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Chromium(II)-catalyzed diastereoselective pinacol type cross coupling: studies of substrate-controlled effects

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ABSTRACT

Using 20 mol % of $CrCl_2$ as catalyst, manganese powder as reducing agent, and TMS–Cl as scavenger, various acroleins and aldehydes were coupled with moderate to high yields and diastereomeric excesses. Alkyl aldehydes usually favor *syn* configuration while aldehydes with functional groups containing chelating hetero atoms promote the formation of *anti* configuration. Using sterically demanding alkyl residues on the acrolein substrate, the *syn* configuration is definitely preferred.

1,2-Diols are found within a wide variety of natural products, many of which exhibit highly interesting pharmacological properties. Synthetic effort has therefore been focused on the synthesis of these compounds.[1] Basically two different synthetic approaches emerged, the first being performed by bishydroxylation with subsequent epoxide ring opening.[2] Yet, retro synthetic approaches always require convenient cleavage possibilities. Therefore, reductive couplings of carbonyl compounds,[3] the second approach, offer a good access to 1,2-diol compounds. Enabling, for example, a facile total synthesis of Taxol[4] or Cotylenol,[5] two well-known natural compounds having high antitumor activities along with numerous HIV-protease inhibitors bearing 1,2-diols.[6]

Aldehyde coupling reactions are therefore a quite convenient way to pinacols. However, most of the previously reported coupling protocols produce exclusively homocoupling products,[7,8] limiting the scope of this strategy to only a few total syntheses.

One notable exception is the chromium-catalyzed coupling of the acetals of acroleins with aldehydes in the presence of trimethylsilylchloride, sodium iodide, and stoichiometric amounts of manganese.[9]

In 2002, we reported the first chromium(II)-catalyzed diastereoselective pinacol type cross coupling between α,β-unsaturated carbonyl compounds and aliphatic aldehydes.[10]

This coupling protocol was extended to an intramolecular[11] pathway to form cyclic diols. Moreover, the influence of different silanes as scavenger was further investigated.[12] With 20 mol % Cr(II), we observed yields up to 80% and up to >95% de diastereoselectivity (Equation 1).

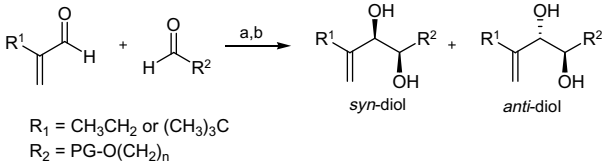
Several observations lead to the following transition state model (Scheme 1) where the initial step, the formation of a chromium allyl species via a single electron-transfer step (SET), is the determining factor.

Upon subsequent reduction (SET) of the resulting radical species, two different enolates (*Z*)-**2** and (*E*)-**3** may be formed, whereas **2** might be favored due to the chelating effect and steric reasons.

These two species undergo a nucleophilic attack on the aldehyde, forming two distinct Zimmermann–Traxler-transition states (**4** and **5,** Scheme 1).

Transition state **5** contains no strong steric constraints, and therefore should lead exclusively via pathway **E** to the *anti*-diol (**9**).

However, transition state **4** in contrast does not form one distinct diol. Due to the bulkiness of the axial trimethylsilyl combined with the interactions of R^1 and R^2, two conformations are possible, depending on the nature of R^1 and R^2.



$R_1 = CH_3CH_2$ or $(CH_3)_3C$
$R_2 = PG\text{-}O(CH_2)_n$

Conditions: a) 0.1 eq $CrCl_2$, 2.0 eq TMS-Cl, 2.0 eq Mn, DMF
b) 2.0 eq TBAF, THF

Equation 1. Chromium-catalyzed pinacol type cross coupling.

