Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 1897–1900

Unexpected 1,2 *syn* diastereoselectivity in the three-component 'aza Sakurai–Hosomi' reaction

Jean-René Ella-Menye, William Dobbs, Manuella Billet, Philippe Klotz* and André Mann*

Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081, Faculté de Pharmacie, 74, route du Rhin, BP 60024, F-67401 Illkirch, France

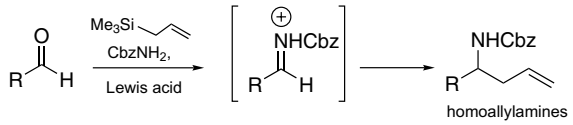
Received 7 December 2004; revised 17 January 2005; accepted 18 January 2005

Abstract—The three-component 'aza Sakurai–Hosomi' reaction performed on (±) O-protected mandelic aldehydes provided the unexpected *syn* hydroxy homoallylamines **2** and **2d** as the major adducts. An intramolecular chelated transition state via a hydrogen bond is proposed to explain this 1,2 *syn* diastereoselectivity.

The Sakurai–Hosomi reaction performed on protected α-hydroxy aldehydes has proved to be a valuable device for the production of diastereomerically enriched homoallylic alcohols by 1,2 substrate control. In these reactions both the Lewis acid used, and the protecting group on the oxygen atom of the substrate, can influence the *syn*/*anti* distribution of the homoallyl adducts. Usually the *syn*/*anti* ratio obtained can be rationalised by chelation or non-chelation Cram models.[1–4]

Recently a three-component reaction (3CR) was reported, which provided homoallylamines from various aldehydes in excellent yields via an 'aza' version of the Sakurai–Hosomi reaction (Scheme 1).[5]

In this one-pot reaction the acyliminium, produced in situ from an aldehyde and a carbamate reacted with an allylsilane[5–7] or propargylsilane,[8] in the presence of a Lewis acid, to afford homoallylic amines. However the diastereoselectivity achievable in this reaction using substrate 1,2-control, has not yet been investigated. A study of the influence of an α-hydroxy stereogenic centre next to the acyliminium would provide a one-step stereocontrolled route from aldehydes to α-hydroxy-homo-allylamines, which are desirable motives for targeting the 1,2-amino-alcohol units present in natural or biological active compounds. In this letter we report a 'aza Sakurai–Hosomi' reaction with a unexpected *syn* 1,2 diastereocontrol irrespective to the nature of the protecting groups and the Lewis acids, and we propose a model to explain this *syn* stereoselectivity.



Scheme 1. 'Aza' version of the Sakurai–Hosomi reaction.

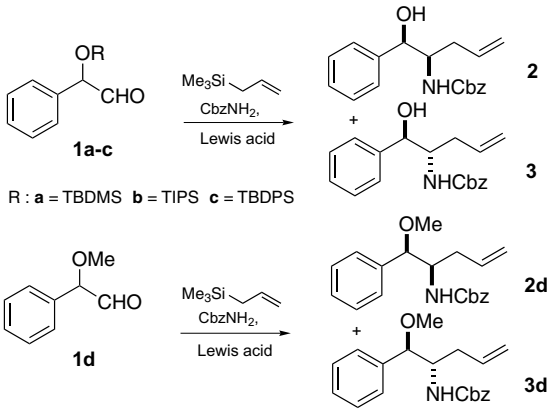
There have been a few reports on the reaction of allylsilane with semi-cyclic N,O acetals bearing an α-hydroxy stereocentre.[9–11] But in our present work the substrates are acyclic and the acyliminium precursors are formed in situ directly from the aldehydes. We examined the reactivity and the 1,2 stereocontrol in the 'aza-Sakurai–Hosomi' 3CR of the aldehydes **1a**–**d** prepared from (±) mandelic acid by conventional methods.[12] (Scheme 2).

Different protecting groups (silyl ethers in **1a**–**c** and a methyl ether in **1d)** were used, in order to evaluate their influence on the diastereoselectivity (Scheme 2).

