ("superaxial") ligand inwards; (2) the relatively small ion radius of Cr^{III} (≈ 61 pm; most other ions, e. g. $Li^{I} \approx Zn^{II} \approx 75$ pm), a matter well treated for transition metal alkyls by Kauffmann *et al.*;[10,14,15] (3) the YR group (e. g. alkoxy) which adds additional 1,3-diaxial strain compared to α-unsubstituted

Table. Competition experiments of aldehydes *vs.* methyl ketones



1 **4a**: R^1 = Et **5a**: R^1 = Me **6a, b** **7a, b**
4b: R^1 = Ph **5b**: R^1 = Ph



2: R^3 = H **4a**: R^1 = Et **5a**: R^1 = Me **8a, b** **10a, b**
3: R^3 = Me **4b**: R^1 = Ph **5b**: R^1 = Ph **9a, b** **11a, b**

Bromo ester	R^1 **4**	R^1 **5**	Ratio **1/2/3 : 4 : 5**	Solvent/ catalyst	Yield (isol.) [a]	Aldehyde selectivity[b]
1	Et	Me	1 : 4 : 40	DMF	83%	50 : 1
			1 : 4 : 40	DMF/LiI	72%	25 : 1
			1 : 4 : 40	THF/LiI	77%	60 : 1
			1: 1.1: 11	THF/LiI	77%	30 : 1
			1 : 4 : 40	CH_3CN/LiI	75%	100 : 1
	Ph	Ph	1 : 4 : 40	DMF	71%	60 : 1
			1 : 4 : 40	THF/LiI	70%	40 : 1
			1 : 4 : 40	CH_3CN/LiI	65%	90 : 1
2	Ph	Ph	1 : 2 : 20	DMF/LiI	31%	30 : 1
			1 : 2 : 20	THF/LiI	46%	50 : 1
			1 : 2 : 20	CH_3CN/LiI	5%	-
3	Et	Me	1 : 4 : 40	DMF/LiI	82%	15 : 1
			1 : 4 : 40	THF/LiI	88%	8 : 1
	Ph	Ph	1 : 2 : 20	THF/LiI	67%	7 : 1

a) All experiments[11] were run under identical conditions: 2.3 eq. $CrCl_2$, 30 min. at room temp. (~20°C), 5-20 mol% LiI. In a non-competitive, optimized setup better yields are achieved, usually 80-98%.[9]

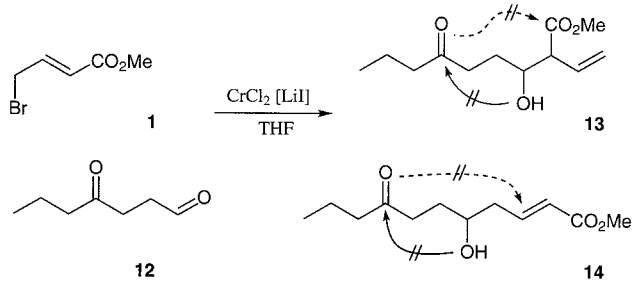
b) Calculated from signal intensities of secondary alcohols **6**, **8**, **9** *vs.* tertiary alcohols **7**, **10**, **11** in the ^{1}H NMR-spectra of crude

allylchromium. Furthermore, irreversibility of the reaction through inhibited ligand exchange locks the kinetic product.[8]

In competition experiments with aldehydes only methyl ketones as electrophiles exhibited reasonable rates to allow reliable data. The influence of R^1 in aldehydes **4** or in methyl ketones **5** on the relative rate is negligible, with the exception of benzaldehyde which usually gives lower selectivity and yield. With higher ketones tertiary alcohols could not be detected at all (by NMR, *cf.* also Schemes 1 and 2). They may even be used as solvent if sufficient aldehyde is present. This is in accordance with earlier studies in pure systems showing that the influence of R^1 in aldehydes on reactivity and product distribution is low. Without a competing aldehyde the influence of R^1 in methyl ketones is a little more pronounced,[6] ethyl- and higher ketones again show almost no influence of R^1. In the presence of aldehydes we found all other electrophiles to be inactive with the exception of the 1-2% conversion observed with methyl ketones. No products were formed with esters, nitriles,[16] amides, imines, iminium salts (e. g. Eschenmoser's salt), Michael acceptors or simple halides. Thus in multifunctional molecules the selective Reformatsky-aldol reaction of an aldehyde moiety is possible in the presence of these electrophilic groups (*cf.* reactions in DMF or acetonitrile as solvent).

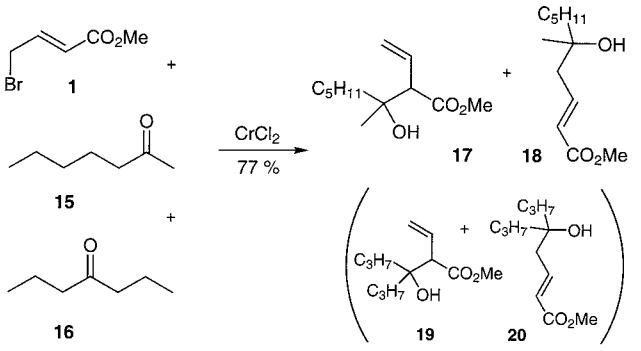
A comparison of the nucleophiles **1-3** reveals no definite difference in the selectivity of propionate **2** and the vinylogous substrate **1**. Both give rise to tertiary carbons at C-α in the course of the reaction (compounds **6** and **8**). However, isobutyrate **3** gives lower selectivities. Accepting the model from Figure 1, isobutyrate must have a pseudo-axial methyl group at C-α ($R^3 \neq H$), generating a 1,2-interaction between R^1 and R^3 at the α-face which is equally effective for aldehydes and ketones and thus may reduce the relative effect of the 1,3-interaction at the β-face.

