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Expedient Synthesis of Chiral 1,2- and 1,4-Diamines: Protecting Group Dependent Regioselectivity in Direct Organocatalytic Asymmetric Mannich Reactions

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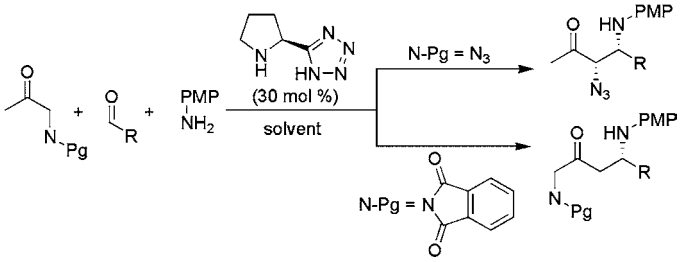
ABSTRACT



Organocatalytic asymmetric Mannich reaction of protected amino ketones with imines in the presence of an L-proline-derived tetrazole catalyst afforded diamines with excellent yields and enantioselectivities of up to 99%. The amino ketone protecting group controlled the regioselectivity of the reaction providing access to chiral 1,2-diamines from azido ketones and 1,4-diamines from phthalimido ketones.

Chiral diamines are important building blocks for the synthesis of pharmaceuticals and are motifs frequently encountered in natural products.[1] For example, chiral ethylenediamine derivatives are used in the preparation of *cis*-platin analogues employed in cancer therapy.[2] As synthetic tools, chiral diamines are used extensively as chiral auxiliaries and catalysts.[3] Despite their significance, the asymmetric synthesis of diamines is not straightforward. Chiral diamines are most frequently synthesized from diols or aziridines[1] or by addition of glycine ester enolates to imines.[4] The direct reductive coupling of imines has also been reported, but this approach is limited to the preparation of symmetrical vicinal diamines and has low stereoselectivity.[5] Thus, more direct and efficient routes are needed for the synthesis of this significant class of compounds.

In recent years, organocatalysis has emerged as a powerful tool for asymmetric aldol,[6] Mannich,[7] Michael,[8] Diels−Alder,[9] amination,[10] oxidation,[11] halogenation,[12] Robinson annulation,[13] and multicomponent reactions.[14] Although hydroxy ketones have been employed in organocatalysis,[6b,7j,8c] use of amino ketones has not yet been reported. Amino ketones are not stable; therefore, we envisioned use of azido ketones and protected amino ketones as surrogates for amino ketones. We previously used amino aldehydes in direct

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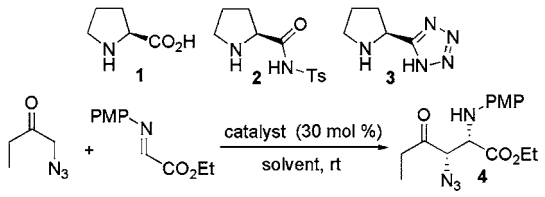
organocatalytic aldol reactions as an effective route to β-hydroxy-α-amino acids.[6j] Here, we report direct, regiospecific, asymmetric synthesis of 1,2- and 1,4-diamines based on the Mannich reaction of imines with azido ketones and with protected amino ketones, respectively.

We initially studied the Mannich reaction of *N*-*p*-methoxyphenyl (*N*-PMP) protected α-imino ethyl glyoxylate with azidobutanone using a catalytic amount of L-proline **1** (30 mol %) in dimethyl sulfoxide (DMSO) at room temperature. The reaction was complete within 48 h and provided the Mannich product in 84% yield with excellent enantioselectivity (>92% ee) albeit poor diastereoselectivity (*syn*/*anti* = 51:49) (Table 1, entry 1). At 4 °C in DMF, the diastereoselectivity improved to 92:8, but the reaction required 187 h to reach completion (entry 2). When 2-propanol (IPA) was used the reactivity and enantioselectivity were increased relative to the room-temperature reaction, but diastereoselectivity was decreased (entry 3).

