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Influence of chelating silyl scavengers on the diastereoselectivity of chromium catalyzed pinacol cross couplings☆

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Abstract—The choice of the silyl scavenger shows a substantial influence on the diastereoselectivity of the chromium catalyzed pinacol cross coupling. In the case of the intramolecular cyclization, two competing effects are observed. If the silylation reagents contain chelating heteroatoms in the side chain, a remarkable *trans*-selectivity is observed. Conversely the *cis*-diols are preferred if bulky substituted scavengers are used. A suitable transition state model for this reaction is reported, based on formerly published results.

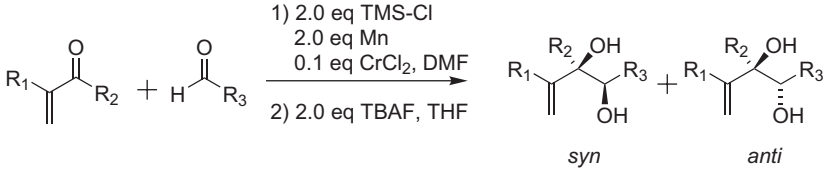
Recently, we have reported a chromium catalyzed diastereoselective pinacol cross coupling.[2] It was found that the diastereoselectivities of the coupling reactions are mainly substrate dependent (Scheme 1).[3]

Furthermore, we have reported an intramolecular cyclization of 2-methylene-α,ω-dicarbonyl compounds by chromium catalyzed pinacol cross coupling.[4] In this case, the diastereoselectivities are mainly dependent on ring sizes and the substitution of the ω-carbonyl group.

The starting point of our catalytic cross coupling reaction of acroleins with aldehydes was a publication by Takai and co-workers reporting a chromium-mediated process using a high excess of chromium(II) chloride to couple vinylketones with various aldehydes.[5] Takai described that changing the silyl scavenging reagent only had little effect on diastereoselectivities under his reaction conditions.

Encouraged by former results dealing with the effect of different scavenger reagents in the homo pinacol coupling,[6] we tried to substitute our scavenging trimethylsilyl chloride (TMS-Cl) with acetyl chloride, which we thought to be suitable to liberate chromium(III) chloride from the intermediate chromium alcoholate.[7] We found that the reaction was no longer catalytic in chromium or proceeded very slow albeit with a dramatic increase in diastereoselectivity (coupling of ethyl acrolein with 3-phenylpropionic aldehyde: 23% de, *syn*, with TMS-Cl, 78% yield; 54% de, *syn*, with AcCl, 10% yield).

Maintaining the apparently positive chelating effect in the side chain of the scavenger, we switched back to silyl chlorides of the type $ROMe_2Si$-Cl.[8] Although diastereoselectivities were not as high as in the case of acetyl chloride, a significant increase, compared to TMS-Cl, could be observed (50% de, *syn*, 83% yield).



Scheme 1. Chromium catalyzed pinacol cross coupling. R^1, R^2, R^3 = alkyl, aryl, H, subst. alkyl.

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☆ See Ref. 1.
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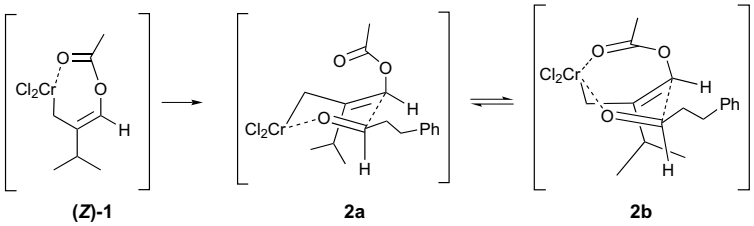


Scheme 2. Effect of a chelating carbonyl group. The coupling between 2-phenyl propionaldehyde and *iso*-propylacrolein is shown as an example.

