Chromium(II)-mediated Conversion of α,β-Unsaturated Aldehydes to Cyclopropanols

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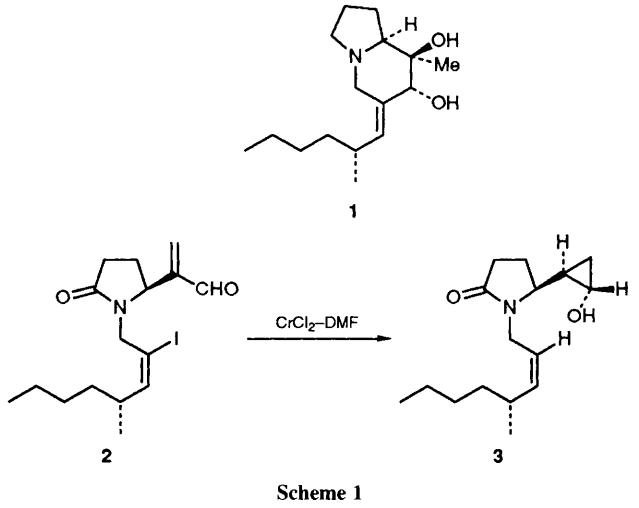
Chromium(II) chloride converts α,β-unsaturated aldehydes to the corresponding cyclopropanols.

Chromium(II) salts are powerful reducing agents and the reduction of α,β-unsaturated ketones to saturated ketones, alkyl halides to alkanes, epoxyketones to β-hydroxyketones, acetylenes to alkenes and diendiones to enediones in aqueous solution is well documented.[1] Recently, there has been intense interest in the inter- and intra-molecular addition of vinyl and allyl halides to aldehydes catalysed by chromium(II) salts under anhydrous conditions and this has been the subject of two recent reviews.[2]

In recent synthetic endeavours directed towards synthesis of allopumiliotoxin 267A **1** the intramolecular addition of vinyl halides to α,β-unsaturated aldehydes mediated by chromium(II) chloride was investigated. Under standard aldehyde vinyl iodide coupling conditions using 4 mol of chromium(II) chloride doped with 1% nickel chloride per mol of vinyl iodide in dimethylformamide (DMF) as solvent, substrate **2** reacted over two days at room temp. to give, after aqueous workup, the cyclopropanol derivative **3** in 72% yield as a single stereoisomer[3] (Scheme 1). The relative stereochemistry of the substitutents in the three-membered ring was readily assigned by NMR spectroscopy (the alcohol and the pyrrolidinone are *trans*) the absolute stereochemistry between the original chiral centre in the pyrrolidinone ring and the new chiral centres has not yet been firmly established. The vinyl iodide was also stereoselectively reduced to the alkene. Because no cyclisation products derived from vinyl chromiums are observed, then we must conclude that reduction of the α,β-unsaturated aldehyde is faster than reduction of the vinyl iodide with chromium chloride. This makes α,β-unsaturated aldehydes unsuitable substrates for coupling with vinyl iodides, though it should be noted that successful intramolecular additions of *allyl* bromides to α,β-unsaturated aldehydes have been reported.[4]

Although chromium(II) salts are known to cyclise 1,3-dihalo compounds to cyclopropanes[5] this is the first report of a chromium-mediated transformation of an α,β-unsaturated aldehyde to a cyclopropanol. Indeed, no other reagent has ever been reported to directly effect this transformation. Sato *et al.*[6] have reported a two-stage procedure for the same conversion based on 1,4-addition of a trimethylstannyl group to an α,β-unsaturated aldehyde or ketone followed by Lewis acid-mediated cyclisation of the β-stannyl carbonyl compound.

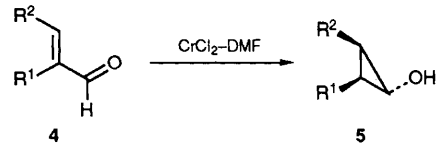


Scheme 1

The generality of this new cyclopropanation reaction was next investigated on simpler systems (**4** → **5**, Scheme 2) and the results of this study are summarised in Table 1. 2-Methylene aldehydes (**4a–c**) were readily prepared from the corresponding saturated aldehydes by the method of Greenand and Hickinbottom[7] and disubstituted α,β-unsaturated aldehyde (**4g**) was obtained by the aldol dimerisation of hexanal. Since chromium chloride is a single electron donor then theoretically 2 mol of chromium chloride per mol of aldehyde are required for the cyclopropanation. Typically 2.2 mol of chromium chloride and 2 mol% nickel chloride per mol of aldehyde were employed in the cyclisations. Treatment of 2-methylene aldehydes (**4a–c**) with chromium chloride in DMF for 3 h at room temp. gave the corresponding cyclopropanols exclusively as the *trans* isomers (Table 1, **5a–c**). In the case of aldehyde **4a**, a pinacol dimer was formed (45%), substantially reducing the yield of the desired cyclopropanol. As the degree of substitution at the β′-carbon increased, the formation of these dimers was suppressed and the yield of the desired cyclopropanation reaction increased (Table 1, **5b–c**). Linear α,β-unsaturated aldehydes were next investigated (Table 1, **5d–f**). Treatment of non-2-enal with chromium chloride gave cyclopropanol **5d** in 51% yield, again solely as the *trans*-isomer. Surprisingly in this case no pinacol dimer was formed. With crotonaldehyde **4e** only small amounts of intractable material could be isolated from the reaction mixture and we believe that the cyclopropanol is being formed but is too volatile for isolation in our workup. When cinnamaldehyde **4f** was used as substrate, large amounts of intractable material were isolated with no formation of cyclopropanol. This reaction therefore appears to be general for 2- and 3-alkyl-substituted acroleins.

Disubstituted α,β-unsaturated aldehyde **4g** was inert to the chromium reagent and was recovered qualitatively when treated with this reagent (Table 1, **5g**). Therefore, highly substituted α,β-unsaturated aldehydes may be used in chromium-mediated halide addition reactions. Indeed one intramolecular reaction of an *allyl* bromide to a highly substituted α,β-unsaturated aldehyde has been reported to proceed in high yield.[4]

The role of the nickel chloride in these reactions is unclear. When it was omitted the reactions were slower and typically did not go to completion; it is therefore recommended that nickel chloride is added.



Scheme 2

Table 1

5	R^1	R^2	*t*/h	Yield (%)
a	Bu	H	3	32
b	Cyclohexyl	H	3	63
c	1,1-Dimethylpropyl	H	3	69
d	H	Hexyl	3	51
e	H	Me	3	0
f	H	Ph	3	0
g	Pent	Bu	16	0

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