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Catalytic Enantioselective Synthesis of α,β-Diamino Acid Derivatives

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Vicinal diamines are important structural motifs that have been incorporated into chiral auxiliaries, catalysts, and ligands.[1] α,β-Diamino acids and their derivatives are part of many biologically active natural products and synthetic materials.[2] Here we report a convenient method for the highly enantio- and diastereoselective preparation of *syn*-α,β-diamino acid derivatives. Our approach relies on Mannich reactions between α-isothiocyanato imides and sulfonyl imines (eq 1) using readily available organocatalysts at relatively low catalyst loadings and ambient temperature.

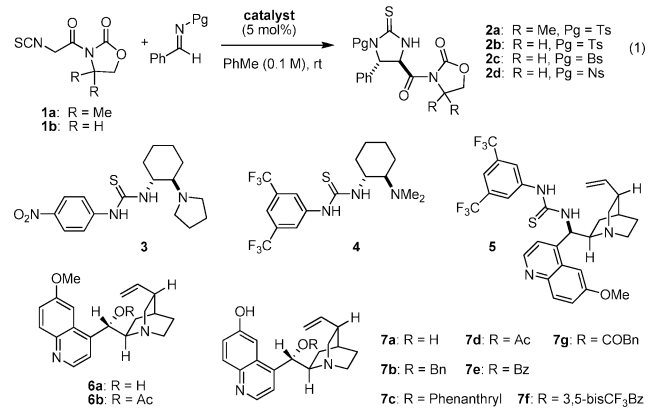
Various diastereoselective methods for the synthesis of α,β-diamino acid derivatives have been reported.[3] Catalytic enantioselective approaches have focused on Mannich reactions of glycine imines[4] or nitro esters[5] with various imines. Catalytic enantioselective Mannich reactions of nitroalkanes or silyl nitronates with α-imino esters have also been reported.[6] In addition, α-isocyano esters[7] and azlactones[8] have been employed as glycine equivalents in Mannich reactions. Willis and co-workers have recently used the α-isothiocyanato imide **1b** in highly enantioselective aldol and Mannich reactions.[9,10] Using a chiral magnesium complex derived from DBFox, products such as **2b** were obtained with high levels of enantioselectivity favoring the *anti* product.[9b]

Based on our recent success in using α-isothiocyanato imide **1a** in catalytic enantioselective aldol reactions employing catalyst **3**,[11] we sought to expand this methodology to the use of imines. A reaction of **1a** with the tosyl imine derived from benzaldehyde was incomplete after 3 days when using 5 mol % of catalyst **3**. Product **2a** was obtained in modest enantioselectivity and yield but with good diastereoselectivity favoring the *syn*- diastereomer (Table 1, entry 1). Subsequently, other readily available organocatalysts[12−14] were evaluated. To our delight, the quinidine derived bifunctional catalyst **7d**, pioneered by Deng,[14b] provided product **2a** in excellent enantio- and diastereoselectivity (entry 6). However, a low reaction rate was observed. Interestingly, significant rate acceleration was achieved by using the unsubstituted α-isothiocyanato imide **1b** in place of **1a** (entry 9). It was found that product **2b** shows a lower solubility in toluene as compared to **2a**, limiting the possibility of product inhibition. This should serve at least in part to explain the faster reaction rates observed with this substrate. The nature of the acyl group on catalyst **7** was found to have little effect on the ee and dr of the product, with more electron-withdrawing groups resulting in lower reaction rates (entries 9−12).

We next focused on the use of other imine protecting groups.[15] Remarkably, replacement of the tosyl group for the simpler benzenesulfonyl (Bs) analogue resulted in a 10-fold rate increase (compare entries 9 and 13). While subtle electronic effects can be invoked to partially rationalize this dramatic rate acceleration, we noted a marked solubility difference in the two products with **2c** being less soluble than **2b**. This allowed for reduction of the catalyst loading to 1 mol % while maintaining reasonable reaction rates and without adverse effects on the stereoselectivity (entry 15). Employment of the synthetically useful 4-nosyl (Ns) protecting group allowed for complete conversion in only 5.5 h with 1 mol % of catalyst **7d** (entry 16). Control experiments with structurally related quinidine derivatives showed that a free hydroxyl group on the quinoline ring is important for both reactivity and selectivity (entries 17−19). In agreement with Deng's findings,[14b] this suggests a bifunctional role for catalyst **7d**.

With the optimized reaction conditions in hand, a series of different Bs protected imines was evaluated (Table 2). Electron-rich and electron-poor aromatic imines with different substitution patterns provide products in generally good yields and with high levels of diastereo- and enantioselectivity (entries 1−13). Heteroaromatic and α,β-unsaturated imines are also viable substrates

