

Proline-Catalyzed Direct Inverse Electron Demand Diels–Alder Reactions of Ketones with 1,2,4,5-Tetrazines

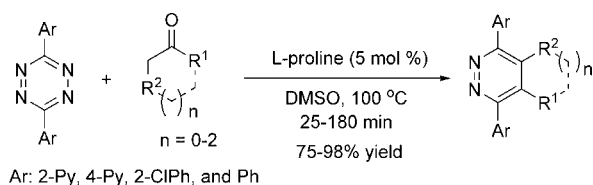
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ABSTRACT



An organocatalytic direct inverse electron demand Diels–Alder reaction of ketones with 1,2,4,5-tetrazines has been developed. The process is efficiently catalyzed by proline to give Diels–Alder adducts pyridazines in high yields.

Substituted and/or functionalized pyridazines have received increasing interest in the fields of inorganic, organic, and medicinal chemistry.¹ 3,6-Di(pyridin-2-yl)pyridazines (DPPs) are well-known ligands for the self-assembly of [2 × 2] gridlike metal complexes with copper(I) and silver(I) ions, which afford unique properties.² The functionalized pyridazines are versatile building blocks in natural-product

syntheses³ and have received much attention in physical organic chemistry.⁴ Moreover, the pyridazine-based scaffolds have been explored in medicinal chemistry and as new α -helix mimetics in peptide and peptidomimetic chemistry.⁵ Accordingly, the preparation of the molecular architectures is of considerable synthetic significance. Among the most widely utilized synthetic methods are the well-defined inverse electron demand Diels–Alder reactions of the reactive and readily accessible substituted 1,2,4,5-tetrazines with electron-rich dienophiles.¹ Despite the fact that electron rich enolates and enamines often used as dienophiles can facilitate the cycloaddition process and

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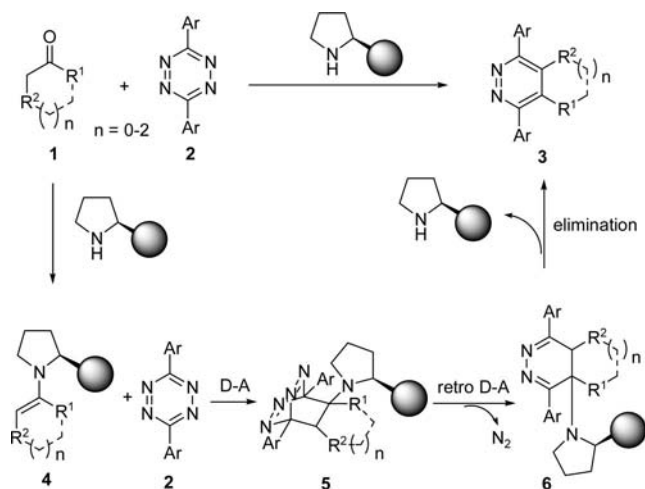
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Scheme 1. Secondary Amine-Catalyzed Inverse Electron Demand Diels-Alder Reactions



provide one-pot access to pyridazines,⁶ the preformation of these species are generally required from the corresponding ketones and aldehydes. From the viewpoint of atom economy, direct reactions of readily available aldehydes and ketones are more attractive. Recently, Schubert and co-workers described a microwave-assisted direct approach to the synthesis of pyridazines from ketones and aldehydes.⁷ However, the process suffers from low reaction yields (typical yields ranging from 9 to 75%), high reaction temperatures (120–200 °C), and relatively long reaction times (20–60 min) for a microwave-assisted reaction.

In this Communication, we wish to disclose the results of our investigation, which has led to a novel organocatalytic direct inverse electron demand Diels–Alder reaction of ketones with 1,2,4,5-tetrazines.⁸ The process is efficiently catalyzed by simple amino acid L-proline and affords a direct approach to synthetically and medically useful substituted pyridazines. Significantly, the products are produced in high efficiency (75–98% yield) under mild reaction conditions with a broad substrate scope.

