Enantioselective Synthesis

The Direct Catalytic Enantioselective Synthesis of Protected Aryl β-Hydroxy-α-Amino Acids**

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β-Hydroxy-α-amino acid units are present in a significant number of biologically interesting compounds. Aryl-substituted variants are an important subclass and are responsible for a range of biological functions. For example, natural products such as vancomycin,[1] ristocetin,[1] and biphenomycin A[2] display significant antibiotic activity, the cyclomarins[3] display anti-inflammatory properties, whereas the exochelins are involved in cellular iron(III) transport.[4] Designed molecules have also been implicated in functions such as hypotension.[5] A variety of methods for the enantioselective synthesis of this important structural unit have been

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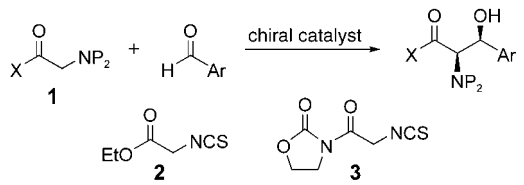
reported.[6,7] One of the most attractive routes, which involves the simultaneous formation of a C–C bond and the creation of two stereogenic centers, is the aldol addition of a glycine equivalent **1** to a suitable aldehyde (Scheme 1).



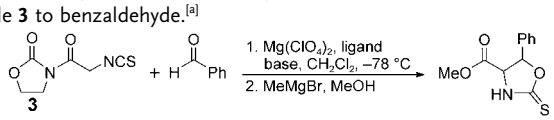
Scheme 1. The direct catalytic aldol route to aryl β-hydroxy-α-amino acids. X = OR, NR_2; P = protecting group.

A number of highly selective variants of this process are established, although in the majority of examples a preformed enolate or an enolate surrogate, such as an enol silane, is employed.[8] Direct catalytic enantioselective variants are still scarce.[9] We recently reported the direct addition of isothiocyanate-substituted ester **2** to a range of aryl aldehydes using an achiral catalyst generated from $Mg(ClO_4)_2$, bipyridine, and triethylamine.[10] Herein we document the extension of this system into a highly enantioselective variant that employs commercially available catalyst components.

Early attempts at developing an enantioselective reaction were based on our achiral reaction and involved exchange of bipyridine for a range of enantiomerically pure bidentate ligands, which were used in combination with $Mg(ClO_4)_2$, Hünig base, and ester **2**. The enantioselectivities obtained were uniformly low. In the expectation of generating more-ordered enolates, we refocused on the use of oxazolidinone **3**[11] as a glycine equivalent.[12] The addition of **3** to benzaldehyde was selected as a test reaction, and a range of ligands, bases, and solvents were evaluated (Table 1). To aid in the determination of *ee* values of the products, the direct adducts were treated immediately with a solution of magnesium alkoxide to yield the corresponding ester derivatives.[12a] Bidentate bis(oxazolines) used in combination with $Mg(ClO_4)_2$ and Hünig base generated poorly selective catalysts (entries 1 and 2),[13] however, the switch to a pyridine bis(oxazoline) (pybox) ligand generated a catalyst that delivered the product with a much improved value of 76% *ee* (entry 3). Variation of the ligand substituents from phenyl to *tert*-butyl and benzyl resulted in decreased selectivities (entries 4 and 5). All of the reactions described so far had been conducted in methylene chloride; the use of a 1:1 mixture of CH_2Cl_2 and THF had a dramatic effect and reduced the enantioselectivity to only 10% (entry 6). Increasing the reaction temperature to ambient temperature also resulted in reduced selectivity (entry 7). As a precaution against degradation of the hygroscopic $Mg(ClO_4)_2$, molecular sieves were added to the system, and an increase in selectivity to 90% *ee* was observed (entry 8).[14] Finally, variation of the base employed was also explored and Hünig base was found to be optimal (entries 9 and 10).

With optimized conditions in hand, we next explored the scope of the process with respect to the aryl aldehyde component (Table 2).[15] A wide variety of heteroatom, alkyl, and aryl substituents were readily accommodated in the *para* position of the aldehyde with observed enantioselectivities of up to 94% *ee* (entries 1–7). In all cases the *syn*-aldol adduct was obtained as the major diastereomer with selectivities of up to 91:9. Substitution in the *meta* position was also tolerated well (entry 8), however the presence of an *ortho* substituent

Table 1: Catalyst evaluation and optimization for the direct addition of imide **3** to benzaldehyde.[a]



Entry	Ligand	Base	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**6**	iPr_2EtN	30	55:45	12
2	**7**	iPr_2EtN	65	65:35	7
3	**8**	iPr_2EtN	76	80:20	76
4	**9**	iPr_2EtN	51	65:35[d]	44
5	**10**	iPr_2EtN	53	70:30	45
6[e]	**8**	iPr_2EtN	75	95:5	10
7[f]	**8**	iPr_2EtN	72	95:5	60
8[g]	**8**	iPr_2EtN	86	85:15	90
9[g]	**8**	Et_3N	75	80:20	82
10[g]	**8**	Bu_3N	60	85:15	80

[a] General conditions: imide (1 equiv), benzaldehyde (1.1 equiv), $Mg(ClO_4)_2$ (10 mol%), ligand (11 mol%), base (20 mol%), CH_2Cl_2, −78 °C. [b] Isolated yields. [c] Measured by ^1H NMR spectroscopy. [d] *ee* value of major diastereomer, measured by chiral HPLC using a Chiracel OD column. [e] 1:1 CH_2Cl_2/THF. [f] Reaction at room temperature. [g] 4 Å molecular sieves added.

