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Catalytic Enantioselective Iodoaminocyclization of Hydrazones

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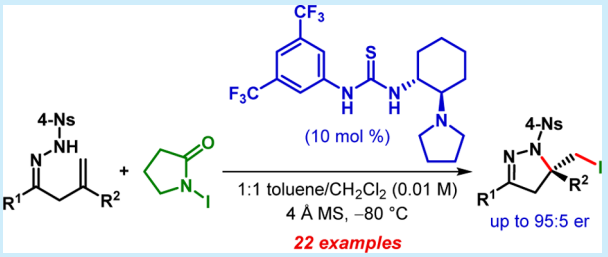
Supporting Information

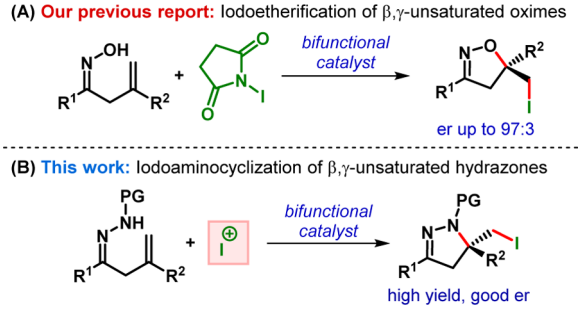
ABSTRACT: The first catalytic enantioselective iodoaminocyclization of β,γ-unsaturated hydrazones has been developed with the help of a *trans*-1,2-diaminocyclohexane-derived bifunctional thiourea catalyst and allows for the direct access to Δ^2-pyrazolines containing a quaternary stereogenic center in high yield with good enantioselectivity (up to 95% yield and 95:5 er).



Stereospecificity associated with electrophilic halogen-induced reactions of unactivated olefins has established them as a general strategy for olefin *trans*-heterodifunctionalization.[1] Compared to other heterodifunctionalizations, this class of reactions holds greater synthetic potential due to the presence of an easily modifiable halogen handle. Tremendous advancement has been made in the area of asymmetric olefin halofunctionalization during the past few years.[2,3] Particularly noteworthy are the intramolecular versions, often referred to as halocyclization.[4] With the development of various strategies and diverse range of catalysts, synthesis of a wide variety of enantioenriched heterocycles consisting of any of the four halogens has been accomplished.[5−8] However, while diversification with respect to the electrophilic component has been realized to include dienes,[8b] enynes,[4d] allenes,[7d] and even alkynes,[6c] the choice of nucleophilic component has remained mostly restricted to acids, alcohols, amines, and their derivatives. In contrast, aldehyde- or ketone-derived nucleophiles have largely been overlooked.[9]

We have recently reported an enantioselective iodoetherification of β,γ-unsaturated oximes, a ketone derivative, using a dihydrocinchonidine-derived bifunctional thiourea catalyst, resulting in the formation of Δ^2-isoxazolines containing a quaternary stereogenic center with good to excellent er's (Scheme 1A).[9b] With this reaction, a ketone derivative was used for the first time as a nucleophile in enantioselective halofunctionalization reaction. Encouraged by the success of this iodoetherification reaction, we reasoned that an analogous iodocyclization could be achieved with the closely related ketone derivative, namely hydrazones (Scheme 1B). Herein we disclose an efficient catalytic enantioselective iodoaminocyclization of β,γ-unsaturated hydrazones.[10]

Scheme 1. Ketone Derivatives in Asymmetric Halocyclization



Pyrazolines are privileged substructure in many natural products and also possess diverse biological activities.[11] A series of studies have recently established *N*-acetyl 3,5-diaryl Δ^2-pyrazolines containing a quaternary stereogenic center as potent kinesin spindle protein (KSP) inhibitors.[12] Although a number elegant routes to enantioenriched pyrazolines has been reported,[13] enantioselective synthesis of pyrazolines containing a quaternary stereogenic center remained challenging.[14] Our method enables direct access to enantioenriched Δ^2-pyrazolines containing a quaternary stereogenic center.

