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DIASTEREOSELECTIVE ADDITION OF IMIDAZOLIDIN-2-ONE CONTROLLED ENOLATES TO ACTIVATED IMINES

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ABSTRACT : Ephedrine-based imidazolidin-2-one chiral auxiliaries afford good *syn* stereoselectivity in the addition of their derived titanium enolates with an activated imine system. This provides entry into β-amino acid systems.

We and others have reported on the utility of imidazolidin-2-one chiral adjuncts in a variety of asymmetric transformations. The competitive value of this class of chiral controller has been recognized and their preparation and applications recently reviewed.[1] The most widely utilized example is the readily accessible ephedrine-derived (4R, 5S)-1,5-dimethyl-4-phenylimidazolidin-2-one **1a**. With respect to one of our current aims, this auxiliary and its hydrogenated cyclohexyl analogue **1b** presented themselves as attractive options for a stereoselective enolate-imine aldol-type approach to β-amino acids (**Figure**).

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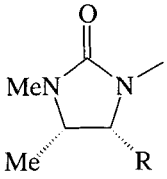
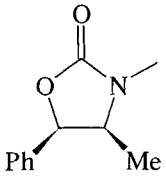


1a R = Ph
1b R = cycloC_6H_{11}



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The development of stereoselective routes to β-amino acids and β-lactams remains topical due to the occurrence of these sub-units in many antibiotics and alkaloids.[2] One of the primary strategies to β-amino acids remains the addition of enolate equivalents to suitably activated imines.[3] In a recent example of this approach, Wyatt and co-workers[4] have sought to exploit the lithium and titanium enolates of an Evans' oxazolidin-2-one chiral controller **2** in this role. This group found that the enolates of the *N*-acyl derivatives **3** added in chelated form to *N*-(benzylidene)toluene-4-sulfonamide to give a mixture of the diastereomers **6** and **7**, essentially uncontaminated by the other diastereomers **5** and **8** (**Scheme**).

As can be seen from the **Table**, the oxazolidinone-mediated reactions (Entries 1 - 3) afforded *anti*-selective products except where R = Ph which demonstrated a

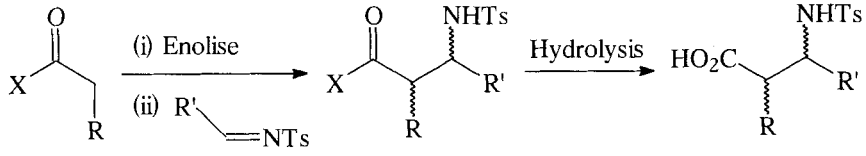

Figure: General Enolate-Imine Approach to β-Amino Acids

Scheme

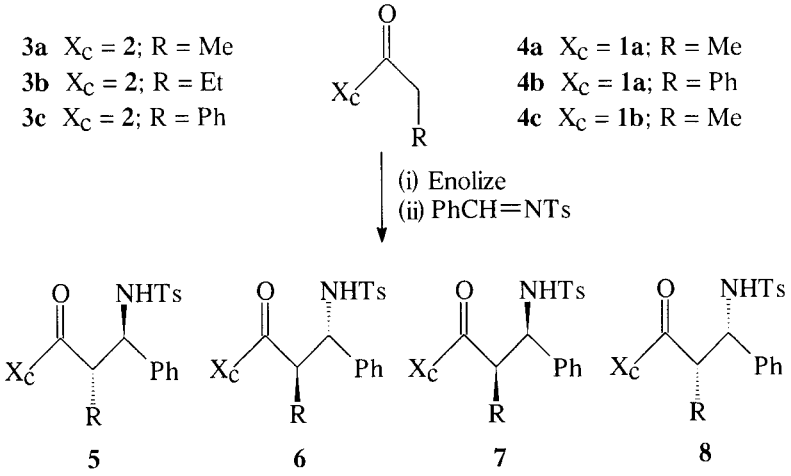

Table: Titanium Enolate Additions to *N*-(benzylidene)toluene-4-sulfonamide

Entry	Substrate	% Yields		Mp(°C) **6**	Mp(°C) **7**
		6	**7**		
1	**3a**	66	12.5	153	163.5
2	**3b**	74	8	[a]	[b]
3	**3c**	22.5	74	[a]	237
4	**4a**	9	72	**a** 210	**a** 242
5	**4b**	trace	75	[b]	**b** 262

[a] Not crystalline. [b] Not isolated

syn preference.[4] The reporting authors reasoned that this switch was due to increased steric demand.