Table 1. Effect of Various Catalysts and Solvents on the Organocatalytic Asymmetric Synthesis of 1,2-Azidoamines[a]



entry	catalyst	solvent	time (h)	yield (%)	*syn*/*anti*	ee (*syn*/*anti*)
1	**1**	DMSO	48	84	51/49	92/98
2	**1**	DMF, 4 °C	187	82	92/8	96/99
3	**1**	IPA, 4 °C	24	80	89/11	99/99
4	**2**	DMSO	24	80	56/44	79/69
5	**3**	DMSO	4	93	94/6	98/70
6	**3**	DMF	6	90	82/18	75/88
7	**3**	DMF, 4 °C	39	92	91/9	97/65
8	**3**	NMP	6	88	84/16	85/86
9	**3**	NMP, 4 °C	40	90	91/9	97/90
10	**3**	IPA, 4 °C	24	80	95/5	99/99
11	**3**	CH_2Cl_2	120	93	83/17	90/43
12	**3**	CH_3CN	72	84	78/22	72/45
13	**3**	dioxane	31	80	78/22	91/22
14	**3**	toluene	95	76	76/24	89/16
15	**3**	[bmim]BF_4	48	83	78/22	73/44

[a] ee was determined by chiral HPLC analysis. Syn/anti ratio was based on ^{1}H NMR. Stereochemistry was assigned on the basis of previous Mannich reactions.[7j]

We then tested L-proline-derived sulfonamide **2** and tetrazole **3** as catalysts; these catalysts are stronger acids than proline and have been used previously in enamine-based organocatalysis.[6h,7g,15] The reaction rate was acceptable for catalyst **2** (24 h for completion); however, diastereoselectivity was poor (entry 4). Catalyst **3** performed very well with respect to reaction time (4 h), diastereoselectivity (*syn*/*anti* = 94/6), and enantioselectivity (98%) (entry 5). Catalyst **3** performed well in a variety of solvents (entries 5−15). Of the solvents screened, DMSO was the best in terms of reaction time, yield, and diastereo- and enantioselectivities. At

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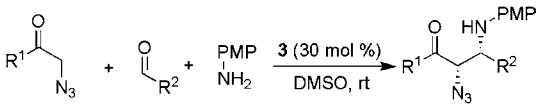
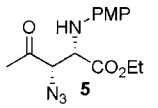
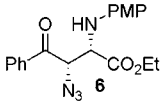
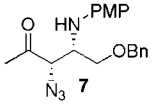
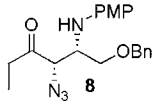
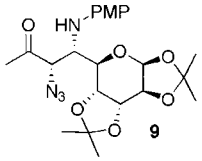
(15) For preparation of catalyst **2**, see ref 6m: For catalyst **3**, see: Almquist, R. G.; Chao, W.-R.; White, C. J. *J. Med. Chem.* **1985**, *28*, 1067. Franckevièius, V.; Knudsen, K. R.; Ladlow, M.; Longbottom, D. A.; Ley, S. V. *Synlett* **2006**, *6*, 889.

4 °C, IPA, *N*,*N*-dimethylformamide (DMF), and *N*-methyl-2-pyrrolidone (NMP) also provided good diastereo- and enantioselectivity but required longer reaction times (24−40 h). Reaction rates were relatively slow in CH_2Cl_2, CH_3CN, 1,4-dioxane, toluene, and [1-butyl-3-methylimidazolium]BF_4. We also tested (*S*)-2-(methoxymethyl)pyrrolidine[7m] and (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/CF_3CO_2H,[6g] but these catalysts provided product in negligible amounts.

Under these optimized conditions (catalyst **3** in DMSO), we next studied three-component Mannich reactions using different azidoketones and various aldehydes (Table 2). The