Considering the similarities between the OH group of oximes and the acidic NH of protected hydrazones, we anticipated the compatibility of similar bifunctional thiourea catalysts[15] for this iodoaminocyclization. Consequently, the protecting group on the nitrogen (PG in Scheme 1B) was expected to play a key role, both in deciding the reactivity as well as enantioselectivity.

With this premise in mind, we began our investigation by studying the iodoaminocyclization of phenyl-substituted β,γ-unsaturated 4-nitrobezenesulfonyl (4-Ns) hydrazone **1a** with *N*-iodosuccinimide (NIS, **2a**) as the electrophilic iodine source (Table 1). This protecting group was chosen to render sufficient acidity to NH. For efficiently evaluating the catalyst influence, we had to suppress the strong background reaction (entry 1), which was possible by lowering the reaction temperature to −80 °C. Under these conditions, no product formation was detected, even after 48 h (entry 2). The subsequent catalyst screenings were therefore conducted at −80 °C.[16] As with our previously studied oxime iodoetherification reaction,[9b] the necessity of bifunctional catalyst for this iodoaminocyclization reaction was

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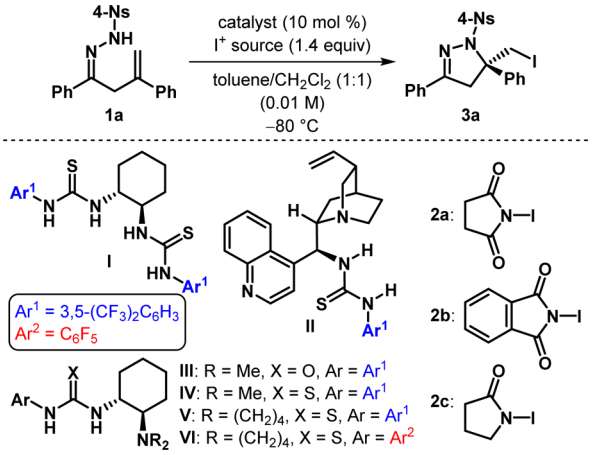
Table 1. Catalyst Evaluation and Reaction Conditions Optimization for Enantioselective Iodoaminocyclization of Hydrazone 1a



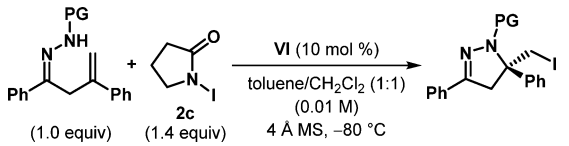
entry	cat.	I+ source	additive	time (h)	conv[a] (%)	er[b]
1[c,d]		**2a**		1	>95	
2[c]		**2a**		48	<5	
3[c]	**I**	**2a**		48	<5	
4[c]	**II**	**2a**		12	>95	50:50
5[c]	**III**	**2a**		36	>95	53:47
6[c]	**IV**	**2a**		36	>95	67.5:32.5
7	**IV**	**2a**		30	>95	79:21
8	**V**	**2a**		30	>95	79:21
9	**V**	**2b**		48	>95	55:45
10	**V**	**2c**		45	>95	85:15
11	**V**	**2c**	MS 3 Å	48	>95	89:11
12	**V**	**2c**	MS 4 Å	48	>95	92.5:7.5
13	**V**	**2c**	MS 5 Å	48	>95	91:9
14[e]	**V**	**2c**	MS 4 Å	48	>95	90:10
15	**VI**	**2c**	MS 4 Å	48	>95	94:6

[a]Conversion as determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Enantiomeric ratio (er) was determined by HPLC analysis using a stationary phase chiral column (see the Supporting Information). [c]Reaction in CH_2Cl_2 at 0.1 M concentration. [d]Reaction at 25 °C. [e]Reaction with 5 mol % of I_2.