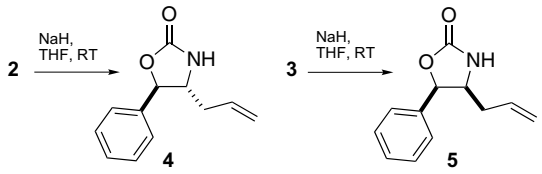
In all reactions benzylcarbamate was the nitrogen source, and various Lewis acids and solvents were used. All the reactions were performed with a stoichiometric amount of the three reaction partners (aldehyde,

Keywords: Sakurai–Hosomi reaction; Three-component reaction; Allylsilane; Homoallylamine; Diastereoselectivity.
* Corresponding authors. Tel.: +33 03 90 24 41 65; fax: +33 03 90 24 43 10; e-mail addresses: ph.klotz@pharma.u-strasbg.fr; mann@aspirine.u-strasbg.fr; andre.mann@pharma.u-strasbg.fr

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.077



Scheme 2.



Scheme 3.

benzylcarbamate and Lewis acid) starting the reaction at 0 °C and allowing it to warm to room temperature. The results are shown in Table 1.

To our surprise the silylethers **1a**–**c** gave a mixture of the desilylated hydroxy-homoallylamines **2/3** as adducts (entries 1–10), while with substrate **1d** a mixture of the adducts **2d/3d**, still bearing the ether function, was obtained (entries 11 and 12). The adducts **2** and **3** could be separated by column chromatography on silica gel and directly transformed into the corresponding oxazolidones **4** and **5** allowing determination of their relative stereochemistry (Scheme 3).

The chemical shifts and the direct measurement of the coupling constants of the vicinal hydrogens for **4**: $J = 5.9$ Hz (*trans* relationship),[13] and for **5**: $J = 8.1$ Hz (*cis*)[13] allowed assignment of the *syn* stereochemistry for **2** and *anti* for **3**. In further experiments the diastereomeric ratio was determined by ^{1}H NMR of the **2/3** mixture using the signals of the two allylic protons as internal probe. In order to determine the *syn*/*anti* ratio obtained with aldehyde **1d** (entries 11 and 12), alcohols **2** and **3** were first converted to the corresponding methylethers **2d** and **3d** using the conventional Ag_2O/CH_3I procedure. By comparing the sets of ^{1}H NMR spectra it was found that the major adduct obtained from **1d** was again the *syn* diastereomer (**2d**), and the minor adduct was the *anti* diastereomer (**3d**). Concerning the influence of the solvent, in CH_3CN the *syn* diastereomer was always the major adduct, but in CH_2Cl_2, an erosion of the diastereoselectivity was observed (entries 2 and 5) in line with a recent report.[14] The influence of the Lewis acids ($BF_3{\cdot}Et_2O$, $TiCl_4$, TMSOTf or $Sc(OTf)_3$) on the diastereoselectivity is marginal (compare entries 1, 3, 4 and 6). The yield of the reaction was reduced when the size of the silyl residue was enlarged (entries 7–10) but the *syn* selectivity was preserved in CH_3CN. Clearly the best solvent for performing the 'aza Sakurai–Hosomi' reaction is CH_3CN, and surprisingly, both chelating and non-chelating Lewis acids favour the formation of the *syn* diastereomers.

These findings are rather puzzling since both the *syn* selectivity as well as the desilylation are unexpected. Indeed, in the case of the Sakurai–Hosomi reaction with protected α-hydroxy-aldehydes, the *syn* diastereocontrol in the resulting hydroxy-homo-allylalcohols is observed **only** with chelating Lewis acids and O-alkyl protecting groups. On the other hand with O-silyl protecting groups, the *anti* diastereoselectivity is observed with chelating or non-chelating Lewis acids (rationalised by the poor basicity of the oxygen atom),[15,16] but desilylation was never mentioned. Those reports are in strong contrast with our present findings for which we suggest the following explanation: in a first step, during the formation of the acyliminium, one equivalent of water is produced, and the Lewis acid, present in the reaction

