Enantioselective synthesis of homoallylic alcohols using (*E*)-but-2-enyltrichlorosilane and chiral diamines

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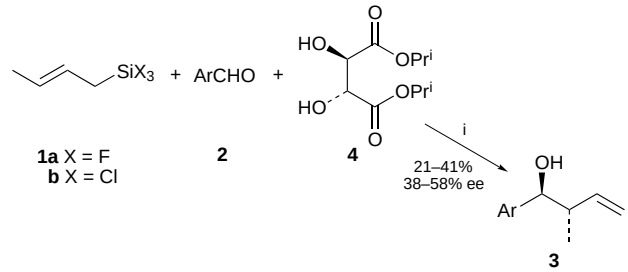
Condensation of aromatic aldehydes and (*E*)-but-2-enyltrichlorosilane in the presence of (*S*)-(+)-4-(2-methylpropyl)-2-(2-pyridinyl)-2-oxazoline gives the corresponding homoallylic alcohols in excellent *anti*-diastereoselectivity (> 99%) and good enantioselectivity (36–74%).

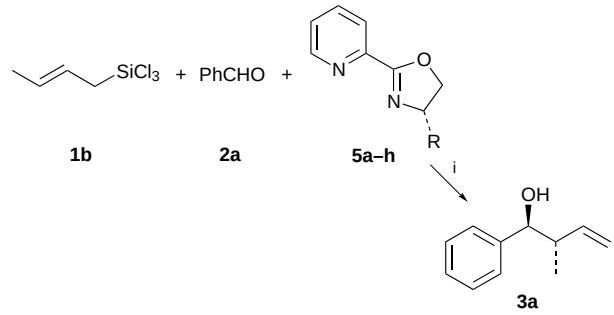
The nucleophilic addition of allylmetal moieties to carbonyl compounds is a powerful method for the construction of carbon–carbon bonds and represents an invaluable tool in organic synthesis.[1] The catalytic use of chiral Lewis acids derived from titanium(iv) complexes and (*R*)- or (*S*)-BINOL developed independently by the groups of Keck and of Tagliavini and Umani-Ronchi for the addition of allylstannane reagents to achiral aldehydes has been demonstrated to furnish homoallylic alcohols both in excellent yield and enantiomeric excess for aromatic and aliphatic aldehydes alike.[2,3] Similarly, modified titanium(iv)–BINOL systems have been found to catalyse the Sakurai–Hosomi allylation of aldehydes.[4–6] Here the advantage lies in the use of inexpensive, non-toxic silicon derivatives. A mechanistically distinct approach is the use of Lewis bases to mediate the addition of crotyltrifluorosilane **1a** to aldehydes. For instance, Sakurai has shown that the addition of stoichiometric amounts of lithium fluoride,[7] dilithium catecholate[8] or catechol[9] furnishes homoallylic alcohols in excellent yield and with relative stereochemical control. Kobayashi has pioneered the use of DMF and HMPA as the Lewis base for the addition of crotyltrichlorosilane **1b** to aldehydes[10] and some success has also been achieved by the replacement of these achiral additives with chiral phosphoramides providing homoallylic alcohols in high yield and variable enantiomeric excess (21–88% ee).[11] Very recently Wang *et al*[12] have shown that (2*R*,3*R*)-(+)-diisopropyl tartrate **4**, a bidentate *O*-donor, can be used as the asymmetric Lewis base additive giving the alcohol product **3** in 27–71% ee, and these results prompt us to disclose our own observations in this area. Herein, we now report the enantioselective crotylation of aldehydes using (*E*)-but-2-enyltrichlorosilane **1b** in the presence of chiral bidentate Lewis bases.

Our investigations commenced with the use of bidentate *O*-donors for the addition of crotyltrifluorosilane **1a** to aromatic aldehydes **2**. Whereas (±)-BINOL and (2*S*,3*S*)-butanediol were ineffective, we found that (2*R*,3*R*)-(+)-diisopropyl tartrate **4** promoted the condensation, but gave only racemic homoallylic alcohol adduct **3**. Employing crotyltrichlorosilane **1b** in place of fluorosilane **1a** resulted in the isolation of enantiomerically enriched products **3** (Scheme 1) and these results closely parallel those reported by Wang.[12]