confirmed by the lack of catalytic activity of the bisthiourea derivative **I** (entry 3). The cinchonidine-derived thiourea **II**, a highly efficient catalyst for the enantioselective oxime iodoetherification, showed high catalytic activity but failed to induce any enantioselectivity in this reaction (entry 4). Therefore, we turned our focus toward bifunctional catalysts derived from *trans*-1,2-diaminocyclohexane. Whereas the urea derivative **III** resulted Δ^2-pyrazoline derivative **3a** with poor enantioselectivity (entry 5), promising results were obtained with the corresponding thiourea derivative **IV**, commonly known as Takemoto catalyst (entry 6).[15a] At this point, an extensive solvent and concentration optimization revealed a mixture of toluene and CH_2Cl_2 (1:1) as the optimum reaction medium, and at 0.01 M concentration, **3a** was obtained with an er of 79:21 (entry 7).[16] Catalyst **V** containing a pyrrolidine ring at the Brønsted basic nitrogen proved to be equally efficient as **IV** (entry 8). The nature of I^+ source was found to have a considerable influence on the enantioselectivity of this reaction: while *N*-iodophthalimide **2b** led to a drastic drop in er, product with improved er was obtained with *N*-iodopyrrolidinone **2c** (entries 9 and 10). The presence of molecular sieves improved the er, with 4 Å MS emerged as the optimal (entries 11−13). However, unlike in the case of oxime iodoetherification reaction, no positive effect of I_2 was observed (entry 14). Finally, the best result in terms of enantioselectivity was obtained with catalyst **VI** containing a pentafluorophenyl ring (entry 15).

The compatibility of other protecting groups on hydrazone was tested with catalyst **VI** under the optimized reaction conditions (Table 2). These protecting groups include 3-nitrobezenesulfonyl (3-Ns), *p*-tolylsulfonyl (*p*-Ts), and 4-bromobezenesulfonyl (4-Bs). Although poor enantioselectivity was observed for *p*-Ts hydrazone, both 3-Ns and 4-Bs hydrazones returned with good er. However, 4-Ns remained the protecting group of choice under our catalyst and reaction conditions.

Table 2. Effect of Hydrazone Protecting Group on the Catalytic Enantioselective Iodoaminocyclization



entry	PG	time (h)	product	yield[a] (%)	er[b]
1	4-Ns (**1a**)	48	**3a**	95	94:6
2	3-Ns (**4**)	48	**7**	91	84:16
3	*p*-Ts (**5**)	48	**8**	97	67:33
4	4-Bs (**6**)	48	**9**	90	86:14

[a]Isolated yield. [b]Enantiomeric ratio (er) was determined by HPLC analysis using a stationary-phase chiral column (see the Supporting Information).

Having identified the optimum catalyst and reaction conditions, we set out to demonstrate the generality of our enantioselective iodoaminocyclization protocol. However, our initial attempt toward this end with catalyst **VI** was severely jolted as we failed to replicate the same level of enantioselectivity for other substrates.[16] To our relief, when catalyst **V** was employed instead, high level of enantioselectivity was ensured for a wide range of *β*,*γ*-unsaturated (4-Ns)-hydrazones (**1**) under otherwise identical reaction conditions (Table 3). Electron-deficient aryl substituents on either end of the substrate (R^1 and R^2) are generally tolerated, and the resulting Δ^2-pyrazoline derivatives (**3**) were obtained with good er. However, products with significantly reduced enantioselectivities were obtained for the highly electron-rich aryl substituent on olefin (entry 7) and a sterically hindered *o*-chlorophenyl substituent on the hydrazone carbon (entry 10). Electron-rich or heteroaryl substituents on the hydrazone carbon, on the other hand, afforded the products with fairly good level of enantioselectivity (entries 18 and 19). *β*,*γ*-Unsaturated (4-Ns)-hydrazones with aliphatic substituents showed good reactivities, but poor enantioselectivities (entries 20−22), leaving room for further improvement. It must be noted that irrespective of the nature of the substrate, a uniform reaction time (86 h) was followed in all cases to ensure complete conversion as reaction monitoring (by TLC) proved challenging.

Single-crystal X-ray diffraction analysis of the pyrazoline derivative **3a** established its absolute configuration to be *R* (Figure 1).[17] The configurations of the other products reported herein were tentatively assigned as the same assuming that a similar catalytic mechanism was followed.

