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

Richard M. Angell,[b] Anthony G. M. Barrett,*[a] D. Christopher Braddock,[a] Steven Swallow[c] and Benjamin D. Vickery[a]

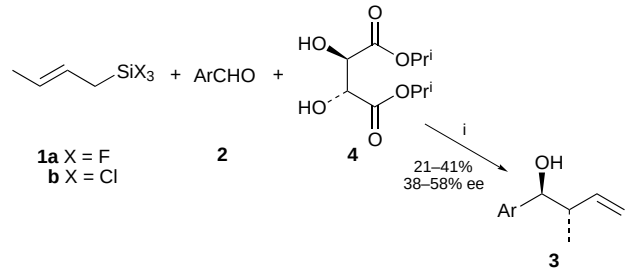
[a] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY*
[b] *Department of Medicinal Chemistry, Glaxo Wellcome Research Ltd., Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*
[c] *Department of Chemistry, Roche Discovery Welwyn, 40 Broadwater Road, Welwyn Garden City, Hertforshire, UK AL7 3AY*

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%).

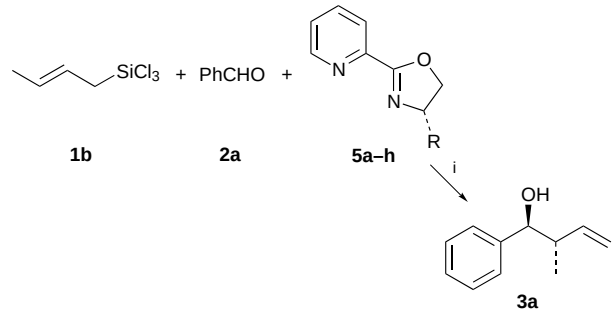
The nucleophilic addition of allylmetal moieties to carbonyl compounds is a powerful method for the construction of carbon–carbon bonds and represents an invaluable tool in organic synthesis.[1] The catalytic use of chiral Lewis acids derived from titanium(iv) complexes and (*R*)- or (*S*)-BINOL developed 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

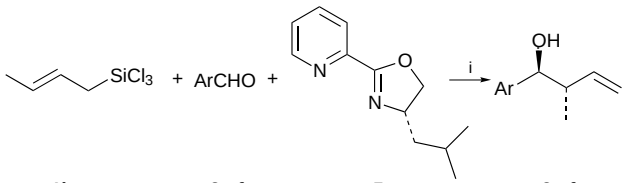


Scheme 2 *Reagents and conditions*: i, CH_2Cl_2, −78 °C, 4 h

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.

We thank Glaxo Wellcome Research Ltd. for the most generous endowment (to A.G.M.B.), the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College, the EPSRC, the DTI, Glaxo Wellcome Research Ltd. and Roche Discovery Welwyn for a studentship under the Link Asymmetric Scheme (to B. D. V.), and Dr D. J. Berrisford (UMIST) for helpful discussions.

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.

References

1 W. R. Roush, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and C. H. Heathcock, Pergamon, Oxford, 1991, vol. 2, pp. 1–53.
2 A. L. Costa, M. G. Piazza, E. Tagliavini, C. Trombini and A. Umani-Ronchi, *J. Am. Chem. Soc*., 1993, **115**, 7001; G. E. Keck, K. H. Tarbet and L. S. Geraci, *J. Am. Chem. Soc*., 1993, **115**, 8467; G. E. Keck and L. S. Geraci, *Tetrahedron Lett*., 1993, **34**, 7827; G. E. Keck, D. Krishnamurthy and M. C. Grier, *J. Org. Chem*., 1993, **58**, 6543; J. W. Faller, D. W. I. Sams and X. Liu, *J. Am. Chem. Soc*., 1996, **118**, 1217; S. Weigard and R. Brükner, *Chem. Eur. J*., 1996, **2**, 1077.
3 For the use of boron derived chiral Lewis acid, see J. A. Marshall and Y. Tang, *Synlett*, 1992, 653.
4 For a review of the Sakurai–Hosomi allylation, see A. Hosomi, *Acc. Chem. Res*., 1988, **21**, 200.
5 Boron derived chiral Lewis acid: K. Furuta, Makoto Mouri and H. Yamamoto, *Synlett*, 1991, 561; Titanium derived Lewis acid: D. R. Gauuthier, Jr. and E. M. Carreira, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 2363.
6 For the use of a titanium–(*R*)-BINOL derived Lewis acid which generates ene adducts from the addition of allysilanes to aldehydes, see K. Mikami and S. Matsukawa, *Tetrahedron Lett*., 1994, **35**, 3133.
7 M. Kira, M. Kobayashi and H. Sakurai, *Tetrahedron Lett*., 1987, **28**, 4081.
8 M. Kira, K. Sato and H. Sakurai, *J. Am. Chem. Soc*., 1988, **110**, 4599.
9 M. Kira, K. Sato and H. Sakurai, *J. Am. Chem. Soc*., 1990, **112**, 257.
10 S. Kobayashi and K. Nishio, *Tetrahedron Lett*., 1993, **34**, 3453; S. Kobayashi and K. Nishio, *J. Org. Chem*., 1994, **59**, 6620; S. Kobayashi and K. Nishio, *Chem. Lett*., 1994, 1773.
11 S. E. Denmark, D. M. Coe, N. E. Pratt and B. D. Griedel, *J. Org. Chem*., 1994, **59**, 6161; K. Iseki, Y. Kuroki, M. Takahashi and Y. Kobayashi, *Tetrahedon Lett*., 1996, **37**, 5149.
12 Z. Wang, D. Wang and X. Sui, *Chem. Commun*., 1996, 2261.
13 C. Bolm, K. Weickhardt, M. Zehnder and T. Ranff, *Chem. Ber*., 1991, **124**, 1173.
14 H. Brunner and U. Obermann, *Chem. Ber*., 1989, **122**, 499.

Received in Liverpool, UK, 24th February 1997; Com. 7/01244E