Table 2. Mannich Reactions for the Synthesis of Various 1,2-Azidoamines

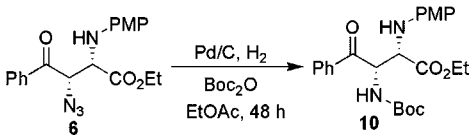


product	time (h)	yield (%)	*syn*/*anti*	ee (*syn*/*anti*)
 **5**	0.5	96	91/9	99/99
 **6**	40	87	88/12	99/64
 **7**	0.5	83	80/20	85/29
 **8**	6	80	85/15	82/79
 **9**	36	60	70/30	–

reaction with azidoacetone was complete within 30 min, whereas azidoacetophenone reacted slowly and required 40 h for completion. These reactions also worked well with 10 mol % of catalyst as exemplified for azidoacetone; in this case the product **5** was obtained in 1.5 h with 94% yield, excellent diastereoselectivity (*syn*/*anti* = 86/14), and enantioselectivity (99%). Reaction with benzyloxyacetaldehyde- and carbohydrate-derived aldehydes yielded the azidoamines **7**−**9** with protected hydroxyl and polyhydroxy functionalities. All of these products were obtained regiospecifically with good diastereoselectivity (*syn*/*anti* = 70/30 to 91/9) and enantioselectivity (82−99% ee).

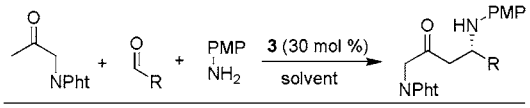
The reaction with azidoacetophenone was very slow (40 h), most likely due to the conjugative stabilization of the reactive enamine by the phenyl group. The decreasing reactivity observed from azidoacetone to azidobutanone and from benzyloxyacetaldehyde to the carbohydrate-derived aldehyde can be ascribed to increased steric hindrance with the latter substrates. A one-pot reduction and butoxy-carbonyl (Boc) protection of Mannich product **6** to provide differentially protected 1,2-diamine **10** was achieved by using Pd/C and Boc_2O under hydrogen atmosphere (Scheme 1).[16]

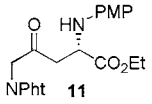
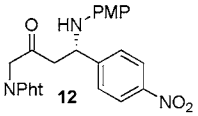
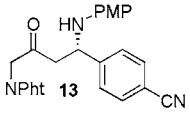
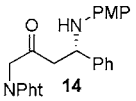
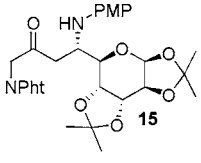
Scheme 1. Synthesis of Differentially Protected 1,2-Diamine **10**



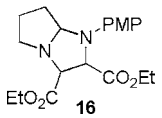
Next we used phthalimidoacetone, a phthaloyl-protected amino ketone, as donor (Table 3). Reaction of ethyl glyoxalate imine in DMSO in the presence of catalyst **3** at room temperature provided the Mannich product **11** in 86% yield

Table 3. Mannich Reactions for the Synthesis of Protected 1,4-Diamines



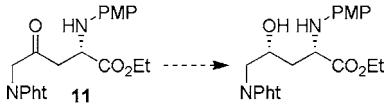
product	conditions	yield (%)	ee
 **11**	DMSO, rt, 16 h	86	64
	DMF, 4 °C, 40 h	83	90
	NMP, 4 °C, 60 h	88	91
	NMP, rt, 48 h	95	83
	DMSO, rt, 14 h	80	73(−)[a]
	DMF, 4 °C, 72 h	87	74(−)[a]
 **12**	DMSO, rt, 45 h	53	57
	DMF, 4 °C, 60 h	41	93
	NMP, 4 °C, 84 h	68	97
 **13**	NMP, 4 °C, 60 h	56	95
 **14**	NMP, 4 °C, 120 h	71	77
 **15**	NMP, 4 °C, 48 h	53	–[b]

[a] (−) Represents opposite enantiomer obtained using D-proline-derived tetrazole catalyst *ent*-**3**. [b] Diasteriomers are formed with 10:1 ratio.


