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Enantioselective and Catalytic Method for α-Crotylation of Aldehydes with a Kinetic Self-Refinement of Stereochemistry

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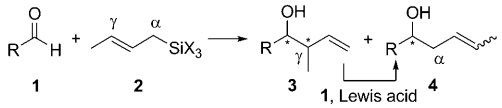
Dedicated to Professor Rudolf Zahradník on the occasion of his 80th birthday

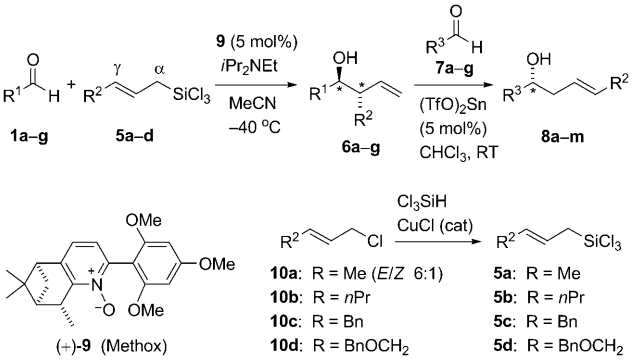
Asymmetric allylation of carbonyl compounds with allylsilanes has evolved into a valuable synthetic tool for the construction of C–C bonds.[1,2] As a rule, allylation of aldehydes **1** with organosilicon **2** and other organometallic reagents affords γ-adducts **3**, resulting from the attack at carbonyl by the distal carbon of the allylic system (Scheme 1). High enantio- and diastereoselectivities have been attained for this reaction by using various chiral catalysts.[1,2] On the other hand, stereoselective synthesis of linear products **4** represents a formidable synthetic challenge.[3]



Scheme 1. Allylation of aldehydes with allylsilanes.

It has been shown that branched alcohols **3** can rearrange into their linear isomers **4** in the presence of aldehyde **1** and a Lewis acid,[4,5] or Lewis acid only.[5] In fact, the stoichiometric allyl transfer from secondary and tertiary alcohols to aldehydes constitutes an established method.[4,6] In the asymmetric variant, the best results were attained by using tertiary alcohols derived from chiral ketones, such as menthone[7] or camphor;[8] notably, these reagents were either used in up to a three-fold excess and/or required additional chromatographic purification. In the case of chiral secondary alcohols of type **3**, *anti* isomers react with aldehydes in a stereospecific manner, giving exclusively (*E*)-**4** with inversion of configuration of the parent alcohol **3**, whereas the analogous rearrangement of the corresponding *syn* isomers **3** is less stereoconvergent.[4] However, to date, only a handful of examples employing chiral secondary alcohols **3** as allyl-transfer reagents have been reported.[9]

Herein, we present a practical, catalytic approach towards the enantioenriched homoallylic alcohols (*E*)-**8**, using a two-step protocol combining a highly enantioselective Lewis base-catalyzed addition of crotyltrichlorosilanes (*E*)-**5** to an auxiliary non-chiral aromatic aldehyde **1**, followed by a Lewis acid-catalyzed allyl transfer from the resulting alcohols **6** to the receptor aldehydes **7** (Scheme 2).



Scheme 2. A two-step, double catalytic γ-allylation sequence; for **a**–**m** in **1**, **6**, **7**, and **8**, see Tables 1 and 2.

Recently, we have developed a family of pyridine *N*-oxide catalysts for the enantioselective allylation of aromatic alde-