Table 1. Synthesis of the amino alcohols **2/3** and **2d/3d** from **1a**–**d**

Entry	Substrate	Lewis acid (LA)	Solvent	Yield[a] (%)	**2** *syn*/**3** *anti*[b]
1	**1a**	$BF_3{\cdot}Et_2O$	CH_3CN	84[c]	90/10
2	**1a**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	68	40/60
3	**1a**	$TiCl_4$	CH_3CN	63	85/15
4	**1a**	TMSOTf	CH_3CN	75	90/10
5	**1a**	TMSOTf	CH_2Cl_2	62	35/65
6	**1a**	$Sc(OTf)_3$	CH_3CN	60	90/10
7	**1b**	$BF_3{\cdot}Et_2O$	CH_3CN	50	90/10
8	**1b**	$TiCl_4$	CH_3CN	54[d]	95/5
9	**1c**	$BF_3{\cdot}Et_2O$	CH_3CN	59	90/10
10	**1c**	$TiCl_4$	CH_3CN	47[d]	95/5
11	**1d**	$BF_3{\cdot}Et_2O$	CH_3CN	62	95/5[e]
12	**1d**	$TiCl_4$	CH_3CN	64	90/10[e]

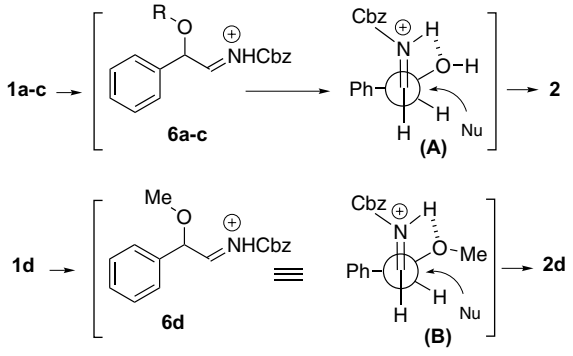
[a] Determinated after purification by chromatography.
[b] Determinated by ^{1}H NMR.
[c] Typical experience see Ref. 21.
[d] See Ref. 22.
[e] **2d/3d** ratio.

mixture, will be hydrolysed to give a nucleophilic species, which is probably responsible for the observed desilylation even in the case of bulky siloxy residues (entries 7–10). To support this assumption the O-TBDMS protected mandelic ester, the precursor of **1a** was added as spectator into the 'aza Sakurai–Hosomi' reaction mixture, and indeed O-desilylation to the corresponding mandelic ester was observed. The addition of molecular sieves to the reaction did not prevent the desilylation. At present, the exact timing of the desilylation is not known, but we believe that it takes place during the formation of the acyliminium.[17]

Secondly the formation of the same adducts **2** and **3** from **1a–c** with a prevalence for the *syn* adduct suggests a common desilylated intermediate and a chelated transition state according to Cram's rules. We propose that the acyliminiums **6a–c** are desilylated and an intramolecular hydrogen bond is developed between the oxygen atom (the acceptor) of the secondary alcohol and the hydrogen (the donor) of the acyliminium nitrogen giving a five-member ring. Thus a chelated transition state (**A**) is obtained without the assistance of the external Lewis acid (Scheme 4).[18,19]

These arguments are in line with the observation that the nature of the Lewis acids have no influence on the diastereoselectivity (see Table 1). Furthermore the *syn* diastereoselectivity, obtained with **1d**, bearing a nucleophilic oxygen atom (methylether) is also insensitive to the nature of the Lewis acid clearly supporting the hypothesis of an intramolecular hydrogen bond. Presumably the chelated transition state (**B**) deriving from acyliminium **6d** is responsible for the observed *syn* diastereoselectivity (Scheme 4). Interestingly, in similar cases Kobayashi and co-workers[11] and Kiyooka et al.[20] proposed a chelated transition state via an intramolecular hydrogen bond to explain an unexpected *syn* selectivity in the Sakurai–Hosomi reaction, respectively, with acyliminiums bearing an α-benzyloxy group and with *N*-carbamoyl α-amino-aldehydes.

