Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 3615–3618

A highly enantioselective, moderately *anti*-selective aldol reaction using a novel hydrazone moiety as stereo director

Gerard P. McGlacken and Simon W. Breeden*

Department of Chemistry, National University of Ireland, Galway, Galway, Ireland

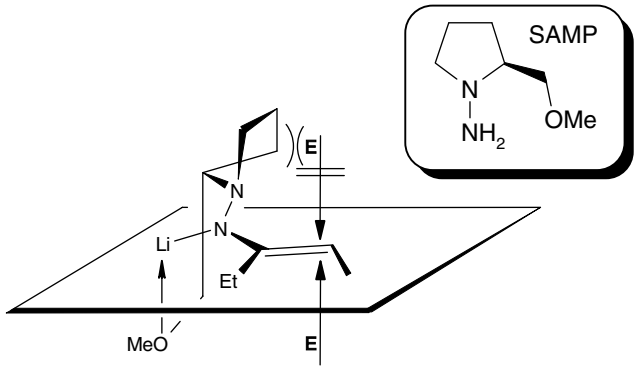
Received 1 July 2005; revised 5 August 2005; accepted 26 September 2005
Available online 14 November 2005

Abstract—The use of novel hydrazones as stereo directors with a view to develop a highly enantioselective, *anti*-diastereoselective aldol addition procedure has been investigated. A number of proline-derived hydrazones were produced and their effectiveness in directing simple alkylation of aza-enolates investigated. The most promising of these hydrazones were then used in the aldol reaction. The substituent on the oxygen of the proline had a profound effect on both the magnitude and the sense of asymmetric induction. The optimum hydrazone for the formal aldol reaction between pentanone and propionaldehyde gave a diastereoselectivity of 37% in favour of the *anti*-isomer while both isomers had an ee of 83–84%.

1. Introduction

Aldol addition reactions have long been recognised as one of the most useful tools in the construction of stereochemically defined carbon–carbon bonds.[1] The formation of carbon–carbon bonds adjacent to a carbonyl group in a diastereo- and enantioselective manner is amongst the most widespread of reactions used in the production of many natural and bio-active compounds.[2]

Classic aldol addition reactions using enolate chemistry can be accompanied by side reactions, however, these are minimised by the use of imine derivatives that often give enhanced yields and selectivities.[3] The first reported use of an imine derived auxiliary in asymmetric synthesis was an (*S*)-proline derived enamine used by Yamada et al.[4] The field was further developed by Meyers et al.[5] Concurrently, Corey was developing the non-asymmetric use of dimethylhydrazones as a controlled method for alkylating carbonyl compounds.[6] The combination and extension of these methodologies by Corey and Enders in 1976 resulted in the publication of a method permitting the asymmetric synthesis of α-substituted ketones in good yield and enantiopurity; this was then further extended to the first enantioselective aldol reaction.[7] These were the first reported uses of the widely investigated SAMP/RAMP methodology whose success is evident by a recent review and a substantial number of applications.[8] Condensation of the hydrazine, SAMP, with various ketones followed by deprotonation using LDA and trapping with electrophiles led to enantioenriched, alkylated ketones after hydrolysis.[7b,9] Investigations into the aza-enolate geometry formed when SAMP-hydrazones are treated with LDA showed only the $E_{CC}Z_{CN}$-species to be formed.[10] In the transition state, the lithium atom of the enehydrazide is intramolecularly chelated: electrophilic attack on this rigidly held intermediate occurs with good to excellent diastereofacial differentiation.[11]



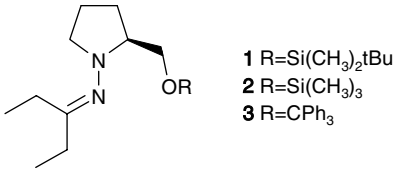
It was felt that as differentiation relies on the rigidity of the transition state, which in turn is due to the ability of

* Corresponding author at present address: Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK. Tel.: +44 (0)1904 432 568; fax: +44 (0)1904 432 705; e-mail: SWB1@york.ac.uk

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.09.027

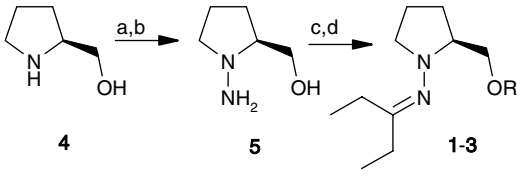
the methoxy group to donate its pair of electrons, then a siloxy group could better donate to the lithium in the aza-enolate intermediate leading to improved selectivities.