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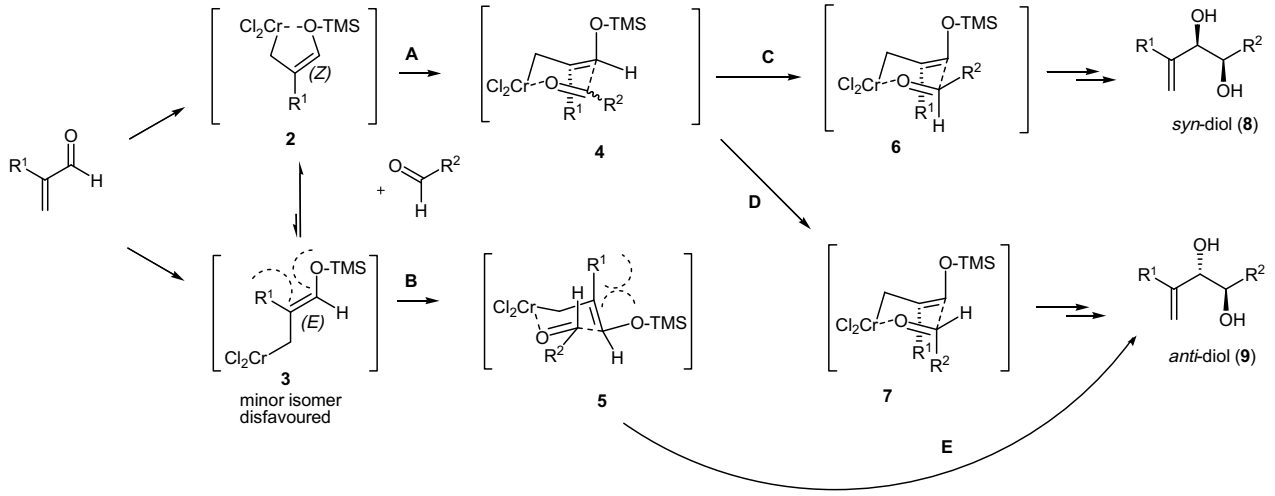


Scheme 1. Postulated transition state model.

Transition state **6** is favored if R^1 and R^2 are sterically demanding substituents. Therefore, aldehydes and acroleins with bulky substituents should predominantly lead to *syn* diols. Especially, if R^2 is less bulky and it contains a chelating atom, **7** (Path **D**) might be energetically preferred over **6** as the chelating effect will only stabilize transition state **7**. Hence, aldehydes bearing residues of moderate bulkiness and chelating ability should lead to an excess of *anti*-diol.

For the overall picture paths, **B/E** should not significantly contribute to the final product distribution because of the decreased stability of (*E*)-**3** compared to the chelation-stabilized enolate (*Z*)-**2**.

In order to determine the accuracy of the proposed transition state model, coupling reactions of differently substituted *O*-chelating aldehydes with two acroleins were performed, and the yields and diastereomeric excesses determined by isolation and NMR methods, respectively.

Table 1 displays the coupling results of 2-methylene-butanal[13] with various aldehydes containing *O*-chelating residues. 2-methylene-butanal being a less bulky substituted aldehyde led predominantly to *anti* diols.

In contrast, coupling reactions with the sterically demanding 3,3-dimethyl-2-methylenebutanal produced *syn* diols with considerable diastereomeric excesses. Results are shown in Table 2 below.

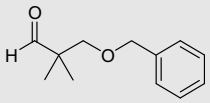
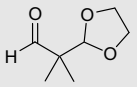
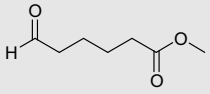
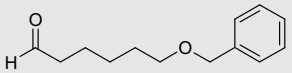
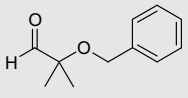
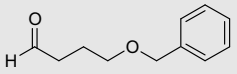
The aldehydes used in entries 1–4 of both Tables 1 and 2 are identical, but they show a completely different stereochemical outcome owing to the different acrolein partners employed. In agreement with the postulated reaction pathways that are mentioned above, bulky substituents at the acrolein site produce *syn* diols, no matter what the aldehyde looks like.

For aldehydes bearing chelating groups at γ or ζ position, transition state **6** leading to the *syn* diol seems nevertheless being quite instable, resulting in low yields (Table 2, entries 2–4). Chelating groups at the δ position (entries 5 and 6) on the other hand seem to stabilize transition state **6** much more. Yet, this substitution brought about a significant decrease in *syn* selectivity.