In conclusion, we have developed the first catalytic enantioselective haloaminocyclization of hydrazones using a bifunctional thiourea catalyst. Starting from easily accessible *β*,*γ*-

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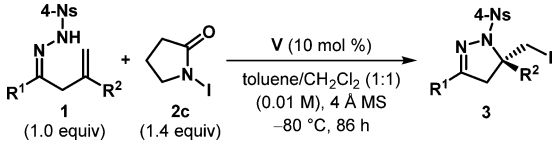
Table 3. Scope of Catalytic Enantioselective Iodoaminocyclization of β,γ-Unsaturated Hydrazone[a]



	R^1	R^2	3	yield[b] (%)	er[c]
1	Ph	Ph	**3a**	95	92.5:7.5
2	Ph	4-FC_6H_4	**3b**	88	91.5:8.5
3	Ph	4-ClC_6H_4	**3c**	79	90.5:9.5
4	Ph	4-MeC_6H_4	**3d**	93	94:6
5	Ph	3-MeC_6H_4	**3e**	82	93:7
6	Ph	2-MeC_6H_4	**3f**	78	90:10
7	Ph	4-$OMeC_6H_4$	**3g**	79	75:25
8	4-ClC_6H_4	4-MeC_6H_4	**3h**	73	92:8
9[d]	3-ClC_6H_4	4-MeC_6H_4	**3i**	78 (95)[e]	94:6
10	2-ClC_6H_4	4-MeC_6H_4	**3j**	80	75:25
11	4-BrC_6H_4	4-MeC_6H_4	**3k**	85	92:8
12	3-BrC_6H_4	Ph	**3l**	80	90:10
13[f]	3-FC_6H_4	4-MeC_6H_4	**3m**	61 (92)[e]	91:9
14[g]	3,4-$Cl_2C_6H_3$	Ph	**3n**	64 (86)[e]	85.5:14.5
15	4-$CF_3C_6H_4$	4-MeC_6H_4	**3o**	86	90:10
16	4-MeC_6H_4	4-MeC_6H_4	**3p**	83	92:8
17[h]	2-naphthyl	4-MeC_6H_4	**3q**	62 (80)[e]	95:5
18	3,4-$(OCH_2O)C_6H_3$	Ph	**3r**	77	90.5:9.5
19	2-furyl	4-MeC_6H_4	**3s**	91	86:14
20	*c*-Hex	4-MeC_6H_4	**3t**	88	60:40
21	Ph	Me	**3u**	94	56:44
22	*c*-Hex	Me	**3v**	85	56:44

[a]Reactions were carried out on 0.048 mmol scale. [b]Isolated yield. [c]Enantiomeric ratio (er) was determined by HPLC analysis using a stationary-phase chiral column (see the Supporting Information). [d]*E*:*Z* ratio for hydrazone 4.5:1. [e]Yields in parentheses are based on the reactive geometrical isomer (*E*) of the substrate. [f]*E*:*Z* ratio for hydrazone 2:1. [g]*E*:*Z* ratio for hydrazone 2.9:1. [h]*E*:*Z* ratio for hydrazone 3.4:1.

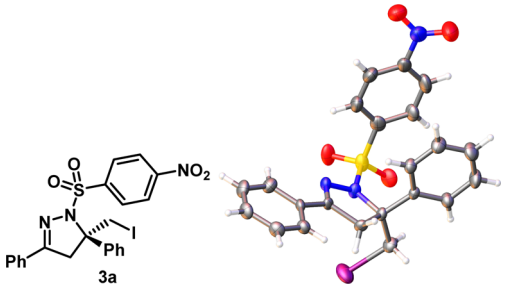


Figure 1. Absolute configuration of **3a** and its X-ray structure.

unsaturated hydrazones as the substrate and *N*-iodopyrrolidinone as the electrophilic iodine source, several Δ^2-pyrazolines containing a quaternary stereocenter were obtained in high yields with good enantioselectivities. This is also the first example of the use of hydrazones as nucleophile in olefin halofunctionalization reactions.[10] Given the diverse biological activities of pyrazoline derivatives, our method would be useful for generating such compounds in enantioenriched form. Further investigations toward this goal are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and crystallographic data (CIF). 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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(17) CCDC 1002958 contains the crystallographic data for **3a** (also available as Supporting Information). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.