Similarly, it has been shown that extra steric bulk about the oxygen is sometimes necessary for good stereo differentiation.[12] Therefore, three hydrazones **1**, **2** and **3** were targeted.[13]



2. Results and discussion

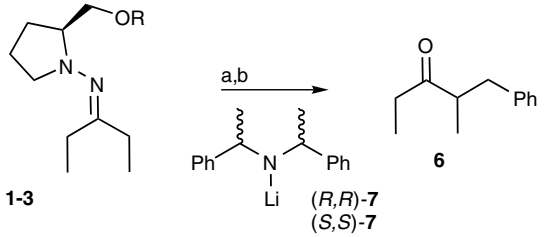
Nitrosation of the commercially available amino alcohol **4** was conveniently carried out using ethyl nitrite in alcohol.[14] However, this expensive reagent could be avoided by using silica sulfuric acid and sodium nitrite to give equally good isolated yield.[15] Although it was possible to introduce the functionality onto the oxygen at this stage and then form the hydrazone, it was practically simpler to reduce the nitroso compound and condense with pentanone prior to functionalisation. Reaction with *tert*-butyldimethylsilyl chloride, trimethylsilyl chloride or triphenylmethyl chloride gave the desired hydrazones.[16]



a) Silica sulfuric acid, $NaNO_2$; b) $LiAlH_4$, THF;
c) 3-Pentanone, TsOH; d) Imidazole, DMF, R-Cl.

With each of these hydrazones in hand, we investigated their effectiveness in a standard screening reaction (**1**–**3** to **6**) using benzyl bromide as an electrophile to trap the intermediate aza-enolate. The results are summarised in Table 1.

Initially, hydrazone **1** was treated with LDA in THF and gratifyingly gave the expected product in 61% yield with 61% ee in favour of the (*S*)-enantiomer (entry 1). This is in agreement with the SAMP methodology (R = Me) where the (*S*)-enantiomer is also preferred. Changing the solvent had a substantial effect on the reaction with both pentane and hexane causing a lowering of both yield and ee (entries 2 and 3) whereas toluene gave an improved yield and ee (entry 4). The effect of additives was then investigated and both HMPA and TMEDA caused a lowering of yield and a dramatic erosion of ee, in comparison to lithium chloride, which retained the enantioselection but increased the yield to 90% (entries 5–7). Changing the substituent on the oxygen from a TBDMS group to the less sterically demanding TMS group increased enantioselection with an ee of 86% (entry 8).



a) LDA, (*R*,*R*)-**7** or (*S*,*S*)-**7** (see Table 1) -78 °C to room temperature: recool to -78 °C then benzyl bromide to room temperature;
b) amberlyst, acetone/water

The use of lithiated chiral amines (*S*,*S*)-**7** and (*R*,*R*)-**7** as a base was then investigated with a view to potentially have a matched and a mis-matched pair of diastereomeric transition states. However, both enantiomers gave a reduced ee showing that the reaction was governed entirely by the chiral auxiliary (entries 9 and 10). With a change in substitution to the $-CPh_3$ group a surprising

Table 1. Benzyl bromide trapping of aza-enolates

Entry	Hydrazone	Base	Solvent	Additive	Yield %[a]	ee % (configuration)[b]
1	**1**	LDA	THF	—	61	61 (*S*)
2	**1**	LDA	Hexane	—	41	41 (*S*)
3	**1**	LDA	Pentane	—	37	37 (*S*)
4	**1**	LDA	Toluene	—	74	74 (*S*)
5	**1**	LDA	Toluene	HMPA	64	38 (*S*)
6	**1**	LDA	Toluene	TMEDA	57	29 (*S*)
7	**1**	LDA	Toluene	Lithium chloride	90	73 (*S*)
8	**2**	**LDA**	**Toluene**	—	**65**	**86 (*S*)**
9	**2**	(*R*,*R*)-**7**	Toluene	—	29	74 (*S*)
10	**2**	(*S*,*S*)-**7**	Toluene	—	29	55 (*S*)
11	**3**	LDA	THF	—	59	64 (*R*)
12	**3**	LDA	THF	—	63	59 (*R*)
13	**3**	LDA	Hexane	—	72	18 (*R*)
14	**3**	LDA	Toluene	—	64	7 (*R*)

[a] Isolated yield of ketone following in situ hydrolysis of hydrazone.
[b] The ee was determined by chiral GC analysis of the isolated ketones and, in some cases, confirmed by NMR investigations of the diastereomeric hydrazones prior to hydrolysis. The configuration is assigned on the basis of the predictability of the corresponding SAMP hydrazones with the reversal being confirmed by comparison of the direction of specific rotation for entries 11–14 and by chiral GC.

