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Catalytic Asymmetric Synthesis of 4-Nitropyrazolidines: An Access to Optically Active 1,2,3-Triamines

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Supporting Information

ABSTRACT: The first catalytic enantio- and diastereoselective synthesis of 4-nitropyrazolidines is presented. Asymmetric hydrogen-bonding activation of nitro-olefins facilitated the 1,3-dipolar cycloaddition with hydrazones, affording optically active 4-nitropyrazolidines containing three continuous stereogenic centers as a single diastereomer in up to 99% ee. Furthermore, it is demonstrated that the optically active 4-nitropyrazolidines can be applied as precursors for the synthesis of highly interesting 1,2,3-triamines.

Due to the importance of amine-containing biologically active natural products and pharmaceutical compounds, the development of methodologies giving access to stereodefined nitrogen-containing compounds is a cornerstone in contemporary organic synthesis.[1] Amino stereotriads, an array of three continuous amine-bearing stereogenic carbons, are essential parts of the scaffold of several bioactive compounds (Figure 1).[2] Given the biological importance of such nitrogen-dense compounds, comprehensive multistep syntheses have attracted considerable attention.[3]

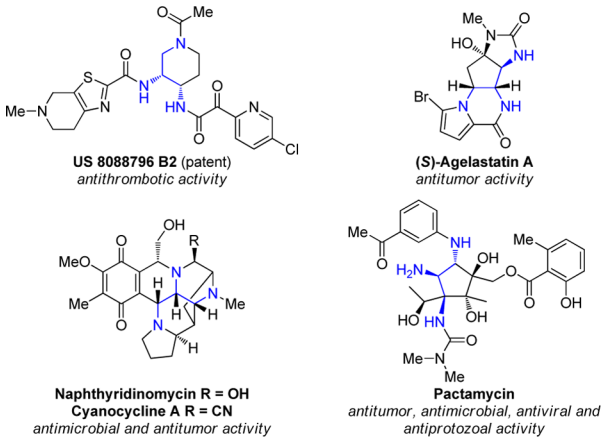
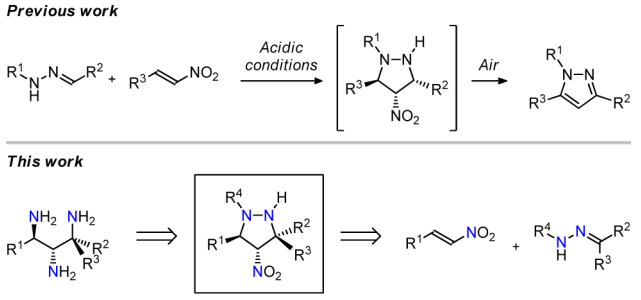


Figure 1. Bioactive continuous triamine-containing compounds.

Despite being appealing structural motifs, only a few asymmetric routes for the synthesis of 1,2,3-triamino compounds have been reported.[4] Trost et al. have established a catalytic stereoselective transformation of allylic carbonates to 1,2,3-triamines employing sequential palladium-catalyzed allylic amination/rhodium-catalyzed aziridination/azide addition sequence.[5] Additionally, Gotor et al. have demonstrated a highly enantioselective chemoenzymatic desymmetrization of 2-*N*-Boc-propane-1,2,3-triamine.[6]

The development of organocatalytic asymmetric methods for the synthesis of vicinal diamines has attracted considerable attention over the past decade.[7] An access to this important structural motif is the aza-Michael addition of ammonia precursors to nitro-olefins, which, due to the diverse chemistry of the nitro functionality, generates surrogates of 1,2-diamino compounds.[8] Along this line, we envisioned that catalytic asymmetric 1,3-dipolar cycloaddition of hydrazones with nitro-olefins would furnish 4-nitropyrazolidines which, upon reduction of the nitro group and cleavage of the *N*–*N* functionality, would afford 1,2,3-triamino compounds. In previous reports, Deng et al. have demonstrated that aldehyde-derived hydrazones efficiently react in a 1,3-dipolar cycloaddition with nitro-olefins, forming racemic 4-nitropyrazolidines, which readily undergo oxidation in air to afford pyrazoles (Scheme 1).[9] We speculated that employing ketone-derived hydrazones would yield the desired 4-nitropyrazolidines, which, due to the formed quaternary stereogenic center, would be blocked from the oxidative formation of the heteroaromatic compound.