Table 1. Evaluation of Catalysts and Protecting Groups[a]



entry	catalyst	sm	Pg	time [h]	yield [%][b]	dr [%][c]	ee [%][d]
1[e]	**3**	**1a**	Ts	72	49	94:06	−56
2[e]	**4**	**1a**	Ts	72	33	90:10	−31
3[e]	**5**	**1a**	Ts	72	27	87:13	−56
4[e]	**7b**	**1a**	Ts	72	31	>95:05	60
5[e]	**7c**	**1a**	Ts	72	22	>95:05	84
6[e]	**7d**	**1a**	Ts	72	35	>95:05	95
7[e]	**7e**	**1a**	Ts	72	29	>95:05	96
8	**3**	**1b**	Ts	48	81	91:09	−61
9	**7d**	**1b**	Ts	15	94	>95:05	98
10	**7e**	**1b**	Ts	18	96	>95:05	98
11	**7f**	**1b**	Ts	42	95	>95:05	95
12	**7g**	**1b**	Ts	17	94	>95:05	98
13	**7d**	**1b**	Bs	1.5	95	>95:05	98
14[e]	**7d**[f]	**1b**	Ts	72	92	>95:05	97
15	**7d**[f]	**1b**	Bs	10	95	>95:05	97
16	**7d**[f]	**1b**	Ns	5.5	95	>95:05	97
17[e]	**6a**	**1b**	Ts	72	80	92:08	55
18[e]	**6b**	**1b**	Ts	72	62	93:07	50
19[e]	**7a**	**1b**	Ts	72	79	94:06	52

[a] Reactions were performed at rt on a 0.2 mmol scale in anhydrous toluene (0.1 M) using 2 equiv of imine. Reactions were run to full conversion as judged by TLC analysis. The ee's were determined by HPLC analysis of the ester derivatives. [b] Combined yield of both diastereomers. [c] *trans*:*cis*, determined by ^{1}H NMR. [d] *trans* isomer. [e] The reaction is incomplete. [f] Run with 1 mol % catalyst loading.

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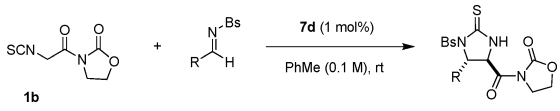
Table 2. Scope of the Reaction[a]

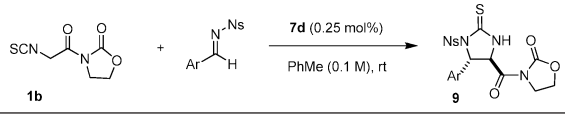


entry	R	product	time [h]	yield [%][b]	dr[c]	ee [%]
1	Ph	**2c**	15	97	>95:05	98
2	4-Me-C_6H_4	**8a**	10	96	>95:05	99
3	4-NO_2-C_6H_4	**8b**	3	85	92:08	93
4	4-Cl-C_6H_4	**8c**	15	92	>95:05	98
5	4-F-C_6H_4	**8d**	10	93	>95:05	97
6	4-MeO-C_6H_4	**8e**	9	87	>95:05	99
7	3-Me-C_6H_4	**8f**	10	95	>95:05	99
8	3-Br-C_6H_4	**8g**	7	94	>95:05	97
9	3-MeO-C_6H_4	**8h**	15	99	>95:05	97
10[d]	2-Cl-C_6H_4	**8i**	48[e]	80	72:28	91
11	2-Me-C_6H_4	**8j**	48[e]	90	>95:05	98
12	2-naphthyl	**8k**	3	90	>95:05	99
13	1-naphthyl	**8l**	48[e]	82	92:08	95
14	2-thienyl	**8m**	8	95	>95:05	97
15	2-furyl	**8n**	12	97	81:19	92
16	cinnamyl	**8o**	44	90	85:15	95
17	CH_2CH_2Ph	**8p**	40	90	91:09	89
18	*n*-Bu	**8q**	48[e]	53	83:17	91

[a] Reactions were run at rt on a 1 mmol scale using 1.5 equiv of imine. The ee's were determined by HPLC analysis of the ester derivatives. [b] Combined yield of both diastereomers. [c] *trans*:*cis*, determined by ^{1}H NMR. [d] 1.1 equiv of imine was used. [e] The reaction is incomplete.

(entries 14−16). In addition, although aliphatic aldimines are typically less stable, these substrates are compatible with the current method. In the reaction yielding product **8q**, an aminal byproduct was isolated in 27% yield. This byproduct results from **8q** reacting with an additional equivalent of imine.[16]

Table 3. Reactions with Lower Catalyst Loading[a]



entry	Ar	product	time [h]	yield [%][b]	dr[c]	ee [%]
1	4-Me-C_6H_4	**9a**	20	90	95:05	98
2	3-MeO-C_6H_4	**9b**	24	92	91:09	97
3	2-naphthyl	**9c**	48	87	92:08	94

[a] See footnote a in Table 2. [b] See footnote b in Table 2. [c] See footnote c in Table 2.

It was generally observed that reactions yielding more soluble products (e.g., **8l**) suffer from lower reaction rates. This is in agreement with our hypothesis that rapid catalyst turnover is linked to product precipitation. In an attempt to lower catalyst loadings further, we evaluated several more reactive and less soluble *N*-nosyl imines (Table 3). Gratifyingly, a catalyst loading of 0.25 mol % can routinely be applied to these substrates. High levels of stereoselectivity are preserved while reaction rates remain reasonable.

In summary, we have reported catalytic enantioselective Mannich reactions of α-isothiocyanato imides with sulfonyl protected imines. *syn*-α,*β*-Diamino acid derivatives can be obtained in a highly diastereo- and enantioselective fashion using substrate/catalyst ratios as high as 400:1. Product precipitation based approaches might offer a general solution to achieving lower catalyst loadings in a variety of different processes.

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Supporting Information Available: Experimental procedures and characterization data, transformation of compound **9a** to the corresponding unprotected *syn*-α,*β*-diamino acid, and X-ray crystal structures of **8h**, **8o** and the byproduct derived from **8q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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