After further screening of potential bidentate catalysts, we found that 2,2′-bipyridyl also promoted the reaction between crotyltrichlorosilane **1b** and benzaldehyde **2a** (−55 °C, 60 h, 87% yield). This promising result encouraged us to produce and test chiral pyridine derivatives in enantioselective crotylation reactions. To our great delight, use of (*S*)-(−)-4-isopropyl-2-(2-pyridinyl)-2-oxazoline **5d**[13]† provided product **3a** in 59% yield and 43% ee (−55 °C, 60 h). Consequently, a number of chiral pyridinyloxazolines **5a**–**h** were synthesised[14] and used as auxiliaries‡ with varying degrees of success (Scheme 2 and Table 1). Clearly, the leucine derived ligand **5c** gives the best results and we were able to obtain a reproducible 72% yield of exclusively the *anti*-diastereoisomeric adduct **3a** in 74% ee. A



Scheme 1 *Reagents and conditions*: i, NPr^i_2Et, CH_2Cl_2, −55 °C, 2.5 d

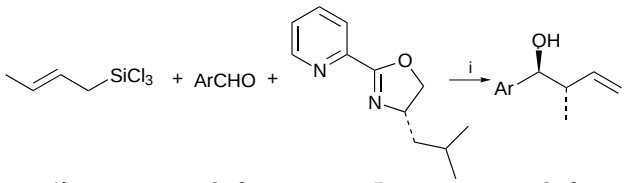


Scheme 2 *Reagents and conditions*: i, CH_2Cl_2, −78 °C, 4 h

Table 1 Preparation of homoallylic alcohol **3a** promoted by ligands **5a**–**h**

Entry	R	Ligand	Yield (%)	Ee (%)[a]
1	Me[b]	**5a**	42	22
2	(*S*)-CH(Me)Et	**5b**	18	42
3	CH_2CHMe_2	**5c**	72	74
4	Pr^i	**5d**	40	45
5	*c*-C_6H_{11}	**5e**	23	55
6	Ph	**5f**	15	41
7	CH_2-*c*-C_6H_{11}	**5g**	43	72
8	Bn	**5h**	41	53

[a] Determined by HPLC analysis (Chiracel OD). [b] Ligand **5a** was prepared from d-alaninol and gave (1*R*,2*R*)-2-methyl-1-phenylbut-3-en-1-ol as the major enantiomer.



1b **2a-f** **5c** **3a-f**

Scheme 3 *Reagents and conditions*: i, CH_2Cl_2, −78 °C, 4 h

Table 2 Preparation of homoallylic alcohols **3a–f** using ligand **5c**

Entry	R	Product	Yield (%)	Ee (%)[a]
1	Ph	**3a**	72	74
2	4-MeC_6H_4	**3b**	70	72
3	4-$MeOC_6H_4$	**3c**	79	46
4	4-$O_2NC_6H_4$	**3d**	66	36
5	4-FC_6H_4	**3e**	61	74
6	PhCH=CH	**3f**	91	60

[a] Determined by HPLC analysis (Chiracel OD, Chiracel OD-H or Chirapak AD).

number of aldehydes were examined to test the scope of the reaction (Scheme 3 and Table 2). In most cases alcohols **3a-f** were obtained in good yield and ee.

There has been much discussion about the transition state of the crotylation reaction. That products with *anti* stereochemistry are produced indicates a closed cyclic transition state, probably involving a penta- or hexa-coordinate silicon. However, the precise nature of the factors controlling the degree of asymmetric induction are as yet not clear. Work is currently underway for a clearer mechanistic understanding of this transformation and to apply our knowledge for the design of novel, second generation catalysts.

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Footnotes

† Pyridinyloxazolines **5a–f,h**[13] were prepared following literature procedures[14] from 2-cyanopyridine and the respective amino alcohol in good yield. Novel diamine **5g** was prepared according to an analogous procedure and was fully characterised.

‡ In a typical procedure, crotyltrichlorosilane **1b** (0.353 ml, 2.2 mmol) was added to a cold (−78 °C) solution of (*S*)-(+)-4-(2-methylpropyl)-2-(2-pyridinyl)-2-oxazoline **5c** (0.450 g, 2.2 mmol) in dry dichloromethane (3.6 ml). To the bright yellow solution, was added a mixture of benzaldehyde **2a** (0.204 ml, 2.0 mmol) in dichloromethane (0.4 ml) dropwise over a period of five min. After 4 h, the mixture was poured into a mixture of saturated aqueous $NaHCO_3$ (5 ml) and 1 m NaF (5 ml). The aqueous layer was extracted with diethyl ether (3 × 25 ml). The ethereal extracts were dried and concentrated to give a yellow residue, which was chromatographed (silica, hexanes–ethyl acetate 12 : 1) to provide 2-methyl-1-phenylbut-3-en-1-ol **3a** (0.235 g, 72%) as a colourless oil.

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