The selectivity is influenced by additives and solvents. It is decreased by lithium iodide and increased by solvents in the order DMF < THF < CH_3CN. The influence on reactivity is exactly opposite. THF/LiI appears to be the best compromise for normal esters, CH_3CN/LiI is fast enough for the more reactive vinylogous systems.



Scheme 1. Only secondary alcohols are formed (80% **13**) without subsequent internal nucleophilic reactions (arrows).

In a more relevant intramolecular competition only the aldehyde group is attacked in ketoaldehyde **12** (>> 98%, Scheme 1). The reaction also demonstrates another advantage of the chromium method. The intermediate aldolate (*cf.* **13**, **14**) usually forms the five membered ring half acetal via 5-*exo*-trig ring closure which subsequently may give 6-*exo*-trig ring closure to bicyclic systems (*cf.* arrows in Scheme 1). However, chromium(III) aldolates exhibit neither sufficiently basic nor Lewis acid activity (in contrast to alkali, titanium or zinc aldolates) nor do they provide enough free aldolate for such a reaction.[8] Product **13** (and **14**) are cleanly formed upon hydrolysis without any evidence for acetal formation.[17] They decompose with base and more slowly on silica gel, on heating or prolonged standing.[18]



Scheme 2. Differentiation of ketones: **17** : **18** : **19** : **20** = 94 : 6 : 0 : 0

Finally, the preference for methyl ketones *vs.* higher ketones is demonstrated by the reaction shown in Scheme 2. Only products of the methyl ketone could be detected and isolated.

In summary chromium "enolates" show excellent chemoselectivity with aldehyde preferences similar to titanium enolates.[13] They are readily obtained from the corresponding Reformatsky substrates (α-halo-esters, -nitriles and -ketones etc.). The reaction is ideally run in Barbier fashion in one step and, with aldehydes, allows isolated yields of 80-98%.[9] Chromium(III) aldolates show neither basic nor noteworthy Lewis acid behaviour, in contrast to alkali metal aldolates and some zinc or titanium(IV) aldolates respectively. Due to the extremely slow dissociation of Cr^{III}-ligand bonds,[19] free association sites leading to "active" Lewis acidity or free aldolate (base) are not easily available. Subsequent reactions and rearrangements are thus inhibited.

References and Notes

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(11) *Typical procedure*: 2.3 equivalents of chromium dichloride (99.9% Strem Chemicals) and 5 to 20 mol% lithium iodide are suspended in the respective solvent under argon. After stirring at room temperature the carbonyl compound/s (1.05 - 4 equivalents) is/are added, followed by one equivalent of the halide. After stirring for 0.5 - 5 h, the suspension (or solution, if DMF is the solvent) is quenched with brine. The resulting mixture is extracted three times with ether/pentane (4:1) and the combined organic layers are washed successively with satd. ammonium chloride solution

and brine (in addition twice with water, if DMF was the solvent), dried with magnesium sulfate and the solvents and excess aldehyde and ketone are evaporated *in vacuo*. Sometimes, especially with THF as solvent, the crude products contain traces of lipophilic complexed paramagnetic chromium(III), often coloured green. In this case, the material is filtered through silica gel. Usually the products are NMR-spectroscopically pure. If not, further purification can be achieved by column chromatography on silica gel.

Competition experiments were run analogously with methyl ketone / ketone or aldehyde / ketone mixtures with a tenfold excess of the ketone as specified in the table.

Preparation of chromium enolates by transmetalation e. g. of lithium enolates is possible but not very practical or at least as difficult as the first attempts reported for titanium enolates.[10,13]

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(17) NMR data of new compounds:

13: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.4 Hz, 3 H), 1.54 - 1.74 (m, 4 H), 2.40 (t, J = 7.3 Hz, 2 H), 2.56 - 2.62 (m, 2 H), 2.94 (d, J = 4.8 Hz, 1 H), 3.06 - 3.13 (m, 1 H), 3.70 (s, 3 H), 3.75 - 3.92 (m, 1 H), 5.22 - 5.33 (m, 2 H), 5.75 - 5.99 (m, 1 H); - ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1, 17.7, 28.4, 28.5, 39.2, 39.3, 45.2, 45.3, 52.4, 52.5, 56.5, 57.5, 71.3, 72.1, 120.1, 120.9, 131.9, 132.9, 173.4, 173.6, 211.3, 211.5.

17: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.9 Hz, 3 H), 1.14 (s, 3 H, *anti*), 1.19 (s, 3 H, *syn*), 1.20 - 1.48 (m, 8 H), 3.10 (d, J = 9.5 Hz, 1 H), 3.16 (s, 1 H, *anti*) 3.23 (s, 1 H, *syn*), 3.72 (s, 3 H), 5.17 - 5.28 (m, 2 H), 5.90 - 6.02 (m, 1 H); - ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = *syn*: 13.9, 22.5, 22.9, 25.5, 32.2, 39.0, 51.9, 58.9, 72.9, 119.8, 132.5, 174.2; *anti*: 14.0, 22.6, 23.3, 23.6, 41.4, 51.9, 59.0, 73.3, 119.9, 132.7, 174.3.

IR, MS and elemental analysis are also in accordance with the theory. Compounds **6** - **11** are known.[6,9]

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