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Study of the Lewis acid-promoted addition of silylenol ethers to imines derived from glyceraldehyde

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Abstract—Chiral *N*-benzylimines derived form D-glyceraldehyde undergo Lewis acid-promoted asymmetric Mannich reactions with *O*-methyl-*O*-trimethylsilyl dimethylketeneacetal to give β-amino acid esters in good yields and with excellent diastereoselectivities.

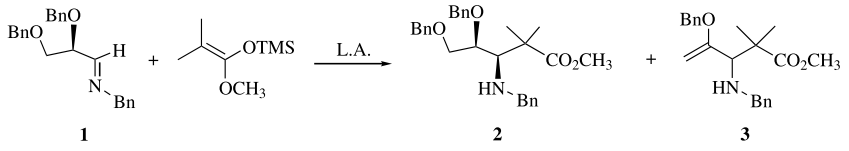
Since Ojima et al. first described[1] the Lewis acid-promoted condensation of silylenol ethers to imines, this procedure has been widely used to obtain valuable β-aminocarbonyl compounds such as β-amino acids and β-lactams.[2] Furthermore, the development of diastereo-[3] and enantioselective[4] processes has become an active area of investigation.

In recent years we have been interested in the use of chiral imines derived from suitably protected D-glyceraldehyde as chiral precursors in the synthesis of amino acids and other nitrogen-containing compounds through cyanide[5] or organometallic reagent additions[6] and in the synthesis of piperidones through hetero Diels–Alder reactions.[6f,7] The excellent results obtained in this area prompted us to investigate the reactivity of these imines towards other interesting carbon-based nucleophiles.

Initially, we searched for effective reaction conditions for the Mannich reaction of chiral imines derived from suitably protected D-glyceraldehyde and silylenol ethers. We selected as a model the reaction of the *N*-benzylimine derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde with *O*-methyl-*O*-trimethylsilyl dimethylketeneacetal, as outlined in Scheme 1, and several reaction factors such as the nature of the Lewis acid, solvent and temperature were examined.

The study revealed that ZnI_2 was the best Lewis Acid promoter tested [$BF_3{\cdot}OEt_2$, Et_2AlCl, $EtAlCl_2$, $CeCl_3$, $MgBr_2$, ZnI_2, $SnCl_4$, $Sc(OTf)_3$, $Yb(OTf)_3$], yielding the corresponding Mannich adduct **2** of 3*R*,4*S* configuration together with a by-product characterised as olefin **3** in a ratio that depended on the reaction conditions. In the presence of certain Lewis acids the *O*-benzyl primary group becomes a good leaving group and an elimination reaction followed by the nucleophilic addition of *O*-methyl-*O*-trimethylsilyl dimethylketeneacetal, giving rise to olefin **3**, competes with the pure imine nucleophilic addition.

Different experimental conditions were tested with ZnI_2 as promoter and the best results were observed when 1 equiv. of Lewis acid was used in acetonitrile as the solvent at low temperature (–20°C); under these condi-



1 **2** **3**

Scheme 1. Asymmetric Mannich reaction of chiral imine **1** with *O*-methyl-*O*-trimethylsilyl dimethylketeneacetal.

Keywords: asymmetric synthesis; imines; Mannich reaction.
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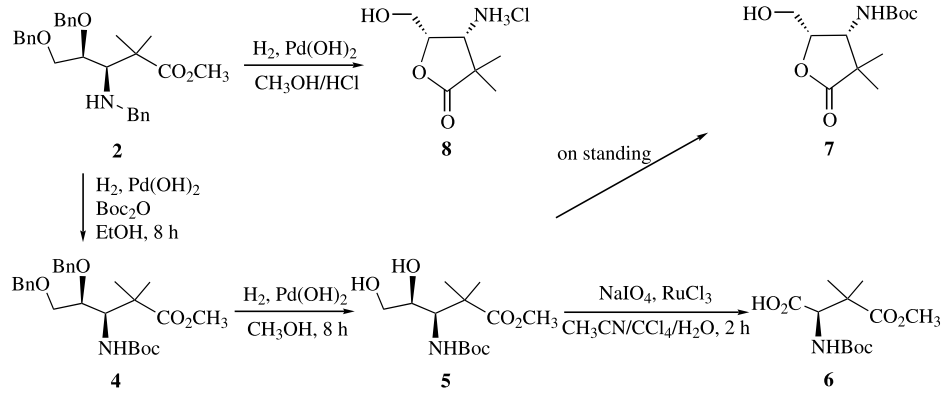


Scheme 2. Synthesis of β,β-dimethyl aspartic acid derivative **6** from Mannich adduct **2**.

tions the elimination reaction was avoided and compound **2**[8] was obtained as a single diastereoisomer in 78% isolated yield. Other reaction conditions, such as the use of diethyl ether, toluene or THF as solvent, or an increase in the temperature, did not improve the results. It is worth noting that the use of 0.1 equiv. of ZnI_2 did not affect the stereochemical result although it did give a slightly lower yield.