16

and 64% ee as a single regioisomer. At 4 °C, ee's were improved: DMF gave 90% ee, whereas NMP provided 91% ee. The *p*-nitrobenzaldehyde imine reaction was also studied using three different solvents, and the highest ee (97%) was obtained in NMP solvent at 4 °C. Using these optimized conditions, we synthesized *p*-cyanophenyl- and phenyl-substituted 1,4-diamines with good to excellent ee's. Imines flanked with electron- withdrawing groups present on their aromatic rings are more reactive than benzaldehyde-PMP-imine. A carbohydrate-based imine also reacted with phthalimidoacetone to provide aza sugar **15** in 53% yield. In contrast to our results using azidoketones that provided vicinal diamine derivatives exclusively, phthalimidoacetone provided only the 1,4-diamine derivatives. Upon selective reduction, **11** should give hydroxyornithine, a constituent of an antifungal peptide natural product (Scheme 2).[17] Unlike

Scheme 2. Synthetic Route to Hydroxyornithine



results obtained using the tetrazole catalyst, with L-proline **1** as catalyst in NMP solvent at room temperature, phthalimidoacetone provided Mannich product **11** in trace amounts accompanying the formation of cycloaddition product **16** with 59% isolated yield based on proline.[18] Proline forms an iminium with ethyl glyoxalate, generated from in situ hydrolysis of glyoxalate imine. Decarboxylation of the iminium species followed by [3 + 2] cycloaddition with ethyl glyoxalate imine provided compound **16**. Catalyst **2** also provided Mannich product **11** in trace amounts.

Based on the regioselectivities of products, we propose that the reaction occurs through the transition states shown in Figure 1. The catalyst reacts with azido ketone to form the enamine with the more highly substituted double bond, and attack of the methylene group gives the 1,2-azidoamine as the Mannich product (TS-1). Here deprotonation at the α-carbon is facilitated by the enhanced acidity provided by azide substitution and this enamine is thermodynamically more stable than the enamine generated by deprotonation at the other α-carbon based on resonance considerations. This

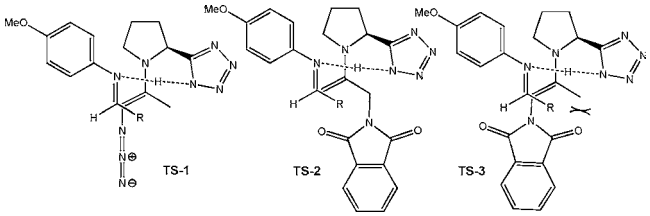


Figure 1. Proposed transition states.

reactivity is in accord with mechanisms of Mannich reactions involving hydroxy ketone and dialkyl ketone donors.[7j] In the case of phthalimidoketone, attack of the methyl group, rather than the methylene group of the ketone, results in the formation of the 1,4-diamine product through the enamine with the less-substituted double bond (TS-2). Here the competing enamine of TS-3 suffers due to steric hindrance.

In conclusion, we have demonstrated for the first time direct asymmetric Mannich reactions of imines with varied protected amino ketones to afford selective access to chiral 1,2- and 1,4-diamines with excellent yields and enantioselectivities. The identity of the protecting group controlled the regioselectivity of the reaction and provided for the synthesis for 1,2- and 1,4-diamines with azidoketones and phthalimidoketones, respectively. The scope of the azidoketone Mannich reaction appears to be very broad, coupling a wide range of azidoketones and imines. The product chiral azidoketones prepared here are interesting substrates for subsequent Click chemistry-based diversification.[19] These reactions can be performed under environmentally friendly conditions without the requirements for an inert atmosphere or for dry solvents and provide expedient access to this significant class of molecules.

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

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(16) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837.

(17) Paintner, F. F.; Allmendinger, L.; Bauschke, G.; Klemann, P. *Org. Lett.* **2005**, *7*, 1423.

(18) Although this type of cycloaddition product was not reported in the Mannich reaction, cyclic products are reported in the literature using two equivalents of aldehyde and proline. See: (a) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055. (b) Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P. *Tetrahedron* **1988**, *44*, 519.

(19) Demko, Z, P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2113.

(20) **General Experimental Procedure for Mannich Reaction.** To a glass vial charged with aldehyde (0.5 mmol) and *p*-anisidine (0.5 mmol) was added DMSO (1 mL). The solution was stirred at room temperature until imine formation was complete as monitored by TLC (30−60 min). Catalyst (30 mol %) and ketone (0.75 mmol) were added, and the reaction was stirred at room temperature. After completion of the reaction as monitored by TLC, half-saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, the layers were separated, and the organic phase was washed with water. The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired Mannich product.