Scheme 1. Strategy for the Synthesis of Optically Active 4-Nitropyrazolidines and 1,2,3-Triamines



Pyrazolidines are highly interesting heterocyclic structural motifs found in numerous biologically relevant molecules;[10] however, only a few protocols for the formation of 4-nitropyrazolidines have been reported,[11] and to the best of our knowledge, no catalytic asymmetric route to this class of compounds has been demonstrated.

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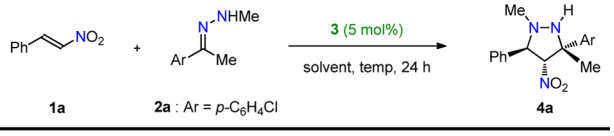
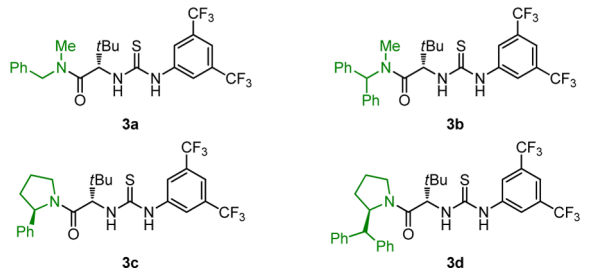
Asymmetric hydrogen-bonding-mediated catalysis has proven to be a reliable strategy for the enantioselective activation of nitro-olefins,[12] thus our studies were initiated by examining the 1,3-dipolar cycloaddition of nitrostyrene **1a** with ketone-derived hydrazones **2** under hydrogen-bonding catalysis. Initial attempts to employ *N*-tosyl or *N*-benzoyl hydrazones derived from acetophenone were unsuccessful, thus we turned our attention to the more electron-rich and hence more nucleophilic *N*-methyl hydrazone. Due to its crystalline nature and increased thermal stability *N*-methyl hydrazone derived from 4′-chloroacetophenone **2a** was employed as a model substrate.

A survey of background reaction revealed that the 4-nitropyrazolidine **4a** was afforded as a single diastereoisomer when the nitrostyrene **1a** and hydrazone **2a** were stirred in chloroform at room temperature, while no conversion was observed when the reaction was conducted in toluene at −30 °C (Table 1, entries 1 and 2). In a previous report, we

Table 1. Selected Screening Results for the Reaction Conditions for Asymmetric Synthesis of 4-Nitropyrazolidine 4a





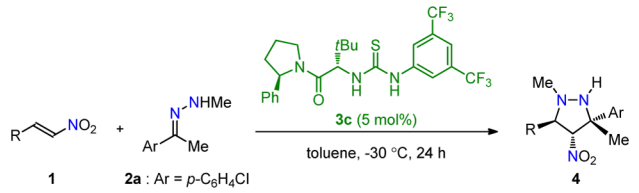
entry[a]	catalyst	solvent	temp (°C)	conv[b] (%)	ee[c] (%)	dr[b]
1	none	$CHCl_3$	rt	>95	nd	>20:1
2	none	toluene	−30		nd	
3	**3a**	toluene	−30	>95	99	>20:1
4	**3b**	toluene	−30	>95	98	>20:1
5	**3c**	toluene	−30	>95	99	>20:1
6	**3d**	toluene	−30	>95	88	>20:1

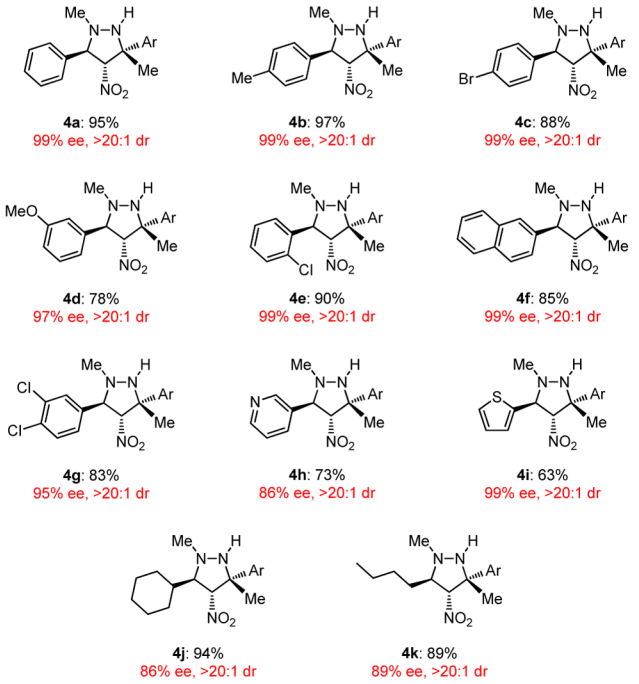
[a]All reactions were performed on a 0.1 mmol scale using **1a** (0.15 mmol), **2a** (0.10 mmol), and **3** (0.005 mmol) in anhydrous solvent (0.1 M) for 24 h. [b]Determined by ^{1}H NMR on the crude reaction mixture. [c]Determined by chiral ultraperformance convergence chromatography (UPC^2).