Compound **2** was successfully converted into suitably protected β,β-dimethylaspartic acid. At the same time the relative stereochemical assignment of a cyclic intermediate was made and the absolute configuration of compound **2** was unambiguously determined. Selective benzylamine hydrogenolysis of the Mannich adduct in the presence of $(Boc)_2O$, using $Pd(OH)_2$ on carbon as a catalyst, afforded *N*-Boc derivative **4** in 87% overall yield. Extensive hydrogenolysis of the resulting compound, using $Pd(OH)_2$ on carbon as a catalyst, cleanly afforded the desired *N*-Boc aminodiol **5**, whose immediate treatment with an excess of sodium periodate in the presence of ruthenium trichloride gave β,β-dimethylaspartic acid derivative **6**[9] in 56% yield from compound **4**. On standing, compound **5** gave the cyclic compound **7** as outlined in Scheme 2. Attempts to remove all the benzyl protecting groups in a single step using $Pd(OH)_2$ on carbon as a catalyst in CH_3OH/HCl led to the formation of lactone **8**.[10]

The relative configuration of compound **7** was assigned by analysis of difference NOE spectra. The specific pattern of NOEs (Fig. 1) can be explained by the *cis* relative configuration for compound **7**, thus the absolute configuration of the diastereoisomer formed in the Mannich reaction is 3*R*,4*S*.

We have noticed previously that in the addition of some organometallic reagents to *N*-benzylimines derived from conveniently protected D-glyceraldehyde, the sense of asymmetric induction and the degree of diastereoselectivity depend on the protecting group.[6b,6g] For this reason we also tested the addition of *O*-methyl-*O*-trimethylsilyl dimethylketeneacetal to the *N*-benzylimine **9** derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde.

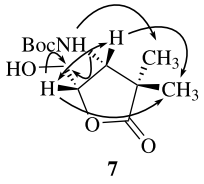


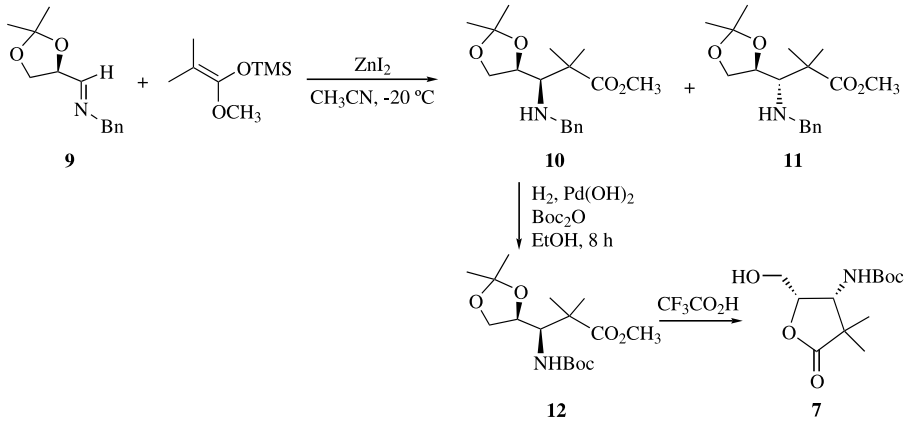
Figure 1. Determination of the relative configuration of cyclic compound **7** by NOE measurements.

When the reaction was carried out at −20°C using 1 equiv. of ZnI_2 in acetonitrile, a 92/8 mixture of diastereoisomers was obtained from which compound **10** was obtained as a single diastereoisomer in 58% isolated yield after column chromatography. This compound was converted into cyclic derivative **7** by hydrogenolysis of the *N*-benzyl group in the presence of $(Boc)_2O$ using $Pd(OH)_2$ on carbon as a catalyst (95% yield), followed by hydrolysis of the isopropylidene acetal with trifluoroacetic acid (92% yield). This latter step allowed the unambiguous assignment of the absolute configuration as 3*R*,4*S* (Scheme 3).

