A Direct Catalytic Aldol Route to Protected β-Hydroxy-α-amino Acids

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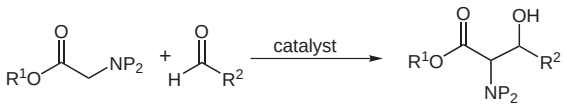
Received 24 June 2002

Abstract: The combination of triethylamine, magnesium(II) perchlorate and bipyridine generates a catalyst system for the efficient combination of ethyl isothiocyanatoacetate and a range of aromatic aldehydes. The products of these reactions are synthetically valuable protected β-hydroxy α-amino acids.

Keywords: catalysis, amino acids, aldol reaction, Lewis acid

Non-proteinogenic β-hydroxy-α-amino acids are constituents in a number of important natural products including vancomycin, cyclosporine A, the polyoxins and the cyclomarins.[1] The wide variety of biological properties displayed by these important amino acids has resulted in a variety of syntheses being reported in the literature.[2] One of the most attractive routes to these compounds involves the direct, catalyst controlled addition of a protected glycine equivalent to an aldehyde fragment (Scheme 1).

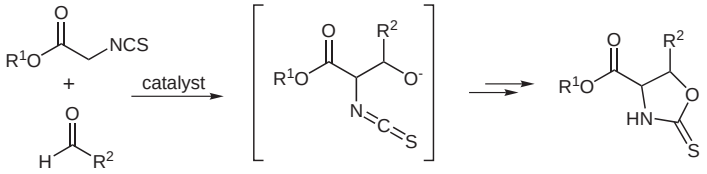


Scheme 1

Several examples of such a bond construction have been documented, although in the majority of examples a preformed enolate or an enolate equivalent such as an enol silane is employed.[3] Imperative in our design of such a reaction system was the desire to involve the catalyst in both the formation of the enolate and in the addition of the enolate to the aldehyde.[4] One potential problem in developing a catalytic variant of the above reaction is that the amino-alcohol functionality present in the products could coordinate to any metal catalyst and cause product inhibition. In an attempt to avoid this issue we chose to use isothiocyanate substituted esters as our glycine equivalents;[5] we reasoned that by incorporating the amino-alcohol functionality in an oxazolidinethione unit the metal chelating ability of the products would be reduced (Scheme 2).

In designing a catalyst we chose to employ a two-component system involving the combination of a Lewis acid and a weak amine base. In doing so we hoped that simple commercially available components could be combined to create an effective catalyst system. One important consideration when selecting the individual components to generate a catalyst system was to avoid the irreversible complexation of amine and Lewis acid; literature precedent suggested several trialkyl amines should bind reversibly to a range of metal triflate salts and thus generate active catalysts.[6]

We elected to study the addition of the commercially available ethyl isothiocyanatoacetate **1** to benzaldehyde **2** as our test reaction and evaluated a range of potential catalyst combinations against this system (Table 1). Our initial reaction conditions involved combining 1.0 equivalent of isothiocyanate-substituted ester **1** with 1.1 equivalents of benzaldehyde in THF at room temperature. Catalysts generated from $Cu(OTf)_2$, $Zn(OTf)_2$ or $Sn(OTf)_2$ in combination with Et_3N failed to deliver any of the desired aldol adduct **3**, even after extended reaction times (entries 1–3). However the combination of $Mg(OTf)_2$ (10 mol%) and Et_3N (20 mol%) delivered thiooxazolidone **3** in 26% yield (entry 4). Either increasing or decreasing the amine basicity resulted in lower yields (entries 5 and 6). The use of stoichiometric amounts of both $Mg(OTf)_2$ and Et_3N delivered the desired product in 76% yield and suggested that poor catalyst turnover may be responsible for the low yields obtained using sub-stoichiometric catalyst loadings (entry 7). Accordingly we investigated the effect of various additives with the hope of expediting catalyst release: The addition of isopropanol or trifluoroethanol increased product yields slightly but extended reaction times were still required (entries 8 and



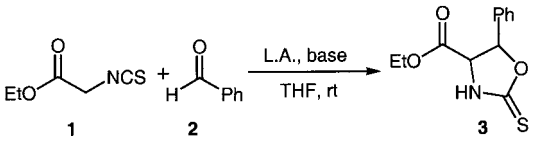
Scheme 2

Synlett 2002, No. 10, Print: 01 10 2002.
Art Id.1437-2096,E;2002,0,10,1625,1628,ftx,en;D13702ST.pdf.