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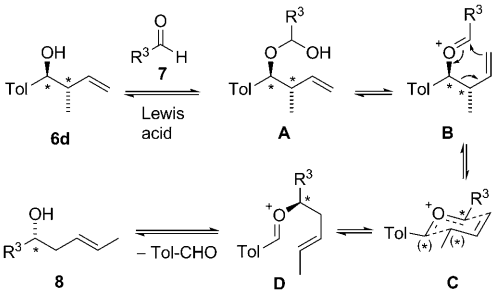
hydes with allyltrichlorosilane.[10–12] We envisioned that this methodology could be applied to the synthesis of the requisite enantio- and diastereoisomerically enriched *anti* alcohols **6** by employing *trans*-crotyltrichlorosilanes **5**, readily obtained on a large scale from the corresponding *trans*-crotyl chlorides **10** in one step (Scheme 2).[13] The Lewis base-catalyzed addition of **5** to aldehydes **1**, proceeding via a cyclic chair-like transition state,[12b] generally displays an excellent diastereocontrol.[1,2] With majority of the known catalysts, the *anti*/*syn* ratio of the products reflects the *trans*/*cis* ratio of the starting crotylsilane **5**.[1,2] The notable exceptions include quinox, an isoquinoline-derived *N*-oxide,[12] which reacts faster with *cis*-crotyltrichlorosilane (*Z*)-**5a**, and the pinene-derived *N*-oxide methox **9**[11b] that exhibits a strong kinetic preference towards the *trans*-isomer (*E*)-**5a**, leaving the *cis*-isomer unreacted.[11b] As an important consequence, the latter catalyst **9** allows the use of crotyl silane **5a** (*E*/*Z* 6:1), obtained from the technical-grade crotyl chloride **10a** (*E*/*Z* 6:1) without additional purification, giving the homoallylic alcohols **6a–d** in excellent diastereo- and enantiopurity ($\leq$98% *ee* and $\geq$96% *de*).[11b,14]

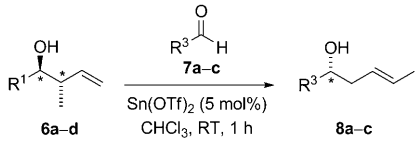
To probe the synthetic potential of alcohols **6** for the enantioselective allyl-transfer reaction, we first carried out the rearrangement of γ- to α-product (**6a**→**8a**; Table 1, entry 1). A 1:1 mixture of benzaldehyde and (1*S*,2*R*)-**6a** (R^1=Ph, R^2=Me; *anti*/*syn* 50:1, 97% *ee*), obtained by allylation of benzaldehyde with **5a** (1.2 equiv, *E*/*Z* 6:1) in the presence of (+)-**9** (5 mol%), was treated with $(TfO)_2Sn$ (5 mol%) in $CDCl_3$. Monitoring of the reaction by ^{1}H NMR spectroscopy showed a complete conversion in just 20 min; the product (*R*)-**8a** (R^2=Me, R^3=Ph) was obtained in 96% *ee* and (*E*/*Z*)>50:1 (entry 1), indicating a complete preservation of the stereochemical information.[15]

Next, we focused on cross-crotylation, employing hydrocinnamaldehyde (**7b**) as a model receptor aldehyde (Table 1). A brief screening led to the identification of $(TfO)_2Sn$ as an optimal Lewis-acidic catalyst, ensuring fast and clean conversion of **6a** into **8b**.[16] In earlier reports,[4] **6a** proved to be a poor allyl-transfer reagent as the benzaldehyde released became involved in the reaction, giving **8a** as an undesired byproduct. We found that using a three-fold excess of the receptor aldehyde **7b** completely suppressed the side reaction (entry 2). However, we felt that the substitution pattern in the auxiliary aldehyde **1** may affect the reactivity and consequently improve the efficiency of the cross-crotylation. Therefore, we examined alcohols **6b–d** (*ee* $\geq$96%, *anti*/*syn* $\geq$25:1; entries 3–5), which in turn were synthesised by using the procedure described for **6a**. According to the mechanism formulated by Nokami (Scheme 3),[4] the driving force for the key oxonia-Cope rearrangement (**B**→**D**, via the transition state **C**), is the formation of the more stable cation **D**, complemented by the shift of the terminal double bond to an internal position and by the release of the steric constrains existing in **B/C** (note the all-equatorial substituents in the transition state **C** in the case of *anti* alcohols **6**). Indeed, the more electron-rich *p*-tolyl derivative **6d** (entry 5) emerged as a clear winner, presumably owing to its enhanced capability to stabilize the positive charge in **D**, compared to the phenyl in **6a** (entry 2). On the other hand, the even more electron-rich methoxy analogue **6c** (entry 4) was found to be unstable under the reaction conditions, resulting mainly in the formation of degradation products, whereas the electron-poor nitro derivative **6b** (entry 3) was virtually inactive. As an additional benefit of **6d**, the reduced electrophilic character of *p*-tolualdehyde released during the reaction makes it less competitive with the receptor aldehyde **7** in the allyl-transfer process, thereby avoiding the formation of the corresponding alcohol (**8c**). Indeed, a competition experiment (entry 6), employing a 1:1 mixture of **7b** and **7c**, showed that the crotyl transfer from **6d** to **7c** proceeded at least 4 times slower than that to **7b**.[17]



Scheme 3. Mechanism of crotyl transfer.