Given the success of secondary amines as a general strategy for catalyzing the formation of enamines from

(6) For selected examples of enamines and enols for inverse electron demand Diels–Alder reactions with 1,2,4,5-tetrazine, see: (a) Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257. (b) Haider, N. *Tetrahedron* **1991**, *47*, 3959. (c) Kotschy, A.; Hajos, G.; Messmer, A. *J. Org. Chem.* **1995**, *60*, 4919. (d) Kotschy, A.; Hajos, G.; Timári, G.; Messmer, A. *J. Org. Chem.* **1996**, *61*, 4423. (e) Panek, J. S.; Zhu, B. *Tetrahedron Lett.* **1996**, *37*, 8151. (f) Kotschy, A.; Smith, D. M.; Bényei, A. C. *Tetrahedron Lett.* **1998**, *39*, 1045. (g) Kotschy, A.; Novák, Z.; Vincze, Z.; Smith, D. M.; Hajos, G. *Tetrahedron Lett.* **1999**, *40*, 6313. (h) Soenen, D. R.; Zimpleman, J. M.; Borger, D. L. *J. Org. Chem.* **2003**, *68*, 3593. (i) Kotschy, A.; Farago, J.; Csampai, A.; Smith, D. M. *Tetrahedron* **2004**, *60*, 3421. (j) Suen, Y. F.; Hope, H.; Nantz, M. H.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2005**, *70*, 8468. (k) Hamasaki, A.; Ducray, R.; Boger, D. L. *J. Org. Chem.* **2006**, *71*, 185.

(7) Hoogenboom, R.; Moore, B. C.; Schubert, U. S. *J. Org. Chem.* **2006**, *71*, 4903.

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Table 1. Exploration of Secondary-Amine-Promoted Inverse Electron Demand Diels-Alder Reaction of Cyclohexanone **1a** with 3,6-Di(pyridine-2-yl)-1,2,4,5-Tetrazine **2a**^d

entry	catalyst	solvent	conversion (%) ^b	yield (%) ^b	3a/7 ^c
1	I	CH ₃ CN	100	84	8.3:1
2	I	H ₂ O	68	32	1.1:1
3	I	EtOH	100	88	7.4:1
4	I	CHCl ₃	93	68	2.6:1
5	I	neat	100	87	7.1:1
6	I	DMSO	100	100	>50:1
7 ^e	I	DMSO	100	100	>50:1
8 ^f	I	DMSO	100	100	>50:1
9	II	CH ₃ CN	50	22	1.5:1
10	III	CH ₃ CN	<5	trace	ND ^d
11	IV	CH ₃ CN	100	4	ND ^d
12	V	CH ₃ CN	90	11	ND ^d
13	none	CH ₃ CN	0	0	ND ^d

^a Unless specified, a mixture of cyclohexanone **1a** (32 μL, 0.3 mmol), 3,6-di(pyridine-2-yl)-1,2,4,5-tetrazine **2a** (24 mg, 0.10 mmol), and catalyst (0.02 mmol) in a specified solvent (0.5 mL) were stirred at 100 °C for 1 h. ^b Determined by ¹H NMR the crude product with 1,1,2,2-tetrachloroethane as internal standard. ^c Determined by ¹H NMR. ^d Not determined. ^e Reaction run using 5 mol % catalyst. ^f Reaction performed at rt for 25 h.

carbonyl compounds in organocatalysis,⁹ we hypothesized that in situ formed enamines **4** derived from ketones **1** in the presence of an amine could serve as nucleophiles for an inverse electron demand Diels–Alder reaction with 1,2,4,5-tetrazines **2** (Scheme 1). The Diels–Alder adducts **5** underwent a subsequent retro-Diels–Alder process to generate intermediates **6**, which proceeded a spontaneous elimination reaction to give rise to pyridazines **3** and release the catalyst. The novel catalytic cascade process represents the first example of employing an organocatalytic one-pot access to pyridazines **3** from simple starting materials.

To demonstrate the feasibility of the proposed organocatalytic inverse electron demand Diels–Alder reaction, we carried out a model reaction between cyclohexanone **1a** (3.0 equiv) with 3,6-di(pyridine-2-yl)-1,2,4,5-tetrazine **2a** (1.0

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Table 2. L-Proline Promoted Inverse Electron Demand Diels-Alder Reaction of Ketones **1** with 1,2,4,5-Tetraazine **2**^a

entry	ketone 1 , 2	product	<i>t</i> (min)	yield (%) ^b
1			50	98
2			35	98
3			50	83
4			35	94
5			60	97
6			70	95
7	Acetone, 2a		25	96
8 ^c			180	77
9 ^c			180	72
10			30	98
11			40	96
12 ^d			40	97

^a Unless specified, see footnote *a* in Table 1, for all cases 2 equiv of ketones used. ^b Isolated yields. ^c Reaction run using 20 mol % catalyst. ^d Reaction run using 10 mol % catalyst.