ISSN 0936-5214

9).[7] Attempts to increase catalyst turnover via silylation of the oxazolidinethione resulted in no product formation (entry 10).[8] Pleasingly, a modest increase in yield (39%) was observed with the addition of a catalytic amount of the ligand bipyridine (entry 11). Using these modified conditions we chose to vary the metal counterion; both $MgBr_2$ and MgI_2 performed similarly to $Mg(OTf)_2$, however the use of $Mg(ClO_4)_2$ as the Lewis acid furnished the desired product in 94% yield after 24 hours reaction (entries 12 to 14). Further experiments confirmed that all three components: amine base, Lewis acid and ligand, were necessary to generate an active catalyst system.[9] The reason for the increase in catalyst activity upon the addition of bipyridine is not clear;[10] one possible explanation is that the added ligand allows easier dissociation of a counterion from the metal centre and thus allows more facile complexation of the substrate to the Lewis acid.

Table 1 Lewis Acid and Base Combinations for the Addition of **1** to **2**[a]

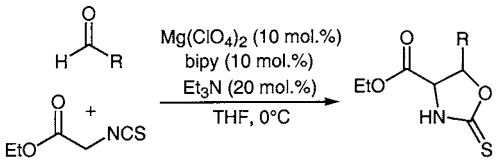


Entry	Lewis Acid (mol%)	Base[b] (mol%)	Additive[c] (mol%)	Time (h)	Yield (%)
1	$Cu(OTf)_2$ (10)	Et_3N (20)	–	63	0
2	$Zn(OTf)_2$ (10)	Et_3N (20)	–	48	0
3	$Sn(TOf)_2$ (10)	Et_3N (20)	–	45	0
4	$Mg(OTf)_2$ (10)	Et_3N (20)	–	95	26
5	$Mg(OTf)_2$ (10)	DBU (20)	–	138	15
6	$Mg(OTf)_2$ (10)	NEP (20)	–	45	9
7	$Mg(OTf)_2$ (110)	Et_3N (110)	–	100	76
8	$Mg(OTf)_2$ (10)	Et_3N (20)	*i*-PrOH (100)	71	14
9	$Mg(OTf)_2$ (10)	Et_3N (20)	CF_3CH_2OH (100)	71	16
10	$Mg(OTf)_2$ (10)	Et_3N (20)	TMS-Cl (100)	72	0
11	$Mg(OTf)_2$ (10)	Et_3N (20)	bipy (10)	103	39
12	$MgBr_2$ (10)	Et_3N (20)	bipy (10)	116	31
13	MgI_2 (10)	Et_3N (20)	bipy (10)	65	35
14	$Mg(ClO_4)_2$ (10)	Et_3N (20)	bipy (10)	24	94

[a] All reactions: ester (1.0 equiv), aldehyde (1.1 equiv).
[b] NEP = *N*-ethyl piperidine.
[c] bipy = bipyridine.