demonstrated that Jacobsen-type thiourea catalyst **3a** is a powerful activator of nitro-olefins,[8c] thus this catalyst was subjected to the model system in toluene at −30 °C. Delightfully, 4-nitropyrazolidine **4a** was afforded in full conversion with excellent enantioselectivity as a single diastereoisomer (entry 3). Related catalysts **3b–d** displayed similar activity with regard to rate of the reaction, affording enantioselectivities ranging from high to excellent (entries 4–6). Catalysts **3a** and **3c** furnished the desired product in 99% ee; however, it was later observed that catalyst **3c** provided better selectivity for more challenging substrates.

Encouraged by the screening results, we tested a representative selection of nitro-olefins in order to investigate the generality of the reaction (Scheme 2). We were pleased to find that the high efficiency demonstrated by catalyst **3c** for the

Scheme 2. Nitro-olefin Scope for the Asymmetric Synthesis of 4-Nitropyrazolidines 4[a]





[a]All reactions were performed on a 0.1 mmol scale using **1** (0.15 mmol), **2a** (0.10 mmol), and **3c** (0.005 mmol) in anhydrous toluene (0.1 M) for 24 h at −30 °C. Isolated yields by FC. Diastereoselectivity was determined by ^{1}H NMR on the crude reaction mixture. Enantioselectivity was determined by chiral ultraperformance convergence chromatography (UPC^2).

model reaction could be sustained for the 1,3-dipolar cycloaddition of a broad range of nitro-olefins. Generally, aromatic nitro-olefins having substituents in the *ortho*-, *meta*-, and *para*-positions furnished the optically active 4-nitropyrazolidine products in high to excellent yields as single diastereomers with excellent enantioselectivities (products **4b–g**). Nitro-olefins in which the electronic nature of the aromatic substituents varied from electron-donating to electron-withdrawing participated successfully in the reaction. However, when aromatic imines with electron-rich substituents, which are able to conjugate a lone pair of electrons to the double bond, were employed (e.g., *p*-MeO-C_6H_4 or 2-furanyl), no product formations were observed. Interestingly, two nitro-olefins bearing heteroaromatic substituents gave rise to the corresponding 4-nitropyrazolidines **4h** and **4i** in good yields with high to excellent enantioselectivities. The lower selectivity of the 3-pyridyl-substituted substrate might be due to nonconstructive hydrogen bonding to the catalyst. Additionally, two aliphatic nitro-olefins also participated in the reaction,

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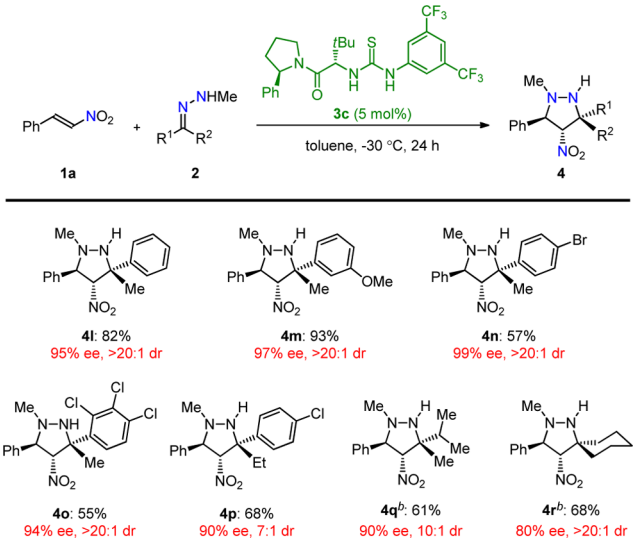
affording 4-nitropyrazolidines **4j** and **4k** in high to excellent yields with high enantioselectivities.

