Communication

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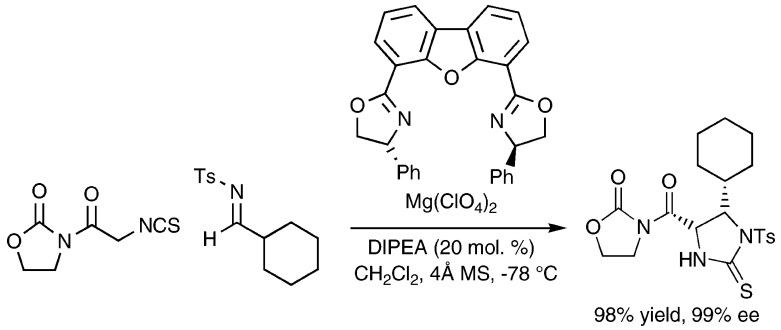

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Direct Catalytic Enantioselective Mannich Reactions: Synthesis of Protected *anti*-α,*β*-Diamino Acids

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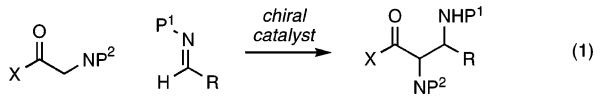
α,*β*-Diamino acids are important structural motifs present in many natural products and medicinal agents, and are implicated in a variety of biological functions.[1] 1,2-Diamines derived from these amino acids have also found wide application as chiral auxilaries and as ligands for asymmetric synthesis.[2] Although a number of methods for their preparation exist, catalytic enantioselective variants remain rare.[1] A direct, catalytic, enantioselective Mannich reaction between a glycine equivalent and an imine, involving the creation of a C−C bond and two stereogenic centers in a single operation, represents an attractive and atom-efficient route to these compounds (eq 1). Although a handful of syntheses corresponding to this approach has been described, all lead to the selective formation of *syn*-configured products.[3] In this communication we detail a new synthesis of protected α,*β*-diamino acids, which delivers *anti*-configured products in good yields and with excellent enantioselectivities.



(1)

Enantioselective Mannich reactions employing enolate surrogates,[4] or carbonyl compounds directly,[5] have been used to prepare a variety of amine-containing systems, although anti-selective reactions are generally limited to unfunctionalized nucleophiles.[6,7] Direct enantioselective Mannich reactions employing nucleophiles at the carboxylic acid oxidation level are also rare.[8] At the outset of our study our goals were to develop a highly selective synthesis of α,*β*-diamino acids that would allow an acid derivative to be employed directly as the nucleophilic component and that both enolizable and non-enolizable imines could be used as electrophiles.

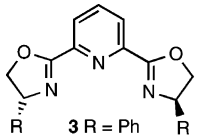
On the basis of our successful synthesis of α-amino-*β*-hydroxy acids,[9] we selected isothiocyanate-substituted oxazolidinone **1** as an ideal nucleophilic partner,[10] and chose to study the union of **1** and the *N*-Ts-imine derived from benzaldehyde **2** as a test reaction. The starting point for catalyst selection was based on those developed for enantioselective aldol reactions employing oxazolidinone **1**; the use of a catalyst composed of $Mg(ClO_4)_2$, Ph-PyBox ligand **3**, and Hünigs base, delivered the Mannich adduct **4** in 99% yield but only 45% ee (Table 1, entry 1). A variety of alternative PyBox ligands[11] were investigated, and the ^{i}Pr-substituted variant delivered the Mannich adduct with the highest selectivity of 70% ee (entries 2−4). Two *bis*(oxazoline) ligands were also evaluated; however, their performance offered no advantages (entries 5 and 6). Given the higher selectivities achieved with the tridentate PyBox ligands, we speculated that the DBFox[12] ligand **10** might also generate a selective catalyst. Pleasingly, a reaction incorporating ligand **10** delivered the required adduct in 94% yield as an 88:12 mixture of *anti*:*syn* diastereomers in 96% ee (entry 7). Reactions employing lower catalyst loadings resulted in significantly reduced enantioselectivites; for example, 5 mol % catalyst delivered material of only 37% ee (entry 8). A reaction employing the magnesium salt and base, in the absence of any chiral ligand was used as a control to establish the inherent diastereoselectivity of the process; the adduct was obtained in 80% yield with the *anti*-isomer again dominating (entry 9).

Table 1. Catalyst Evaluation for the Direct Addition of Imide **1** to Imine **2**[a]

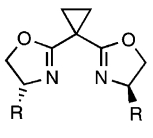
1 **2** **4**

entry	ligand	yield (%)[b]	*syn*:*anti*[c]	ee (%)[d]
1	**3**	99	36:64	45
2	**5**	99	30:70	8
3	**6**	99	20:80	43
4	**7**	99	14:86	70
5	**8**	97	34:66	39
6	**9**	83	40:60	4
7	**10**	94	12:88	96
8[e]	**10**	87	25:75	37
9	−	80	15:85	−

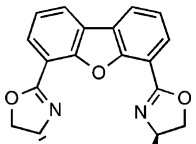
[a] Conditions: imide (1.0 equiv), imine (2.0 equiv), $Mg(ClO_4)_2$ (10 mol %), ligand (11 mol %), DIPEA (20 mol %), CH_2Cl_2, −78 °C, 24 h. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [d] Determined by chiral HPLC using Chiracel OD column. [e] 5 mol % $Mg(ClO_4)_2$, 6 mol % ligand.