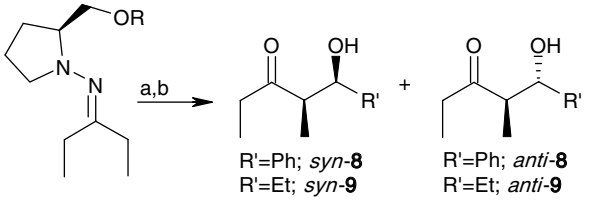
Table 2. Enantioselective aldol addition reactions

Entry	Hydrazone	R′CHO	Yield[a]	de (%)[b]	ee % *syn*-**8** or **9**[c]	ee % *anti*-**8** or **9**[c]
1	**3**	PhCHO	60	60 (*syn*- in excess)	54	30
2	**2**	PhCHO	77	24 (*anti*- in excess)	69	77
3	**2**	EtCHO	37	37 (*anti*- in excess)	83	84

[a] Isolated yield of a mixture of two isomeric ketones.
[b] Determined by ^{1}H NMR analysis of the crude material and confirmed by GC analysis.
[c] Determined by chiral GC analysis of the isolated diastereomerically pure ketone.

reversal of enantioselection was noted (entries 11–14). The change in orientation of the resulting ketone **6** was attributed to the large $-CPh_3$ group hindering chelation of the oxygen to the lithium, thus disrupting the configurationally stable intermediate. Once again, using hexane as solvent, it caused a reduction in yield and ee. In comparison to the silicon substituted case above, using toluene as solvent was detrimental with respect to enantioselection with the product being isolated with a very poor ee of 7% (entries 13 and 14).

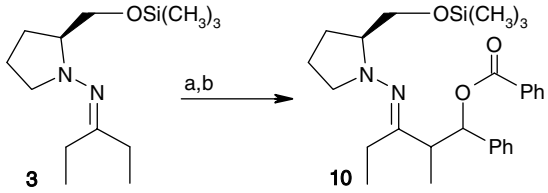
Having established a methodology for the generation of aza-enolates, which gave rise to products with high levels (up to 86% ee) of asymmetric induction we looked at applying this to the aldol addition reaction. Thus, the aza-enolates were generated as in entry 8 (LDA, toluene, −78 °C) and trapped with benzaldehyde or propionaldehyde (Table 2). Following in situ hydrolysis of the hydrazones to ketones *syn*-/*anti*-**8** and *syn*-/*anti*-**9** the diastereoselection was determined by comparison of the proton NMR spectra with independently produced samples and literature data.[17] For comparison purposes, trityl substituted hydrazone **3** was investigated and as expected gave an excess of the *syn* isomer *syn*-**8** with moderate ees for both diastereoisomers (entry 1). Gratifyingly the application of the silicon-substituted variant **2** as stereo director resulted in a reversal of diastereoselection with the *anti*-**8** product being preferentially formed (de 24%) with both isomers being formed in good ee (entry 2).



a) LDA -78 °C to room temperature: re-cooled to -78°C, then R'CHO to room temperature b) Amberlyst, acetone/water

Using propionaldehyde as the electrophile resulted in a further increase in de to 37% with the ees of both isomers being very good: 83% and 84%, respectively, for *syn*- and *anti*-**9** (entry 3).

The tandem aldol-Tishtschenko reaction of enolates has become a very useful method for the formation of up to five stereocentres in a single transformation.[18] These conditions were applied to hydrazone **2** with $R' = Et$ and Ph (2.2 equiv). Although the only isolated products were aldol addition products *syn*-/*anti*-**8** and *syn*-/*anti*-**9**, in the case of the benzaldehyde quench, GC–MS analysis showed peaks consistent with the formation of the expected ester product **10**. Benzyl alcohol was also detected showing that an active hydride was produced in this reaction, as in the enolate case. The challenge is now to enable intra-molecular transfer of this hydride to the hydrazone double bond to produce extremely useful stereochemically defined *anti*-1-amino-3-hydroxy containing materials.



a) LDA -78 °C to room temperature: re-cooled to -78°C, then aldehyde to room temperature; b) Amberlyst, acetone/water.

3. Conclusion

In conclusion, we have synthesised three novel chiral hydrazones. Parallel reactions carried out in our laboratories showed hydrazones **1** and **2** gave comparable yields and enantioselectivities (magnitude and orientation) to SAMP. However, changing to a trityl substituted stereo director resulted in reversal of enantioselection. In the aldol reaction, diastereoselection was also reversed giving an *anti*-selective protocol. An initial extension of this work to a tandem aldol-Tishtschenko reaction shows the process is viable with active hydrides being produced, however, transfer of this hydride to the hydrazone to give a 1,3-amino alcohol is somewhat more challenging.