We felt it worthwhile to report our findings in this area, primarily because of the complementary nature of the stereoselectivity observed.[5] In addition, the ease of

access to the imidazolidin-2-one auxiliary, the generally high crystallinity profile of the imidazolidinone-based derivatives, and the consistency of the stereoselectivity observed all serve to highlight the potential utility of this system.

The reactions in question (**Table**, Entries 4 and 5) were carried out on the *N*-propionyl **4a** and *N*-phenylacetyl **4b** derivatives of auxiliary **1a** to give exclusively a *syn*-dominant mixture of the diastereomers **6** and **7**. Thus, the imidazolidinones were deprotonated at 0°C with $^{i}Pr_2EtN$ / $TiCl_4$ and treated at -55°C with a pre-complexed solution of *N*-(benzylidene)toluene-4-sulfonamide / $TiCl_4$. The analogous derivative **4c** of the cyclohexyl auxiliary **1b** proved to be unreactive under these conditions, an observation that we attribute to the probable severity of steric congestion during the approach of the Ti-imine complex to the Ti-chelated enolate.

The *syn* selectivity observed in our system may be interpreted in terms of the rationale applied to standard aldol reactions.[6] Diastereomer ratios were derived from NMR studies of the crude product mixtures. The absolute product stereochemistry was confirmed by hydrolysis of the auxiliary in diastereomer **6a** and comparison of the rotation of the resulting 2-methyl-3-phenyl-3-(*N*-tosylamino)propionic acid **9** against reported values.

EXPERIMENTAL:

Melting points are reported uncorrected. NMR spectra were recorded at 300MHz

in $CDCl_3$. Pre-coated Merck Kieselgel 60 F_{254} plastic sheets were used for thin layer chromatography, and the imidazolidinone derivatives were visualized using cobalt(III) thiocyanate dip reagent.[7] The imidazolidinone auxiliaries **1a**,[8] 1b,[9] as well as derivatives **4a-4c**[9] were prepared according to the reported procedures.

General Procedure for the Aldol-Imine Reactions

To a stirred solution of the appropriate imidazolidin--2-one (1equiv.) in dry CH_2Cl_2 (4ml) at 0°C were added $^{i}Pr_2EtN$ (1.2equiv.) and titanium(IV) chloride (1.1equiv.). The resultant purple mixture of enolate was stirred at 0°C for 20 minutes. The solution was then cooled to -55°C and treated with titanium(IV) chloride (1.5mmol) and N-(benzylidene)toluene-4-sulphonamide (1.5mmol) in CH_2Cl_2 (4ml) (premixed at -5°C). The mixture was stirred at -55°C for 3h and then quenched with saturated aqueous ammonium chloride (20ml). The mixture was allowed to warm to room temperature and was then extracted with CH_2Cl_2 (3x20ml). The organic phase was dried ($MgSO_4$), concentrated, and purified.

(4R,5S,2′R,3′R)-1,5-Dimethyl-4-phenyl-3-(2′-methyl,3′-phenyl-3′-tosylamino) propanoylimidazolidin-2-one **(6a).**

The Ti enolate of (**4a**), (246mg, 1mmol) was allowed to react with the Ti complex of *N*-(benzylidene)toluene-4-sulphonamide, according to the **General Procedure** to afford (**6a**) as white solid (363mg, 72%), m.p. 242°C ($CHCl_3$).

$[\alpha]_D$ -178° (c = 0.11, CH_2Cl_2). Found C, 66.55; H, 6.12; N, 8.29%. $C_{28}H_{31}N_3O_4S$ requires C, 66.51; H, 6.18; N, 8.31%. δ_H 0.70 (3H, d, J 6.6Hz), 1.25 (3H, d, J 6.6Hz), 2.32 (3H, s), 2.83 (3H, s), 3.85 (1H, dq, J 6.5 and 8.7Hz), 4.51-4.65 (2H, m), 5.15 (1H, d, J 8.7Hz), 6.65 (1H, d, J 7Hz), 6.92-7.42 (14H, m). δ_C 14.9, 15.9, 21.3, 28.1, 43.1, 54.1, 60.4, 61.8, 126.8, 126.9, 127.8, 128.1, 128.6, 128.8, 135.6, 138.3, 139.1, 142.1, 155.9, 174.6.