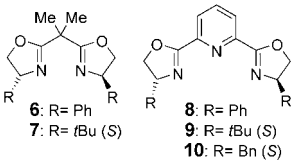
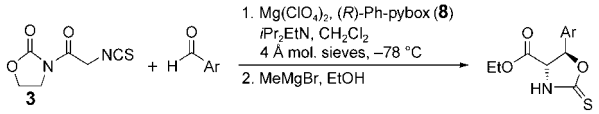


Table 2: The enantioselective addition of imide **3** to aromatic aldehydes.[a]



Entry	Ar	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	C_6H_5	86	85:15	90
2	4-MeO-C_6H_4	69	85:15	86
3	4-EtO-C_6H_4	85	87:13	93
4	4-MeS-C_6H_4	74	85:15	94
5	4-Me-C_6H_4	88	88:12	92
6	4-Et-C_6H_4	95	91:9	91
7	4-Ph-C_6H_4	79	73:27	87
8	3-Me-C_6H_4	84	82:18	86
9	2-Me-C_6H_4	88	50:50	89[e]
10	2-Naphthyl	64	72:28	87
11	3-Cl-4-PMBO-C_6H_4	78	93:7	95

[a] General conditions: imide (1 equiv), aldehyde (1.1 equiv), $Mg(ClO_4)_2$ (10 mol%), **8** (11 mol%), iPr_2EtN (20 mol%), CH_2Cl_2, −78 °C. [b] Isolated yields of combined diastereomers. [c] Measured by ^1H NMR spectroscopy. [d] *ee* value of major diastereomer, measured by chiral HPLC using Chiracel OD column. [e] *ee* of *anti* diastereomer; *ee* = 62% for *syn* diastereomer.

resulted in a 50:50 ratio of diastereomers (entry 9). 2-Naphthaldehyde is also a good substrate with the required aldol adduct obtained in 87% *ee* (entry 10). The final entry is significant as the substitution pattern of the product matches that of one of the functionalized tyrosine residues (AA-6) of vancomycin:[16] Reaction with 3-chloro-4-OPMB-benzaldehyde (PMB = *p*-methoxybenzyl) yielded the protected amino acid in 78% yield as a 93:7 ratio of *syn*:*anti* diastereomers with an impressive 95% *ee*.

In summary, a simple catalyst system assembled from an enantiomerically pure tridentate ligand, a Lewis acidic metal, and an amine base efficiently generates a chiral glycine enolate derived from oxazolidinone **3**. The enolate undergoes enantioselective addition to a range of aryl aldehydes to provide protected aryl β-hydroxy-α-amino acids in good yields with high enantioselectivities. The utility of the method has been exemplified by the preparation of a constituent amino acid of the natural product vancomycin. Importantly, all of the catalyst components are commercially available and the reactions are simple to perform. Studies to explore the addition of similar chiral enolates to alternative electrophiles and to apply these enolization conditions to alternative nucleophilic components are underway and will be reported in due course.

Experimental Section

General procedure for direct catalytic enantioselective aldol reaction, as exemplified by the preparation of (4*S*,5*R*)-ethyl 5-phenyl-2-thioxo-1,3-oxazolidine-4-carboxylate (Table 2, entry 1): $Mg(ClO_4)_2$ (15 mg, 0.07 mmol), 2,6-bis((*R*)-4,5-dihydro-4-phenyl-2-oxazolyl)pyridine (28 mg, 0.08 mmol), and 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one (128 mg, 0.69 mmol) were stirred for 1 h in dry methylene chloride (15 mL) in the presence of activated, powdered 4 Å molecular sieves (200 mg) under nitrogen at room temperature. The temperature was then lowered to −78°C and after 15 min, benzaldehyde (77 μL, 0.76 mmol) and diisopropylethylamine (24 μL, 0.14 mmol) were added, and the mixture was stirred for a further 24 h at −78°C. The reaction was quenched with saturated aqueous ammonium chloride (5 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in dry THF (15 mL), and the solution was cooled to 0°C. A solution of methyl magnesium bromide (3M in diethyl ether, 0.30 mL, 0.89 mmol) in ethanol (3.3 mL) at 0°C was added through a cannula. After 3 min, the reaction was quenched by addition of aqueous phosphate buffer solution (5 mL, pH 7). The mixture was concentrated under reduced pressure, and the residue was taken up in aqueous HCl (1M, 10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic portions were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 98:2 CH_2Cl_2/EtOAc) to provide the title compound as colorless crystals.

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