Referring to the previously postulated transition state model,[3] an explanation for this increase in diastereoselectivity could be the coordination of the carbonyl oxygen or the oxygen in the side chain of the scavenger with the chromium cation (Scheme 2). Similar transition states were described by Trombini and co-workers for an indium-mediated addition of 3-bromopropenylacetate to aldehydes.[9]

Therefore, formation of the (*Z*)-enolate (*Z*)-**1** would be preferred as well as a stabilization of the transition state **2b**. In the intramolecular case, we chose 2-methylene-1,6-hexanedialdehyde (**3**) as a precursor for the cyclization because of its relatively poor *cis*/*trans*-selectivity with the usually used scavenger TMS-Cl.[4] As expected, depending on the nature of the silylating agent, *trans* or *cis* selectivity was observed.

Table 1 shows the remarkable influence of the silylating reagent on the diastereoselectivity. There appears to be competition between steric and chelating effects of the chlorosilane. With non-chelating bulky scavengers, the *cis*-diol is preferentially formed (entry 1) while chelating scavengers lead to an excess of the *trans*-diol (entry 4). In the case of the bulky and chelating scavenger, *t*-BuOSiMe$_2$Cl (entry 3) the steric and the chelating effects seem to be equally important. An explanation for this may be due to the possible transition states (Scheme 3): Stabilized through a chelating silyl ether (*Z*)-**4** is preferentially formed giving *trans*-**6** via transition state (*Z*)-**5**. However, with a bulky and non-chelating scavenger, (*E*)-**4** should be formed giving *cis*-**6** via transition state (*E*)-**5**.

Surprisingly, in the intermolecular case we did not observe the opposed effects of chelation and sterics but only *syn* enhancement. Some representative results are given in Table 2. An explanation for this observation is based on the difference in the transition states as the orientation of the aldehyde is variable in the intermolecular case (Fig. 1). Here, either transitions state can lead to both diastereomeric diols depending whether the

Table 1. Scavenger studies towards pinacol **6**

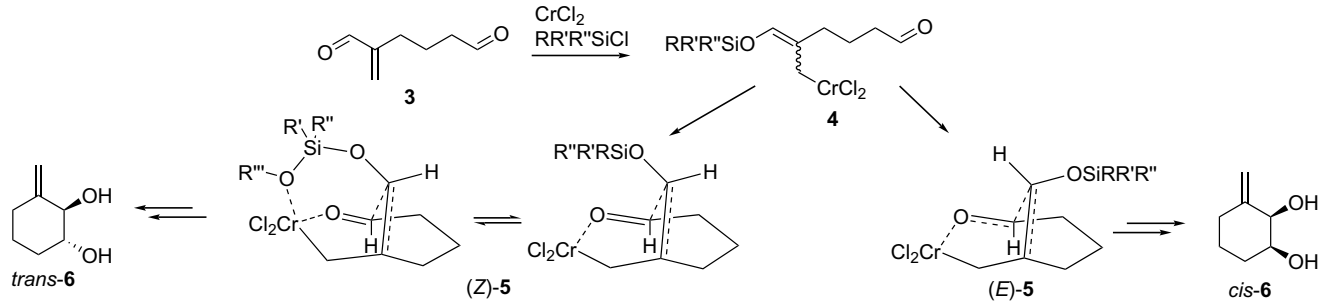
Entry	Scavenger	Yield [%][a]	de [%]
1	TBDMS-Cl	47	62 (*cis*)
2	TMS-Cl	60	18 (*cis*)
3	*t*-BuOSiMe$_2$Cl	74	4 (*cis*)
4	(MeO)$_3$SiCl	51	24 (*trans*)

[a] Yields refer to isolated products.

Table 2. Coupling reactions with chelating scavengers compared to TMS-Cl as scavenger

Entry	Scavenger	Yield [%][a]	de [%] (*syn*)
Pinacol **7**			
1a	TMS-Cl	78	21
1b	TBDMS-Cl	80	45
1c	$C_{18}H_{37}SiMe_2Cl$	82	42
1d	MeOSiMe$_2$Cl	86	36
1e	PhOSiMe$_2$Cl	90	47
1f	(MeO)$_3$SiCl	83	50
Pinacol **8**			
2a	TMS-Cl	96	19
2b	MeOSiMe$_2$Cl	92	29
2c	PhOSiMe$_2$Cl	94	44
2d	(MeO)$_3$SiCl	91	47
Pinacol **9**			
3a	TMS-Cl	67	83
3b	MeOSiMe$_2$Cl	71	>90
3c	PhOSiMe$_2$Cl	80	89
3d	(MeO)$_3$SiCl	93	>95

The target molecules are shown in Figure 1.
[a] Yields refer to isolated products.