The excellent stereoselectivity observed in the Mannich reaction is in accordance with that previously described for the addition of thioesters to 4-methoxyphenylimines derived from 2,3-isopropylidene-D-glyceraldehyde and 2,3-cyclohexylidene-D-glyceraldehyde promoted by $TiCl_4$.[11]

The preferential formation of compounds **2** and **10** (with a *cis*-configuration) can be explained in terms of attack from the *re*-face of the silylenol ether to the α-chelate formed by simultaneous coordination of zinc both to the imine nitrogen and the α-alkoxy group (Fig. 2).

In conclusion, chiral *N*-benzylimines derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde and (*R*)-2,3-*O*-isopropylideneglyceraldehyde react with *O*-methyl-*O*-trimethylsilyl dimethylketeneacetal in the presence of ZnI_2. In both cases the attack of the nucleophile occurs from the *re* face, yielding the corresponding 3*R*,4*S* Mannich



Scheme 3. Asymmetric Mannich reaction of chiral imine **9** with *O*-methyl-*O*-trimethylsilyl dimethylketeneacetal and conversion into known compound **7**.

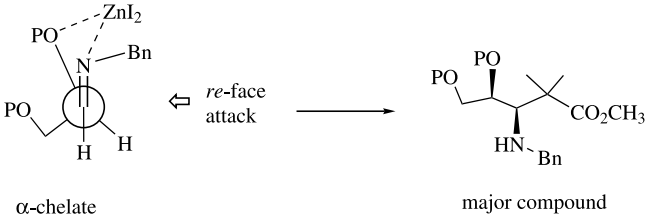


Figure 2. Stereocorrelation model explaining the formation of compounds with a *cis* configuration.

adduct with excellent diastereoselectivity. The resulting Mannich adducts have proven to be useful precursors for β,β-dimethyl aspartic acid.

The synthetic methodology described here can be extended to include silylketene acetals capable of yielding β-substituted aspartic acid precursors with two stereogenic carbon atoms. This work is now in progress and detailed results will be published in due course.

Acknowledgements

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References

1. Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett*. **1977**, *18*, 3643–3646.
2. For some reviews on this field, see: (a) Hart, D. J.; Ha, D. C. *Chem. Rev*. **1989**, *89*, 1447–1465; (b) Brown, M. J. *Heterocycles* **1989**, *29*, 2225–2244; (c) van der Steen, F. H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503–7524; (d) Kleinman, E. F. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, J.; Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p. 893; (e) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517–9582; (f) Arend, M.; Westermann, B.; Rish, N. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1044–1070; (g) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856; (h) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035; (i) Taggi, A. E.; Hefez, A. M.; Lectka, T. *Acc. Chem. Res*. **2003**, *36*, 10–19.
3. For recent papers on diastereoselective additions of silylenol ethers to imines, see: (a) Cozzi, R. G.; Simone, B. D.; Umani-Ronchi, A. *Tetrahedron Lett*. **1996**, *37*, 1691–1694; (b) Guenoun, F.; Zair, T.; Lamaty, F.; Pierrot, M.; Lazaro, R.; Viallefont, P. *Tetrahedron Lett*. **1997**, *38*, 1563–1566; (c) Kunz, H.; Bugard, A.; Schanzenbach, D. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 386–387; (d) Higashiyama, K.; Kyo, H.; Takahashi, H. *Synlett* **1998**, 489–490; (e) Hayakawa, R.; Shimizu, M. *Chem. Lett*. **1999**, 591–592; (f) Müller, R.; Röttele, H.; Henke, H.; Waldmann, H. *Chem. Eur. J*. **2000**, *6*, 2032–2043; (g) Enders, D.; Oberbörsh, S.; Adam, J. *Synlett* **2000**, 644–646; (h) Hen, S. L.; Ji, S. J.; Loh, T. P. *Tetrahedron Lett*. **2003**, *44*, 2404–2408.
4. For recent examples and reviews of enantioselective additions of silylenol ethers to imines, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069–1094; (b) Arend, M. *Angew. Chem., Int. Ed*. **1999**, *38*, 2873–2874; (c) Hagiwara, E.; Fujii, M.; Sodeoka, M. *J. Am. Chem. Soc*. **1998**, *120*, 2474–2475; (d) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed*. **2001**, *40*, 2271–2274; (e) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 12964–12965; (f) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc*. **2003**, *125*, 2507–2515.
5. (a) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron Lett*. **1995**, *36*, 2859–2860; (b) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; García, J. I. *Tetrahedron: Asymmetry* **1996**, *7*, 9563–9574; (c) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1015–1025.
6. (a) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 529–536; (b) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1997**, *53*, 1411–1416; (c) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Synthesis* **1997**, 747–749; (d) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1999**, *55*, 14145–14160; (e) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Eur. J. Org*.