To summarise, the 3CR 'aza Sakurai–Hosomi' reaction performed on the O-protected mandelic aldehydes gave the corresponding homoallylamines *in one step* with good to excellent *syn* diastereoselectivity, irrespective to the protective groups and the Lewis acid. These results are in contrast with the corresponding 'oxo' Sakurai–Hosomi reaction in which *syn* diastereoselectivity can only be achieved by *inter* molecular chelation (chelate Cram model). In the present case, the observed *syn* diastereoselectivity is best explained by an *intra* molecular chelation via an hydrogen bond developed in the acyliminium transition state. Currently we are exploring the scope of the above reaction for the synthesis of amino alcohols of biological significance.



Scheme 4. Proposed transition state.

Acknowledgements

The authors express their gratitude to Professor J. Kilburn for helpful discussions.

References and notes

1. Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729.
2. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
3. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.
4. Meugel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.
5. Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997.
6. Meester, W. J. N.; Rutjes, F. P. J. T.; Hemkens, P. H. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 1601.
7. Billet, M.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2001**, *42*, 631.
8. Billet, M.; Schoenfelder, A.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2002**, *43*, 1453.
9. Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed.* **1986**, *25*, 843.
10. Thaning, M.; Wistrand, L. G. *J. Org. Chem.* **1990**, *55*, 1406.
11. Sugiura, M.; Hagio, H.; Kobayashi, S. *Helv. Chem. Acta* **2002**, *85*, 3678, and references cited therein.
12. Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853.
13. Cainelli, G.; Panunzio, M.; Contento, M.; Mezzina, E.; Giovagnoli, D. *Tetrahedron* **1993**, *49*, 3809.
14. Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *Synlett* **2001**, 1225–1228.
15. Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.
16. Angle, S.; El-Said, N. A. *J. Am. Chem. Soc.* **2002**, *124*, 3608.
17. The positive charge developed on the iminium, and very close to the oxygen–silicium bond may assist the nucleophilic deprotection.
18. The aza-Sakurai–Hosomi reaction performed on the α-hydroxy mandelic aldehyde would have provided additional support for our postulated mechanism, but unfortunately all attempts to prepare the hydroxyaldehyde failed.
19. The ability of CH_3CN to develop intramolecular hydrogen bonding has been proposed: Ciuffarin, E.; Loi, A.; Isola, M.; Lupetti, A.; Sagramora, L.; Senatore, L. *J. Org. Chem.* **1983**, *48*, 1047.
20. Kiyooka, S.-I.; Shiomi, Y.; Kira, H.; Kaneko, Y.; Tanimori, S. *J. Org. Chem.* **1994**, *59*, 1958.
21. *Typical procedure*: The starting aldehyde (1 equiv) was dissolved in freshly distilled CH_3CN ($c = 0.25$ M) and benzylcarbamate was added (1 equiv). The reaction mixture was cooled at 0 °C and allyltrimethylsilane was added

(1 equiv) before $BF_3{\cdot}OEt_2$ (1 equiv). The reaction mixture was stirred first for 1 h at 0 °C then 2 h at room temperature and quenched by the addition of a solution of $NaHCO_3$ (10%). The products were extracted with AcOEt, washed with water, brine and dried over $MgSO_4$. The crude was purified by silica gel flash column chromatography eluting with Et_2O/heptane: 5/5, to give the major adduct (see yields in Table 1). Selected physical data for **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10–2.19 (m, 1H), 2.30–2.40 (m, 1H), 2.87 (broad s, 1H), 3.85–3.98 (m, 1H), 4.67 (t, 1H, J = 5.6 Hz), 4.88–5.11 (m, 5H), 5.68–5.82 (m, 1H), 7.21–7.60 (m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$): 36.28 (CH_2), 56.45 (C–N), 66.69 (Ph–C–O), 75,06 (C–OH), 118.06 (=CH_2), 126.71, 128.11, 128.45, 128.57, 128.73, 128.93, 134.90, 136.78, 140.88, 157.25 (C=O).

22. $PhCOCH_2NHCbz$ (10–15%) is obtained as side product with $TiCl_4$, resulting from an internal 1,2 hydride shift in the transient acyliminium (**A**).