Scheme 3. Postulated transition states leading to either *trans*- or *cis*-pinacol. In case of (*Z*)-**5** a chelating effect is possible.

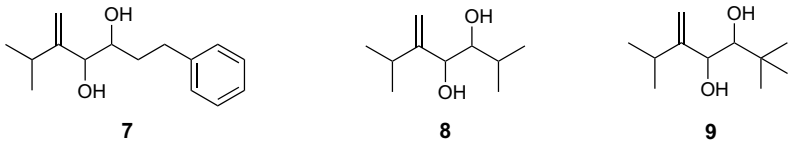


Figure 1. Coupling products summarized in Table 2.

aldehyde residue is orientated equatorially or axially (Scheme 4).[11]

In all cases, even those which already show a high diastereoselectivity with TMS-Cl (pinacol **9**) *syn*-selectivity were improved by adding chelating or bulky silyl scavenging agents (see Table 2).

As discussed previously,[3] the size of R^1 seems to be crucial for the ratio of (*Z*)- and (*E*)-**10**. With α-branched residues, R^1 (*Z*)-**10** is predominantly formed. Also a chelating scavenger should prefer the formation of (*Z*)-**10** due to additional chelating power compared to the standard OTMS group. A sterically demanding scavenger would also lead to a greater amount of (*Z*)-**10** if the relative steric demand of R^1 is higher than that of CH_2CrCl_2 complexed by solvent molecules.[10]

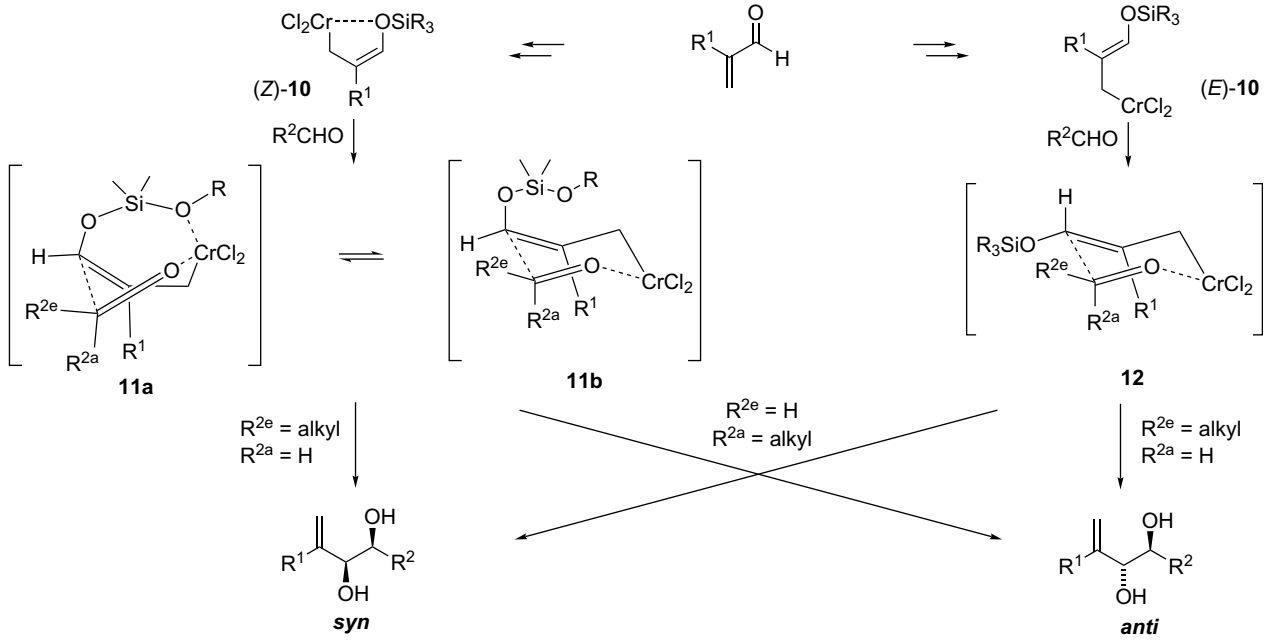
Transition states **11a** and **11b** result from (*Z*)-**10**. The equilibrium would be driven to **11a** by a chelating scavenger. If the addition of the aldehyde R^2CHO is more selective in **11a** than it is in **11b** towards the sterically favoured (pseudo)equatorial position of R^2 an increase in diastereoselectivity would be observed. On the other hand, transition state **12** resulting from (*E*)-**10** could be influenced by the size of the scavenger. Large scavengers lead to unfavourable gauche interactions between the equatorially located R^2 and $OSiR_3$, thereby forcing R^2 into the axial position also yielding an increase in *syn*-pinacol formation.