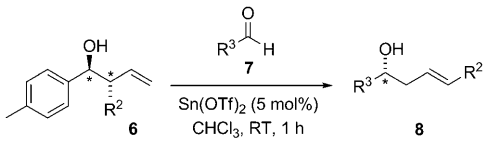
Table 1. Crotyl transfer from **6a–d** (R^2=Me) to aldehydes **7a–c**.[a]



Entry	6	R^1	7	R^3	8	Yield [%][b,c]	*ee* [%][d]
1	**6a**	Ph	**7a**	Ph	**8a**	95	96
2	**6a**	Ph	**7b**	$Ph(CH_2)_2$	**8b**	50	97
3	**6b**[e]	$4\text{-}NO_2C_6H_4$	**7b**	$Ph(CH_2)_2$	**8b**	trace	n.d.
4	**6c**[f]	$4\text{-}MeOC_6H_4$	**7b**	$Ph(CH_2)_2$	**8b**	10[k]	n.d.
5	**6d**[g]	$4\text{-}MeC_6H_4$	**7b**	$Ph(CH_2)_2$	**8b**	95	97
6	**6d**	$4\text{-}MeC_6H_4$	**7b**, **c**[h]	$Ph(CH_2)_2$	**8b**[i]	72[l]	97
7	**6d**	$4\text{-}MeC_6H_4$	**7c**	$4\text{-}MeC_6H_4$	**8c**[j]	70	55

[a] The reactions were carried out with 0.3 mmol of **6** in $CDCl_3$ (2 mL). [b] Determined by ^{1}H NMR. [c] In all cases the (*E*/*Z*) ratio was>100:1 (determined by GC). [d] Determined by ^{19}F NMR of the corresponding Mosher ester for **8a** and **8c**; determined by GC for **8b**. [e] Ref. [19]. [f] Ref. [20]. [g] 98% *ee* (determined by GC). [h] A 1:1 mixture of **7b** and **7c**. [i] **8b** was formed as a major product (see the Supporting Information). [j] **8c** was formed as a major product, unstable in the system. [k] Decomposition was mainly taking place. [l] Determined by ^{1}H NMR after 7 min.

Table 2. Allyl transfer with **6d–g** (R^1 = *p*-tolyl).[a]



Entry	6	R^2	7	R^3	8	Yield [%][b,c]	*ee* [%][d]
1	**6d**	Me	**7d**	4-$NO_2C_6H_4$	**8d**	75	98
2	**6d**	Me	**7e**	$PhCH_2$	**8e**	82	96
3	**6d**	Me	**7f**	*t*Bu	**8f**	60	93
4	**6d**	Me	**7g**	*c*C_6H_{11}	**8g**	80	97
5	**6d**	Me	**7h**	Et_2CH	**8h**	83	≥95
6	**6d**	Me	**7i**	*n*C_6H_{11}	**8i**	85	≥97
7	**6d**	Me	**7j**	$MeS(CH_2)_2$	**8j**	72[e]	≥97
8	**6e**	*n*Pr	**7b**	$Ph(CH_2)_2$	**8k**	83	97
9	**6f**	Bn	**7b**	$Ph(CH_2)_2$	**8l**	85	96
10	**6g**	CH_2OBn	**7b**	$Ph(CH_2)_2$	**8m**	85[e]	95

[a] The reactions were carried out with 1 mmol of **6** and 3 mmol of **7** (ref. [17]) in $CHCl_3$ (15 mL). [b] Isolated yield. [c] In all cases the *E*/*Z* ratio was >100:1 (determined by GC). [d] Determined by HPLC for **8d**,**e**,**k**–**m** and by ^{19}F NMR of the corresponding Mosher ester for **8f**,**i**,**j**; determined by GC for **8g**,**h**. [e] After 12 h.

Alcohol **6d** was employed in crotylation of a range of recipient aldehydes (Table 2). The reaction proved to be very efficient in every instance, with the enantioselectivity varying in the range of 93–98% *ee*, essentially irrespective of the nature of aldehyde **7**.

