



The Chromium-Reformatsky Reaction: *anti*-Selective Evans-type Aldol Reactions with Excellent Inverse Induction at Ambient Temperature

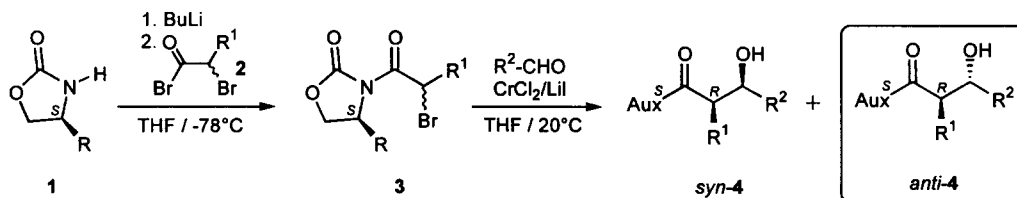
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Abstract: *anti*-Aldol products are available in a two step, one pot reaction of 4-substituted oxazolidone, 2-bromopropionyl halide, chromium dichloride and an aldehyde. The diastereofacial selection (induction) is opposite to those of boron Evans enolates, i. e. the unusual "non-Evans" *anti*-aldol products are formed in excellent excess and yield - without base and at room temperature. In contrast to our previous assumptions α -unsubstituted acetyloxazolidones do give the Evans-type β -*anti*-products preferentially.

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The advantages of Reformatsky reactions include formation of the enolate at an invariably predetermined site, under neutral conditions and in the presence of many functional groups. However, there are few reports on asymmetric syntheses with Reformatsky-type reagents. Only small or no enantiomeric excesses were found in most cases.¹ In addition, simple diastereoselection was either absent or vastly in favor of the *syn*-isomers,^{1,2} as is common with ester or similar enolates generated from deprotonation.³



#	R	R ¹	R ²	3 Yield [‡]	4 Yield [‡]	syn : anti [‡]	d. r. [‡] (α -R : S)
a	<i>i</i> -Pr	Me	<i>i</i> -Pr	85 %	96 %	11 : 89	> 98 : 2
b	CH ₂ Ph	Me	<i>i</i> -Pr	94 %	88 %	< 5 : 95	> 98 : 2
c	<i>i</i> -Pr	Me	Ph	85 %	86 %	23 : 77	> 98 : 2
d	CH ₂ Ph	Me	Ph	94 %	81 %	16 : 84	97 : 3
e	CH ₂ Ph	H	<i>i</i> -Pr	97 %	91 %	< 4 : 96	
f	CH ₂ Ph	H	Ph	97 %	88 %	13 : 87	

[‡] Yields refer to purified material, diastereomeric ratios were calculated from 300 MHz NMR spectra of crude products. Configurational assignments are based on known data,^{1,9,10} NMR, optical rotation of derivatives, chiral phase gc and X-ray. Experimental procedures of chromium-Reformatsky reactions can be found in references 4 and 6 and were applied accordingly.

The recently introduced chromium(II)-mediated Reformatsky reaction⁴⁻⁶ reproducibly yields aldol products without the necessity of activation, with excellent chemoselectivity, and - most important - without retro-reaction,⁴ a drawback of many base catalyzed aldolizations. These advantages enabled a concise synthesis of the aldol fragment of epothilones.⁵ During the latter synthesis we employed Evans oxazolidones of symmetrical 2-haloacetyl derivatives to achieve β -inductions of unusually high diastereomeric excess.^{3,7} In this paper we report the α -induction and simple diastereoselectivity achieved with unsymmetrical derivatives, i. e. 2-bromopropionyl oxazolidones (see scheme and table). We also revise the configuration for products from unsubstituted acetyl derivatives, the previously reported ones,⁵ having been misassigned.⁸

Compounds **4a-d** are "non-Evans" products, i. e. induction at C- α is opposite to that observed with Evans' boron enolates.³ "Non-Evans" products are also available from complex, Lewis acid modified systems, but usually with lower yields, *syn*-preference and much worse diastereomeric excesses despite considerably lower reaction temperatures.^{9,10} The bromoacetyl oxazolidones **3e,f** do give "Evans-like" C ^{β} -*anti*-induction as observed with the corresponding lithium and boron enolates (4% de),^{3,7,10} but with much better excesses.⁸

anti-Products have been difficult to obtain by standard methods, especially in the enantiomeric "non-Evans"-series. They are, however, formed preferentially in the chromium-Reformatsky reaction. The results with the oxazolidone derivatives (s. table) are in accordance with those from the racemic series of simple esters and amides,⁶ yet the diastereoselection is improved quantitatively. This may be due to chelation by the auxiliary or rather to a synergistic effect of direct β -induction, as evidenced by the results with α -unsubstituted acetyloxazolidones (**3e,f**), which are lacking the problem of simple diastereoselection. 4-Benzyloxazolidones thereby often provide better excesses than valinol derived ones (cf. **4b** vs. **4a**).

Benzaldehyde is the least well behaved electrophile in both, simple chromium-Reformatsky reactions,⁶ and titanium-Evans *anti*-aldol reactions (*syn* : *anti* = 1 : 3).⁹ This worst case combination is reflected in the lower excesses and yields compared to aliphatic aldehydes, exemplified in the table by isobutyraldehyde (cf. **4a/b/e** vs. **4c/d/f**). Again, even with benzaldehyde the excesses and yields achieved with chromium(II/III) at room temperature exceed those obtained with conventional methods at -78°C.

Acknowledgements: We wish to thank Prof. Dr. W. Steglich and the Degussa AG for support.

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- The provisional assignments reported in our previous communication (ref. 5) for compounds **10-16** were based on analogy to titanium enolates and the "non-Evans" induction found with propionyl derivatives, and some confusion in the literature (for clarification cf. ref. 10). Most unfortunately the assignment of acid **11**, the absolute configuration of which was supported by optical rotation, was obtained from a batch of (*S*)-oxazolidone (**S**)-**9** mislabeled and accordingly shown as (*R*)-**9**. Thus (*R*)-**9** must be replaced by (*S*)-**9** in the text, and in scheme 3 of ref. 5 the configuration of the oxazolidone moiety must be inverted, whereas scheme 2 gives the correct stereochemistry with (*R*)-**7b** as Reformatsky substrate (based on the optical rotation of derivatives, NMR and the X-ray of a similar compound).
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(Received in Germany 18 April 1997; accepted 9 May 1997)