Consequently, both chelating and sterically demanding scavengers should increase the *syn*-diastereoselectivity in the case of *inter*-molecular couplings: chelating scavengers by preferring (*Z*)-**10** and a more selective equatorial orientation of R^2 in **11a**, sterically demanding scavengers by lowering the *anti*-selectivity of transition state **12**.[3]

Summary: It has been shown that the influence of chelating side chains of the silyl scavenger leads to an increase in the *syn*-diastereoselectivity of the intermolecular chromium catalyzed pinacol cross coupling. In the intramolecular cyclization reaction, the yield of the desired stereoisomer can be enhanced with the appropriate scavenger.

Presently, scavengers such as $(RO)_nMe_{(3-n)}SiCl$ with chiral residues R, which can be easily obtained from carbohydrates, are investigated.

General remarks: With exception of the TMS–ether cleavage using tetrabutylammoniumfluoride, all reactions were carried out under argon using Schlenk techniques. Chromium catalysts and the manganese powder were stored in a glove box under a nitrogen atmosphere.



Scheme 4. Postulated transition states in the intermolecular case. For a detailed discussion, see Ref. 3.

Typical procedure: In a Schlenk tube, DMF (8 ml) and the chlorosilane (4 mmol) were added to Mn powder (220 mg, 4 mmol) and $CrCl_2$ (25 mg, 0.2 mmol). The resulting suspension was stirred at room temperature for 15 min. For the *inter*-molecular couplings, the aldehyde (2 mmol) was added in one portion. The acrolein (2 ml of a 0.5 M DMF solution, 1 mmol) was added slowly over a period of 11 h by the use of a syringe pump. In the *intra*-molecular case, the cyclization precursor was added as a 0.5 M DMF solution over a period of 11 h to the mixture of $CrCl_2$, the chlorosilane and Mn powder in DMF. After additional 4 h of stirring at an ambient temperature, ether (20 ml) and water (20 ml) were added. After separation of the organic layer, the aqueous layer was extracted with ether (3×20 ml), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. THF (10 ml) and TBAF (1.4 g, 4 mmol) were added to the residue and the mixture was stirred for 45 min at room temperature. After adding water (10 ml) and ether (20 ml), the aqueous layer was extracted with ether (4×20 ml), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on 40 g of silica gel (petrol ether/ethyl acetate 4:1 to 1:1). Spectroscopic data for pinacols **6**[4] and **7**, **8**, **9**[3] are as described before.

Determination of the relative stereochemistry: The pinacols were converted into the corresponding acetonides by reaction with 2,2-dimethoxypropane in acetone catalyzed by pyridinium *para*-toluenesulfonate at room temperature under TLC control followed by column chromatography on silica gel. The relative stereochemistry of the resulting acetonide was determined by measuring the difference of the chemical shifts of the introduced methyl groups as well as by NOE spectroscopy.[12]

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