3 R = Ph
(ent)-**5** R = Bn
(ent)-**6** R = ^{t}Bu
7 R = ^{i}Pr



(ent)-**8** R = Bn
9 R = ^{t}Bu



10

We next explored the scope of the imine component (Table 2). The three regioisomeric imines generated from tolualdehyde all provided the Mannich adducts with similarly high levels of yield and selectivity to the parent system (entries 1−4). In general, functionalized aryl imines are excellent substrates for the reaction, with examples of electron-donating and -withdrawing groups, and a number of halo-substituted examples all performing well (entries 5−11). The successful use of 2-thiophenyl-, 3-furyl-, and 2-(*N*-

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Scheme 1 *anti* to *syn* Epimerization

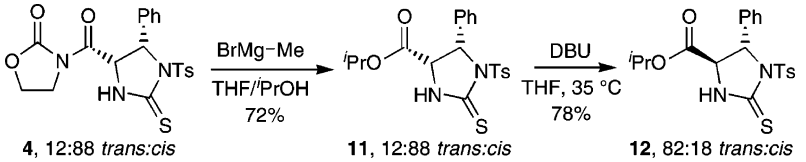
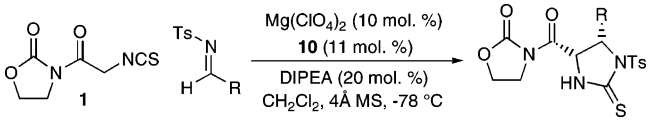


Table 2. Enantioselective Addition of Imide **1** to *N*-Ts-imines[a]



entry	R	yield (%)[b]	*syn*:*anti*[c]	ee (%)[d]
1	Ph	94	12:88	96[e]
2	4-Me−C_6H_4	96	12:88	99[f]
3	3-Me−C_6H_4	91	14:86	99
4	2-Me−C_6H_4	94	14:86	99
5	4-^{t}Bu−C_6H_4	96	18:82	99
6	4-MeO−C_6H_4	86	24:76	97[f]
7	4-Br−C_6H_4	86	16:84	98
8	4-Cl−C_6H_4	98	20:80	95
9	4-F−C_6H_4	98	24:76	93
10	4-CN−C_6H_4	85	32:68	99[f]
11	2-Np	94	7:93	98
12	2-thiophenyl	95	13:87	90[f]
13	3-furyl	94	14:86	91[g]
14	2-*N*-Ts-indolyl	99	10:90	99
15	(*E*)-cinnamyl	97	22:78	97
16	cyclohexyl	98	32:68	99[e]
17	cyclopropyl	96	28:72	85
18	C_5H_{11}	63	32:68	84

[a] Conditions; imide **1** (1.0 equiv), imine (2.0 equiv), $Mg(ClO_4)_2$ (10 mol %), **10** (11 mol %), DIPEA (20 mol %), CH_2Cl_2, −78 °C, 24 h. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [d] Determined by chiral HPLC using Chiracel OD column, of *anti*-isomer. [e] Absolute configuration established by X-ray diffraction study. All others assigned by analogy. [f] ee measured on ethyl ester derivative. [g] ee measured on *iso*propyl ester derivative.

Ts)-indolyl-derived imines demonstrates that heteroaromatic imines can be successfully employed (entries 12−14). The indole-derived imine provides a potentially useful β-amino-tryptophan derivative.[13] The methodology is not limited to aromatic imines; addition of imide **1** to the *N*-Ts imine generated from cinnamaldehyde proceeded smoothly (entry 15). The cyclohexyl-derived imine delivered the Mannich adduct in 98% yield with 99% ee, although the smaller cyclopropyl- and hexyl-derived imines showed reduced enantioselectivity (entries 16−18). In all cases the *anti*-diastereomer was obtained as the major product. This selectivity is opposite that observed in the additions of imide **1** to the corresponding aryl aldehydes[9] and presumably originates from the tosyl group of the *E*-configured imines forcing coordination of the Lewis acid *syn* to the imine substituent.[14] Control experiments established that the diasteromer ratios are constant throughout the reaction.

The in situ protection of the *anti*-diamines as the corresponding *cis*-cyclic thioureas provided an opportunity to access the *syn*-Mannich diastereomers. For example, conversion of imide **4** to ester **11** provides a substrate suitable for α-epimerization; treatment of ester **11** with DBU results in the formation of the *trans*-substituted thiourea **12**, corresponding to the *syn*-Mannich adduct (Scheme 1).

In conclusion, we have developed a new enantioselective route to *anti*-configured protected α,β-diamino acids using a direct enantioselective Mannich reaction. A variety of aryl-, heteroaryl-, alkenyl-, and alkyl-derived imines can all be employed. Conversion of the products to their ^{i}Pr-ester derivatives allows epimerization to the *syn*-diastereomers.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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