With optimised conditions in hand, the range of aldehydes that could be successfully employed in the reaction was investigated (Table 2).[11] The catalyst system generated from $Mg(ClO_4)_2$ (10 mol%), bipy (10 mol%) and Et_3N (20 mol%) was used to promote the combination of ester **1** (1.0 equiv) with a range of aromatic aldehydes (1.1 equiv); in order to avoid the formation of byproducts all reactions were conducted at 0 °C in THF.[12] The benzaldehyde derived adduct was obtained in 84% yield as a 65:35 mixture of diastereomers in favour of the *syn* aldol isomer (entry 1). Electron poor aldehydes such as *p*-NO_2- and *p*-CN-benzaldehydes resulted in good yields of the aldol adducts with the diastereoselectivities remaining similar (entries 2 and 3).[13] Inductively electron-withdrawing bromine substituents had little effect on the reaction efficiency with *ortho*-, *meta*- and *para*-bromobenzaldehydes delivering adducts in 84%, 88% and 84% yields respectively (entries 4–6). Pleasingly, sterically hindered 2,6-dichlorobenzaldehyde also performed well furnishing the product in 89% yield as a 60:40 mix of diastereomers. Electron rich aldehydes such as *para*-anisaldehyde (67%) and 2-naphthaldehyde (89%) are also tolerated well (entries 8 and 9).

Table 2 Variation in Aldehyde Component[a]



Entry	R	Time (h)	*Syn*:*Anti*[b]	Yield (%)[c]
1	C_6H_5	20	65:35	84
2	4-NO_2-C_6H_4	25	70:30	70
3	4-CN-C_6H_4	22	75:25	85
4	2-Br-C_6H_4	23	65:35	84
5	3-Br-C_6H_4	21	65:35	88
6	4-Br-C_6H_4	21	70:30	84
7	2,6-di-Cl-C_6H_4	21	60:40	89[d]
8	4-OMe-C_6H_4	23	60:40	67
9	2-naphth	21	60:40	89

[a] All reactions: ester (1.0 equiv), aldehyde (1.1. equiv).
[b] Diastereomer ratios measured by ^1H NMR.
[c] Combined yield of the isolated diastereomers.
[d] Diastereomers not separable.

In summary, we have demonstrated that a catalyst system generated from three commercially available components can be used to catalyse the addition of ethyl isothiocyanatoacetate, a commercially available glycine equivalent, to a range of aromatic aldehydes. The products of these reactions are synthetically useful protected β-hydroxy-α-amino acids. Finally, we note the significance of the need for an added external ligand (bipyridine) to generate an active catalyst system; this observation is encouraging for the development of an asymmetric version of this process utilizing enantiomerically enriched ligands. Studies towards this goal, and to expand the range of the process, will be reported in due course.

Acknowledgement

We thank the EPSRC, AstraZeneca (strategic research fund) and Pfizer for funding. The EPSRC Mass Spectrometry Service at the University of Wales Swansea is also thanked for their assistance.

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(9) A reaction using only Et_3N (no metal salt or bipyridine) provided an 8% yield of the aldol adducts after 48 h at r.t. Reactions excluding Et_3N provided no product.

(10) For a recent example of Lewis acid catalysed reaction in which the addition of an external ligand was needed to achieve reaction, see ref.[6a]

(11) **The Preparation of 3 Serves as a Typical Procedure**: $Mg(ClO_4)_2$ (31 mg, 0.138 mmol) and bipyridine (22 mg, 0.138 mmol) were stirred for 10 min in dry THF (5.5 mL) under nitrogen at r.t. Triethylamine (39 μL, 0.276 mmol) was then added and the mixture was cooled at 0 °C. After 10 min ethyl isothiocyanatoacetate (170 μL, 1.38 mmol) and benzaldehyde (150 μL, 1.52 mmol) were added. After 20 h at 0 °C, the reaction was quenched with a sat. aq ammonium chloride solution (5 mL). The organic layer was separated and the aq layer was extracted with dichloromethane (3 × 10 mL). The organic portions were washed with a sat. aq copper sulphate solution (5 mL) and with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc–DCM, 2:98) to give a mixture of the *syn*- and *anti*-oxazolidinethiones, **3** (290 mg, 84%, *syn*:*anti* = 65:35), as a viscous oil. Analytical samples were prepared by recrystallisation from dichloromethane/petroleum spirit 40–60 °C.