Chem. **2002**, 3763–3767; (f) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **2002**, *58*, 341–354; (g) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Eur. J. Org. Chem*. **2003**, 2268–2275.

7. (a) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron Lett*. **1997**, *38*, 2547–2550; (b) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1999**, *55*, 7601–7612.
8. A solution of *N*-benzylimine **1**—derived from (*R*)-2,3-di-*O*-benzylglyceraldehyde—(570 mg, 1.58 mmol) in dry acetonitrile (20 mL) under argon was cooled to −20°C. ZnI_2 (506 mg, 1.58 mmol) was added and the reaction mixture was stirred for 10 min at this temperature. *O*-Methyl-*O*-trimethylsilyl dimethylketeneacetal (330 mg, 1.9 mmol) was then added to the solution. The reaction was stirred overnight and then quenched with a saturated solution of NH_4Cl, extracted with ether and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography eluting with ether:hexane (1:4) to afford (3*R*,4*S*)-3-benzylamino-4,5-bis-benzyloxy-2,2-dimethylpentanoic acid methyl ester (**2**): Colourless oil, $[\alpha]_D^{25}$ +11.5 (*c* 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 3H), 1.21 (s, 3H), 1.80 (brs, 1H), 2.99 (brs, 1H), 3.48–3.60 (m, 1H), 3.55 (s, 3H), 3.62–3.70 (m, 2H), 3.67 (d, 1H, $J=13.2$ Hz), 3.86 (d, 1H, $J=13.2$ Hz), 4.47 (d, 1H, $J=11.7$ Hz), 4.50 (d, 1H, $J=11.1$ Hz), 4.54 (d, 1H, $J=11.7$ Hz), 4.76 (d, 1H, $J=11.1$ Hz), 7.20–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 22.4, 48.0, 51.6, 55.1, 63.9, 72.5, 72.6, 73.3, 77.3, 126.7, 127.4, 127.6, 127.7, 128.1, 128.2, 128.4, 138.2, 138.5, 141.5, 178.1.
9. 3-*tert*-Butoxycarbonylamino-2,2-dimethyl-succinic acid 1-methyl ester (**6**): Oil, $[\alpha]_D^{25}$ +4.8 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 3H), 1.28 (s, 3H), 1.42 (s, 9H), 3.68 (s, 3H), 4.57 (d, 1H, $J=9.6$ Hz), 5.39 (bd, 1H, $J=9.6$ Hz), 7.63 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.9, 23.0, 28.2, 45.5, 52.1, 59.6, 80.1, 155.9, 173.8, 176.6.
10. (3*R*,4*S*)-4-Hydroxymethyl-3-*tert*-butoxycarbonylamino-2,2-dimethyl-4-pentanolide (**7**): White solid, mp 103–105°C, $[\alpha]_D^{25}$ +66.9 (*c* 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (s, 3H), 1.36 (s, 3H), 1.44 (s, 9H), 2.83 (brs, 1H), 3.82 (dd, 1H, $J=12.6$ Hz, $J=3.6$ Hz), 3.94 (dd, 1H, $J=12.6$ Hz, $J=4.2$ Hz), 4.34 (dd, 1H, $J=9.6$ Hz, $J=6.9$ Hz), 4.64 (ddd, 1H, $J=6.9$ Hz, $J=4.2$ Hz, $J=3.6$ Hz), 5.34 (bd, 1H, $J=8.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 25.4, 28.0, 43.5, 57.9, 60.3, 78.7, 80.3, 153.3, 181.1.
11. (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *Tetrahedron Lett*. **1992**, *33*, 1113–1116; (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *J. Org. Chem*. **1992**, *57*, 4155–4162.