The second product, ***(4R,5S,2'R,3'S)-1,5-Dimethyl-4-phenyl-3-(2'-methyl-3'-phenyl-3'-tosylamino)propanoylimidazolidin-2-one*** (**7a**) was isolated as white needles (46mg, 9%), m.p.210°C (EtOAc/hexane). $[\alpha]_D$ -7.8° (c = 0.33, CH_2Cl_2). Found: C, 66.51; H, 6.05; N, 8.36% $C_{28}H_{31}N_3O_4S$ requires C, 66.57; H, 6.08; N, 8.27%. δ_H 0.75 (3H, d, J 6.6Hz), 1.11 (3H, d, J 6.6Hz), 2.25 (3H, s), 2.83 (3H, s), 3.90 (1H, dq, J 6.6 and 8.5Hz), 4.40-4.51 (2H, m), 5.25 (1H, d, J 8.49), 6.75 (1H, d, J 9.2Hz), 6.93-7.35 (14H, m). δ_C 14.9, 15.9, 21.3, 28.1, 43.1, 54.1, 60.4, 61.8, 126.8, 126.9, 127.8, 128.1, 128.6, 128.8, 135.6, 138.3, 139.1, 142.1, 155.9, 174.6.

(4R,5S,2'R,3'R)-1,5-Dimethyl-4-phenyl-3-(2',3'-diphenyl-3'-tosylamino) phenylacetylimidazolidin-2-one (**6b**)

The Ti enolate of (**4b**) (30mg, 1mmol) was allowed to react with the Ti complex of *N*-(benzylidene)toluene-4-sulphonamide according to the **General Procedure** to afford (**6b**) as a white solid, (425mg, 75%), m.p 262°C ($CHCl_3$). $[\alpha]_D$ -118.6°

(c = 0.60, CH_2Cl_2). Found: C, 69.81; H, 5.86; N, 7.42%. $C_{33}H_{33}N_3O_4S$ requires C, 69.82; H, 5.86; N, 7.40%. δ_H 0.62 (3H, d, J 6.6Hz), 2.35 (3H, s), 2.73 (3H, s), 3.65 (1H, dq, J 6.6,8.6), 4.51 (1H, d, J 4.5Hz), 4.75 (1H, dd, J 4.5 and 6.6Hz), 4.95 (1H, d, J 8.7Hz), 6.40 (1H, d, J 6.2Hz), 6.89-7.41 (19H, m). δ_C 14.8, 21.4, 28.1, 52.9, 53.8, 59.3, 60.2, 125.9, 127.2, 127.5, 128.2, 128.3, 128.9, 129.0, 129.4, 134.9, 135.5, 136.3, 138.7, 142.6, 154.7, 169.6.

***(2R,3S)-2-methyl-3-phenyl-3-(N-tosylamino)propionic acid* (9).**

To a solution of **6a** (246mg, 0.5mmol) in THF-water (3:1, 10ml) at 0 °C were added hydrogen peroxide (0.28ml of a 30% wt/vol solution, 2.5mmol) and lithium hydroxide (53mg, 1.25mmol). The mixture was stirred at 0°C for 3h and gradually warmed to 20°C overnight. Excess peroxide was quenched at 0°C with sodium sulfite (3.8g) in water (25ml) and saturated aqueous sodium bicarbonate was added to achieve pH 9-10. THF was removed *in vacuo* and the chiral auxiliary was extracted into CH_2Cl_2 (2x40ml). The aqueous layer was then acidified to pH 1-2 with dilute hydrochloric acid and the carboxylic acid extracted with EtOAc (3x60 ml). Drying ($MgSO_4$) and evaporation of the EtOAc layer followed by purification by recrystallisation from EtOAc/hexane gave **9** (92mg, 43%) as white crystals, m.p 135-136 °C. $[\alpha]_D$ –25.6° (c = 0.06 EtOAc), (lit[4] $[\alpha]_D$ –28.1° (c = 1.0, EtOAc). δ_H 1.16 (3H, d, J 7.1Hz), 2.29 (3H, s), 2.88 (1H, m), 4.43-4.57 (1H, br t, J 8.5Hz), 6.32 (1H, br d, J 9.1Hz), 6.98-

7.53 (9H, m). δ_C 16.1, 21.6, 45.2, 61.0, 127.9, 128.3, 128.6, 128.9, 138.4, 139.0, 142.8, 153.2.

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