Subsequently, we turned our attention toward the scope of the hydrazone 1,3-dipoles (Scheme 3). Generally, benzophenone-derived hydrazones bearing substituents of a broad electronegativity range afforded similar excellent selectivity, although slightly lower yields were observed in some cases (products **4n–r**). The decreased diastereoselectivity observed for product **4p** is attributed to the corresponding *E*/*Z* ratio of starting material 4′-chloropropiophenone-derived hydrazone. Interestingly, hydrazones rising from 3-methylbutan-2-one and cyclohexanone also gave rise to the desired 4-nitropyrazolidines **4q** and **4r** when catalyst **3d** was employed and the temperature decreased to −78 °C, affording the products in good yields and high enantioselectivities.

Scheme 3. Hydrazone Scope for the Asymmetric Synthesis of 4-Nitropyrazolidines 4[a]



[a]All reactions were performed on a 0.1 mmol scale using **1a** (0.15 mmol), **2** (0.10 mmol), and **3c** (0.005 mmol) in anhydrous toluene (0.1 M) for 24 h at −30 °C. Isolated yields by FC. Diastereoselectivity was determined by ^{1}H NMR on the crude reaction mixture. Enantioselectivity was determined by chiral ultraperformance convergence chromatography (UPC^2). [b]Performed using catalyst **3d** at −78 °C.

Determination of the absolute configuration of the optically active 4-nitropyrazolidines was carried out by X-ray analysis of **4c**, which proved to be the (3*R*,4*R*,5*R*)-3,5-diaryl-1,3-dimethyl-4-nitropyrazolidine as shown in Figure 2.[13] Hence, the remaining 4-nitropyrazolidines **4** were assigned by analogy assuming a common reaction pathway.

Finally, we set out to investigate the transformation of the optically active 4-nitropyrazolidines into their corresponding 1,2,3-triamines. After several unsuccessful attempts to reduce the nitro and hydrazine functionalities directly, a sequential reductive approach was undertaken. In attempts to reduce the nitro group selectively, either no conversion or decomposition of 4-nitropyrazolidine **4a** was observed when subjected to various hydrogenative conditions. We circumvented this challenge by employing the methodology developed by Anderson,[14] in which mercury-coated alumina strips successfully reduced the nitro group to the hydroxylamine, which subsequently could be turned in the 4-aminopyrazolidine **5** in 67% yield over two steps (Scheme 4). Sequential Cbz protection of the exocyclic primary amine followed by trifluoroacetyl protection of the unsubstituted pyrazolidine nitrogen afforded **6** in 84% yield over two steps. Finally, samariumdiiodide-mediated reduction furnished the desired triamine product **7**.[15]

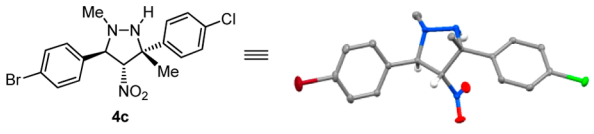
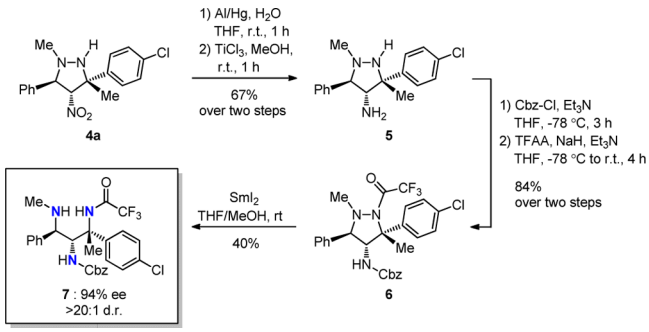


Figure 2. Single-crystal X-ray structure of **4c**.

Scheme 4. Synthesis of Triamine 7 from 4-Nitropyrazolidine 4a[a]



[a]See Supporting Information for experimental details.

In conclusion, this work constitutes the first example of catalytic asymmetric synthesis of 4-nitropyrazolidines. The developed methodology takes advantage of a hydrogen-bonding-catalyzed 1,3-dipolar cycloaddition of aromatic and aliphatic nitro-olefins with ketone-derived hydrazones to afford 4-nitropyrazolidines in good to excellent yields (up to 97%) with high to excellent stereocontrol (up to 99% ee and >20:1 dr). The utility of the developed protocol was highlighted by demonstrating that optically active 4-nitropyrazolidines can be employed as precursors for 1,2,3-triamines.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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