(12) Small amounts of a by-product originating from the addition of a second equivalent of ester **1** to the initially formed aldol adduct could be isolated in several experiments when conducted at r.t.

(13) All new compounds were fully characterised. Selected data for novel compounds:
(4*R,5*R**)-Ethyl 5-(4-nitrophenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.24 (2 H, m), 7.71 (1 H, s), 7.57–7.54 (2 H, m), 6.19 (1 H, d, *J* = 9.8 Hz), 5.00 (1 H, d, *J* = 9.8 Hz), 3.87 (1 H, app. dq, *J* = 10.8 and 7.2 Hz), 3.72 (1 H, app. dq, *J* = 10.8 and 7.2 Hz), 0.89 (3 H, app. t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5, 166.6, 148.8, 140.2, 128.1, 124.0, 83.9, 62.9, 62.8, 14.1.
(4*R,5*R**)-Ethyl 5-(4-cyanophenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.46 (4 H, m), 7.36 (1 H, s), 6.12 (1 H, d, *J* = 9.8 Hz), 4.94 (1 H, d, *J* = 9.8 Hz), 3.85 (1 H, app. dq, *J* = 10.7 and 7.2 Hz), 3.72 (1 H, app. dq, *J* = 10.7 and 7.2 Hz), 0.88 (3 H, app. t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD, 66:33): δ = 189.6, 167.0, 138.9, 132.2, 127.5, 118.0, 113.1, 83.7, 63.0, 62.1, 13.6.
(4*S,5*R**)-Ethyl 5-(4-cyanophenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (1 H, s), 7.75–7.54 (4 H, m), 6.03 (1 H, d, *J* = 6.2 Hz), 4.44 (1 H, d, *J* = 6.2 Hz), 4.41–4.29 (2 H, m), 1.37 (3 H, app. t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.2, 167.2, 141.6, 132.8, 126.1, 117.9, 113.4, 84.0, 64.4, 63.4, 14.2.
(4*R,5*R**)-Ethyl 5-(4-bromophenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (1 H, s), 7.53–7.50 (2 H, m), 7.23–7.18 (2 H, m), 6.04 (1 H, d, *J* = 9.8 Hz), 4.90 (1 H, d, *J* = 9.8 Hz), 3.85 (1 H, app. dq, *J* = 10.7 and 7.2 Hz), 3.74 (1 H, app. dq, *J* = 10.7 and 7.2 Hz), 0.89 (3 H, app. t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 166.9, 132.4, 132.0, 128.6, 124.2, 84.7, 62.9, 62.7, 14.0.
(4*S,5*R**)-Ethyl 5-(4-bromophenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (1 H, s), 7.58–7.55 (2 H, m), 7.31–7.26 (2 H, m), 5.93 (1 H, d, *J* = 6.2 Hz), 4.43 (1 H, d, *J* = 6.2 Hz), 4.39–4.27 (2 H, m), 1.35 (3 H, app. t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.4, 167.5, 135.6, 132.2, 127.2, 123.6, 84.8, 64.5, 63.2, 14.2.
(4*R,5*R**)-Ethyl 5-(3-bromophenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.47 (3 H, m), 7.29–7.27 (2 H, m), 6.04 (1 H, d, *J* = 9.8 Hz), 4.91 (1 H, d, *J* = 9.8 Hz), 3.86 (1 H, app. dq, *J* = 10.8 and 7.2 Hz), 3.76 (1 H, app. dq, *J* = 10.8 and 7.2 Hz), 0.90 (3 H, app. t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 166.8, 135.5, 133.0, 130.5, 130.0, 125.5, 122.8, 84.4, 62.9, 62.8, 14.0.
(4*S,5*R**)-Ethyl 5-(3-bromophenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (1 H, s), 7.57–7.53 (2 H, m), 7.37–7.29 (2 H, m), 5.94 (1 H, d, *J* = 6.2 Hz), 4.45 (1 H, d, *J* = 6.2 Hz), 4.41–4.28 (2 H, m), 1.36 (3 H, app. t, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7, 167.7, 139.1, 132.9, 131.0, 128.8, 124.4, 123.4, 84.8, 64.8, 63.6, 14.6.
(4*R,5*R**)-Ethyl 5-(2-bromophenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.23 (5 H, m), 6.41 (1 H, d, *J* = 9.0 Hz), 5.00 (1 H, d, *J* = 9.0 Hz), 3.80 (1 H, app. dq, *J* = 10.7 and 7.2 Hz), 3.66 (1 H, app. dq, *J* = 10.7and 7.2 Hz), 0.82 (3 H, app. t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 166.9, 132.6, 132.3, 130.7, 127.8, 127.7, 122.1, 84.5, 62.2, 61.2, 13.6.