Significantly, this allyl transfer is not restricted to the products of crotylation (**6a–d**). Thus, a set of γ-derivatives **6e–g**, obtained from (*E*)-3-alkyl allyltrichlorosilanes **5b–d** (Scheme 2), were converted into the corresponding linear homoallylic alcohols **8k–m** in high yields and enantioselectivities (Table 2, entries 8–10).[18]

In summary, we have developed a practical, highly stereoselective, two-step catalytic protocol for the α-allylation of aldehydes **7a–j**, starting from crotyltrichlorosilanes **5a–d**. In each reaction step (**1** + **5**→**6** and **6** + **7**→**8**), one of the stereoisomers [(*E*)-**5** and *anti*-**6**, respectively] reacted faster than the other, which resulted in a kinetic stereochemical (*E*/*Z*) self-refinement of the system and led to the formation of virtually enantiomerically and geometrically pure products **8**. Since the direct highly enantioselective allylation with allyltrichlorosilanes is currently limited to aromatic aldehydes (**6**), this methodology represents a significant expansion into the aliphatic realm (**8**).[21]

Experimental Section

Crotylation: (*E*)-Crotyltrichlorosilane (**5a**; 570 mg, 3 mmol; *E*/*Z* 6:1) was added to a solution of *p*-tolualdehyde (180 μL, 1.5 mmol), Hünig base (1.57 mL, 9 mmol), and methox (+)-**9** (28 mg, 0.075 mmol) in a freshly distilled CH_3CN (10 mL) under argon at −40 °C. The reaction mixture was stirred at that temperature for 24 h and monitored by TLC. The reaction was quenched with a saturated solution of $NaHCO_3$ (30 mL) and ethyl acetate (150 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed in vacuum. The crude product was purified on a column of silica gel (3.5×15 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 → 70:30) to afford **6d** as a colorless oil (237 mg, 90%, 98% *ee*).

Crotyl transfer: Tin(II) triflate (21 mg, 0.05 mmol) was added in one portion to a solution of **6d** (176 mg, 1 mmol) and **7b** (400 mg, 3 mmol[17]) in $CHCl_3$ (15 mL; passed through a pad of basic Al_2O_3 before use) at room temperature and the mixture was stirred at room temperature for 1 h. Subsequently, the mixture was diluted with ethyl acetate (150 mL) and washed with a saturated $NaHCO_3$ solution (2× 100 mL). The organic layer was dried over sodium sulfate and the solvents were removed in vacuum. The product was purified on a column of silica gel (2.5×15 cm), using a gradient of petroleum ether and ethyl acetate (100:0 → 80:20) to afford pure **8b** as a colorless liquid (161 mg, 85%, 97% *ee*).

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Keywords: allylation · asymmetric catalysis · rearrangement · silanes · stereoselectivity

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[15] Using a catalytic amount of benzaldehyde (10 mol%) did not affect diastereo- and enantioselectivity of the rearrangement (for details, see Supporting Information).

[16] Other acids, such as TsOH and $(TfO)_3Yb{\cdot}3H_2O$ exhibited low conversion (10 and 5%, respectively). On the other hand, Me_3SiOTf proved to be equal to $(TfO)_2Sn$; these results will be published in a full paper.

[17] Since the *p*-TolCHO released during the rearrangement is characterized by a reduced propensity to compete with the receptor aldehyde **7** (compared to PhCHO), we could reduce the loading of the receptor aldehyde to 1.5–2.0 equiv with no effect on the conversion. However, for the sake of consistency, we kept the aldehyde **7** loading at 3 equiv throughout this study.

[18] The reaction of alkenol (*S*)-*p*-$TolCH(OH)CH_2CH{=}CH_2$ (91% *ee*) with aldehyde **7b** proceeded at much slower pace and resulted in a gradual loss of enantiopurity of the product $Ph\text{-}(CH_2)_2CH(OH)CH_2CH{=}CH_2$ owing to the degenerate nature of the intermediates in the oxonia-Cope rearrangement. Monitoring the product formation gave the following results: 20% conversion and 72% *ee* after 20 min; 38% and 54% *ee* after 2 h.; and 83% and 14% *ee* after 24 h.; in agreement with an earlier report by Nokami (ref. [7a]).

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