In conclusion, the experimental results were consistent with the proposed reaction paths leading to *syn* and *anti* diols. Reaction paths **B** and **E** are blocked at least in reactions with sterically demanding acroleins in the presence of *O*-chelating residues at the aldehyde site.

The scope of chromium-catalyzed pinacol coupling reactions has been broadened and expanded to new functionalities, which are being tolerated under the reaction conditions. Moreover, the mechanistic results obtained from our work facilitate further applications of this efficient coupling reaction on the way to stereo selectively controlled total syntheses of naturally occurring pinacols.

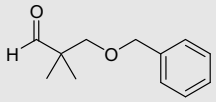
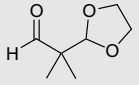
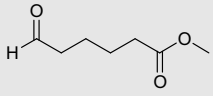
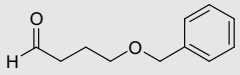
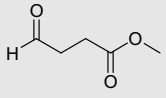
Table 1
Results of coupling reactions with 2-methylenebutanal

Entry	Aldehyde	Pos. of O	Yield[a] (%)	*de*[b] (%)
1		—	75	<5
2		γ	68	10 *anti*
3		γ	58	9 *anti*
4		ζ	69	55 *anti*
5		ζ	21	72 *anti*
6		β	83	60 *anti*
7		δ	29	68 *anti*

[a] Isolated yields.
[b] Diastereomeric ratios determined by NMR.

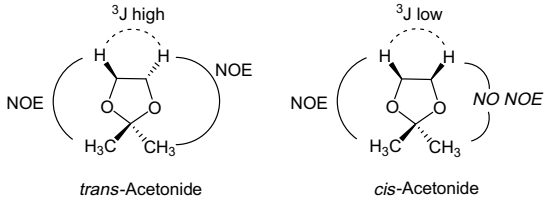
General procedure for the coupling of aldehydes with acroleins: All experiments were carried out under argon or nitrogen atmosphere using Schlenk techniques. 4 mmol (220 mg) of manganese powder and 0.2 mmol (25 mg) of chromium dichloride were suspended in

Table 2
Results of coupling reactions with 3,3-dimethyl-2-methylenebutanal

Entry	Aldehyde	Pos. of O	Yield[a]	*de*[b] (%)
1		–	61%	>95 *syn*
2		γ	26	80 *syn*
3		γ	35	82 *syn*
4		ζ	33	90 *syn*
5		δ	95	71 *syn*
6		δ	63	71 *syn*

[a] Isolated yields.
[b] Diastereomeric ratios determined by NMR.

8 ml of dry DMF. To the green solution was added 4 mmol (435 mg, 0.51 ml) of trimethylsilylchloride. The resulting suspension was allowed to stir at room temperature for 15 min, then 2 mmol of the aldehyde was added in one portion. Then 2 ml of a 0.5 M solution of the acrolein compound (1 mmol in dry DMF) was added over a period of 11 h via a syringe pump. After additional 4 h of stirring, 20 ml of water was added (no argon atmosphere needed any more). The extraction with 4 × 20 ml diethyl ether each followed by drying with magnesium sulphate and evaporation of the solvent afforded a colorless oil consisting of silylated pinacol and traces of DMF. For desilylation a solution of 1.4 g TBAF in 10 ml THF was added to the residue. After 45 min of stirring at room temperature, 10 ml of water was added, and the diol was extracted with 4 × 20 ml of diethyl ether. After drying with magnesium sulphate and evaporation, the crude product was purified by column chromatography using 25 g of silica gel with petroleum ether/ethyl acetate between 2:1 and 6:1 depending on the product ($rf \sim 0.3$).



Determination of the relative configuration of diols: The relative configuration was determined by NOE spectroscopy of the corresponding acetonide (dimethoxy propane, acetone, and PPTS). Depending on the configuration of the acetal, that is, trans or *syn*, different NOE signals and coupling constants are obtained as shown above.

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