(4*S,5*R**)-Ethyl 5-(2-bromophenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (1 H, s), 7.62–7.25 (4 H, m), 6.34 (1 H, d, *J* = 4.7 Hz), 4.46 (1 H, d, *J* = 4.7 Hz), 4.37–4.27 (2 H, m), 1.35 (3 H, app. t, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8, 167.4, 135.5, 133.3, 130.8, 128.1, 127.6, 120.9, 84.6, 64.0, 63.0, 14.2.

(4*R,5*R**)-Ethyl 5-(4-methoxyphenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (1 H, s), 7.25–7.21 (2 H, m), 6.90–6.86 (2 H, m), 6.04 (1 H, d, *J* = 9.8 Hz), 4.86 (1 H, d, *J* = 9.8 Hz), 3.84 (1 H, app. dq, *J* = 10.7 and 7.2 Hz), 3.80 (3 H, s), 3.73 (1 H, app. dq, *J* = 10.7 and 7.2 Hz), 0.88 (3 H, app. t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 167.1, 160.7, 128.3, 125.4, 114.1, 85.5, 63.0, 62.5, 55.7, 14.0.

(4*S,5*R**)-Ethyl 5-(4-methoxyphenyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (1 H, s), 7.34–7.32 (2 H, m), 6.96–6.92 (2 H, m), 5.90 (1 H, d, *J* = 6.2 Hz), 4.47 (1 H, d, *J* = 6.2 Hz), 4.37–4.25 (2 H, m), 3.82 (1 H, s), 1.34 (3 H, app. t, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.6, 167.7, 160.4, 128.5, 127.3, 114.4, 85.8, 64.4, 62.9, 55.4, 14.2.

(4*R,5*R**)-Ethyl 5-(2-naphthyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.83 (4 H, m), 7.55–7.50 (3 H, m), 7.39–7.36 (1 H, m), 6.26 (1 H, d, *J* = 9.8 Hz), 4.97 (1 H, d, *J* = 9.8 Hz), 3.64 (1 H, app. dq, *J* = 10.4 and 7.2 Hz), 3.48 (1 H, app. dq, *J* = 10.4 and 7.2 Hz), 0.55 (3 H, app. t, *J* = 7.2 Hz). 13C NMR (100 MHz, $CDCl_3$): δ = 189.7, 166.7, 133.5, 132.5, 130.3, 128.4, 128.1, 127.6, 126.9, 126.7, 126.4, 123.3, 85.4, 62.8, 62.2, 13.4.

(4*S,5*R**)-Ethyl 5-(2-naphthyl)-2-thioxo-oxazolidine-4-carboxylate**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.85 (5 H, m), 7.55–7.53 (2 H, m), 7.48–7.46 (1 H, m), 6.14 (1 H, d, *J* = 6.2 Hz), 4.56 (1 H, d, *J* = 6.2 Hz), 4.42–4.29 (2 H, m), 1.38 (3 H, app. t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.1, 168.1, 134.1, 133.8, 133.1, 129.7, 128.5, 128.0, 127.3, 127.1, 125.6, 122.6, 86.1, 64.9, 63.4, 14.6.