equiv) in the presence of 20 mol % secondary amine in CH₃CN at 100 °C (Table 1). Examination of the results of catalyst screening revealed that the catalyst activities varied significantly. L-Prolinamide **II**¹⁰ gave 50% conversion with 20% yield for the desired product **3a** (entry 9). Unexpectedly, a significant amount of byproduct **7** was obtained. Surprisingly, diphenylprolinol TMS ether **III**¹¹ was an ineffective promoter for the process (entry 10). High conversion for pyrrolidine **IV** (entry 11) and morpholine **V** (entry 12) were observed; however, the desired product was formed very poorly. On the basis of ¹H NMR analysis, a complicated product mixture was observed although starting material **2a** was consumed. In the absence of a secondary amine, as expected, no reaction occurred (entry 13). Gratifyingly, L-proline **I**¹² was found to be the best catalyst (Table 1, entry 1). In this instance, a high yield (84%) was achieved. It was noted that a pronounced amount of byproduct **7** was also produced. To minimize the formation of the byproduct, we focused on the optimization of reaction conditions. First, the effect of solvents on the reaction was probed (entries 1–6). It was found that DMSO was the optimal reaction medium for the cascade process; the reaction proceeded efficiently to give the adduct **3a** in a quantitative yield (entry 6). A control study without catalyst L-proline **I** showed that only starting materials remained, indicating that L-proline was the catalyst for the inverse electron demand Diels–Alder reaction. Significantly, the formation of the byproduct **7** was not seen in DMSO. Lowering the catalyst loading from 20 to 5 mol % did not lead to reducing reaction efficiency (entry 7). The reaction also proceeded at room temperature to afford desired product **3a** in a quantitative yield without formation of **7** but required long reaction time (25 h) (entry 8).

After establishing the optimal reaction conditions, we studied the scope of the L-proline-catalyzed inverse electron demand Diels–Alder reactions. As revealed in Table 2, a wide range of ketones are suitable for the transformation (entries 1–9). The reaction was inert to the ring size of ketones. Five, six, and seven membered cyclic ketones (entries 1–6) efficiently participated in the process in good to high yields (83–98%). Furthermore, acyclic ketones were also good substrates for the process (entries 7–9). It is noteworthy that the reaction proceeded smoothly when acetophenone, a challenging substrate in aminocatalysis, was used as donor (entry 9).¹³ It appeared that the structural variation of the diene components **2** had little effect on the reaction (entries 10–12).

The utilization of unsymmetric ketones could give rise to the formation of regioisomers. As demonstrated, under the

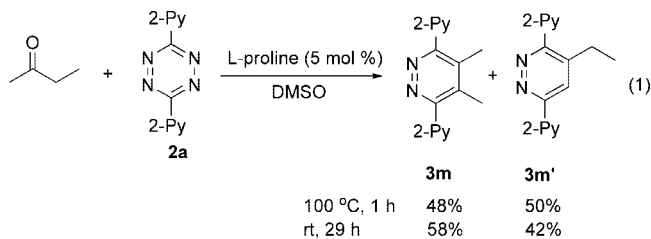
(10) Review of chiral diarylprolinol ethers catalysis, see:(a) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

(11) L-Prolinamide catalyzed reactions, see:(a) Wang, W.; Wang, J.; Li, H. *Org. Lett.* **2004**, *6*, 2817. (b) Wang, J.; Li, H.; Mei, Y.; Lou, B.; Xu, D.; Xie, D.; Guo, H.; Wang, W. *J. Org. Chem.* **2005**, *70*, 5678.

(12) For reviews of proline catalyzed reactions, see:(a) List, B. *Tetrahedron* **2002**, *58*, 5573.

(13) It has been shown that the use of less reactive aryl alkyl ketones for chiral secondary-amine-promoted asymmetric aldol reactions generally gave poor yields and low enantioselectivity. The survey of literature reveals that only a single study was reported with achieving acceptable yields (35–93%) but with highly active trichloro- and trifluoroacetaldehydes as aldol acceptor: Torii, H.; Nakadai, M.; Shihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.

same reaction conditions at 100 °C, two regioisomers **3m** and **3m'** were generated in almost same amount (1). The reaction temperature had a very limited effect on the regioselectivity. Decreasing temperature to rt did not result in a significant alternation of the ratio of product **3m** and **3m'**.



In summary, an unprecedented catalytic version of inverse electron demand Diels–Alder reaction has been successfully developed. The cascade process is efficiently catalyzed by simple amino acid L-proline under mild reaction conditions

with a broad substrate scope. The strategy described in this work affords a direct approach to the preparation of synthetically and biologically interesting pyridazines from readily available ketones. Through variation of both dienes and dienophiles, it is our anticipation that this general organo-catalytic methodology will stimulate further contributions to the rapidly growing family of catalytic processes with a significantly expanded scope.

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Supporting Information Available: Experimental procedures and spectra data for compounds **3a–m'**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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