Acknowledgement

The authors would like to thank Enterprise Ireland and the Millennium Fund of NUI, Galway.

References

1. For reviews see: (a) Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 8; (b) Palomo, C.; Oiabide, M.; Garcia, J. M. *Chem. Eur. J.* **2002**, *8*, 37–44; (c) Machajewski, T. D.; Wong, C.-H. *Angew, Chem., Int. Ed.* **2000**, *39*, 1352–1374; (d) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A.,

Yamamoto, A., Eds.; Springer: Heidelberg, Germany; Vol. III, Chapter 29; (e) Saito, S.; Yamamoto, H. *Chem. Eur. J.* **1999**, *5*, 1959–1962; (f) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, 357–389; (g) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137–1141; (h) Paterson, I.; Cowden, C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000, Chapter 9; (i) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200; (j) Heathcock, C. H.; Kim, B. M.; Williams, S. F.; Masamune, S.; Paterson, I.; Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2; (k) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041–2114.

2. (a) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *112*, 46–126; (b) Mukaiayama, T. *Tetrahedron* **1999**, *55*, 8609–8670.
3. (a) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178–2180; (b) D'Angelo, J. *Tetrahedron* **1976**, *32*, 2979–2990; (c) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517–536.
4. Yamada, S.; Hiroi, K.; Achiwa, K. *Tetrahedron Lett.* **1969**, *48*, 4233–4236.
5. Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032–3033.
6. (a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3–6; (b) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 11–14.
7. (a) Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 549–551; (b) Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1976**, *88*, 579–580; (c) Eichenauer, H.; Friedrich, E.; Lutz, W.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 206–208.
8. Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253–2327.
9. Enders, D.; Eichenauer, H. *Angew. Chem.* **1976**, *88*, 579–580.
10. (a) Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1977**, 191–194; (b) Enders, D.; Eicherauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. M. *Tetrahedron* **1984**, *40*, 1345–1359; (c) Ahlbrecht, H.; Düber, E. O.; Enders, D.; Eichenauer, H.; Weuster, P. *Tetrahedron Lett.* **1978**, 3691–3694; (d) Enders, D.; Bachstädter, G.; Kremer, K. A. M.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1522–1524.
11. Enders, D. *Chem. Scripta* **1985**, *25*, 139–147.
12. (a) Enders, D.; Kipphard, H.; Gerdes, P.; Breña-Valle, L. J.; Bhushan, V. *Bull. Soc. Chim. Belg.* **1998**, *97*, 691–704; (b) Enders, D. *Acros Org. Acta* **1995**, *1*, 37–38.
13. The parent hydrazine of hydrazone **1** has been reported as a resolving agent for racemic aldehydes (Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, pp 275–339; Enders, D.; Mies, W. *J. Chem. Soc., Chem. Commun.* **1984**, 1221–1223). Its reaction with ketones and any synthetic chemistry has not been reported.
14. García-Río, L.; Leis, J. R.; Moreira, J. A.; Norberto, F. *J. Phys. Org. Chem.* **1998**, *11*, 756–760.
15. Zolfigol, M.; Bamoniri, A. *Synlett* **2002**, *10*, 1621–1624.
16. For exemplary analytical data (hydrazone **2**) bp 134–137 °C, 4 mmHg; $[\alpha]_D = +181$ (c 1.02 in $CHCl_3$); ν_{MAX}/cm^{-1} (film) 2967, 2876, 1461 (C=N), 1250, 1082, 873, 840; δ_H (400 MHz; $CDCl_3$); 0.07 (9H, s), 1.02–1.08 (6H, m), 1.55–2.04 (4H, m), 2.13–2.48 (5H, m), 3.03–3.10 (2H, m), 3.33 (1H, dd, *J* 7.3 10.0), 3.59 (1H, dd, *J* 3.9 10.0); δ_C (100 MHz; $CDCl_3$); 0.0, 11.3, 12.1, 22.5, 24.1, 27.1, 29.1, 55.6, 66.0, 68.7, 172.5; *m*/*z* [EI] 256, 156, 153, 75, 56, $C_{13}H_{28}N_2OSi$ requires 256.1971, found 256.1989.
17. For *syn*- and *anti*-**8** (R = Ph) see: (a) Denmark, S. E.; Pham, S. M. *J. Org. Chem.* **2003**, *68*, 5045–5055; For *syn*-**9** (R = Et) see: (b) Razkin, J.; Gonzalea, A.; Gil, P. *Tetrahedron: Asymmetry* **1996**, *7*, 3479–3484; For *anti*-**9** (R = Et) see: (c) Basile, T.; Longobardo, L.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1991**, 391–392.
18. Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674–5675, and references cited therein.