

## Enantioselective Conjugate Addition of Hydrazines to $\alpha,\beta$ -Unsaturated Imides. Synthesis of Chiral Pyrazolidinones

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Enantioselective conjugate addition of heteroatom nucleophiles to electron-poor acceptors continues to attract attention from the synthetic community.<sup>1</sup> The addition of bisnucleophilic donors such as hydroxylamines and hydrazines can provide direct access to valuable small-ring heterocycles of potential medicinal interest.<sup>2</sup> Literature suggests that enantioselective conjugate addition of N-monosubstituted hydroxylamines proceed with good chemoselectivity since there is a clear differentiation of nucleophilicity between the two donor atoms.<sup>3</sup> Diastereoselective addition of chiral hydrazines to achiral acceptors<sup>4</sup> and reactions of chiral acceptors with simple hydrazines have been reported in the literature.<sup>5</sup> At present, there are no reported examples of enantioselective conjugate addition of hydrazines. In this work we report the first examples of highly enantioselective addition of monosubstituted hydrazines to  $\alpha,\beta$ -unsaturated imides using catalytic amounts of chiral Lewis acids (Scheme 1). Furthermore, we also demonstrate that the conjugate addition proceeds with high chemoselectivity using bisnucleophilic hydrazine donors (formation of **3** over **4**, Scheme 1). The hydrazine addition protocol provides direct access to chiral pyrazolidinones.<sup>6</sup>

We began our experiments with the goal of identifying conditions that would allow for conjugate addition of hydrazine and its derivatives selectively.<sup>7</sup> To this end, initial experiments were focused on the addition of the parent hydrazine<sup>8</sup> to oxazolidinone crotonate **1a** in the presence of a variety of Lewis acids. These experiments proved to be not very rewarding because only amidation products were obtained and only traces of the desired conjugate addition product could be isolated. We then examined the addition of monosubstituted hydrazine benzylhydrazine to crotonate **1a** in the presence of a chiral Lewis acid derived from **5** and magnesium salts (Table 1). In these reactions, after conjugate addition, the achiral template is cleaved resulting in the formation of the pyrazolidinone products. Magnesium iodide, triflate, and triflimide salts gave a nearly 1:1 mixture of **3a** and **4a** in good overall yield (entries 1–3) when reactions were carried out at room temperature in the presence of triethylamine as a base.<sup>9</sup> The enantioselectivity for the addition products were low (entries 1–3). In contrast, magnesium perchlorate proved to be more effective as a Lewis acid and gave much improved levels of enantioselectivity for both isomers (entry 4). Other Lewis acids were also examined but did not lead to improvements in selectivity (entries 5 and 6).<sup>10</sup>

We have previously explored the effect of achiral templates on reactivity and/or selectivity in several enantioselective transformations.<sup>11,12</sup> Screening of alternate templates in the hydrazine addition is straightforward. The template is cleaved during the reaction resulting in the same products, making analysis simple. For template evaluation, a chiral Lewis acid prepared from **5** and magnesium perchlorate, benzylhydrazine, triethylamine, and molecular sieves were used as standard conditions. Replacing an oxazolidinone template (**1a**) with a pyrrolidinone (**1b**) gave a slight improvement in selectivity for the major isomer (compare entry 7 with 4). The

Scheme 1

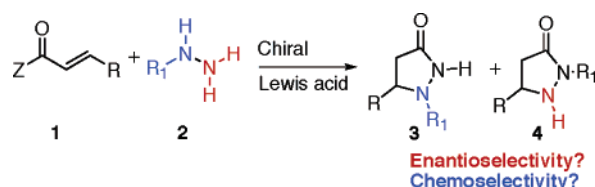
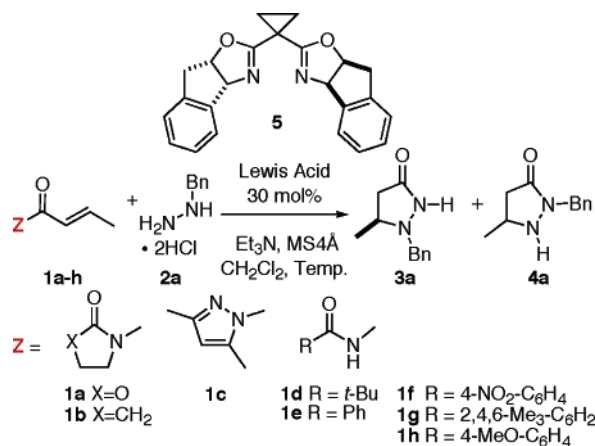


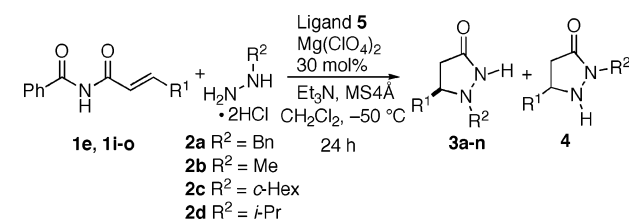
Table 1. Reaction Conditions for Hydrazine Addition<sup>a</sup>



entry	substrate	LA	temp °C	yield % <sup>b</sup>	3a/4a <sup>c</sup>	3a ee % <sup>d</sup>	4a ee % <sup>d</sup>
1	<b>1a</b>	MgI <sub>2</sub>	room temp	74	57:43	6	20
2	<b>1a</b>	Mg(OTf) <sub>2</sub>	room temp	90	63:37	16	12
3	<b>1a</b>	Mg(NTF <sub>2</sub> ) <sub>2</sub>	room temp	88	47:53	9	6
4	<b>1a</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	room temp	92	45:55	55	56
5	<b>1a</b>	Zn(OTf) <sub>2</sub>	room temp	84	63:37	0	0
6	<b>1a</b>	Cu(OTf) <sub>2</sub>	room temp	62	64:36	0	0
7 <sup>e</sup>	<b>1b</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	room temp	84	69:31	67	52
8	<b>1c</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	room temp	93	70:30	58	55
9	<b>1d</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	room temp	90	52:48	30	34
10	<b>1e</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	room temp	86	59:41	69	47
11	<b>1e</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	-30	87	92:8	79	40
12	<b>1e</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	-50	92	98:2	84	52
13	<b>1f</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	-50	63	98:2	54	
14	<b>1g</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	-50	87	98:2	27	
15	<b>1h</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub>	-50	91	98:2	72	

<sup>a</sup> For reaction conditions, see Supporting Information. Reaction times at room temp = 8 h and at -30 or -50 °C = 24 h. <sup>b</sup> The yield is for isolated product. <sup>c</sup> Isomeric ratios (3/4) were determined by <sup>1</sup>H NMR (400 MHz). <sup>d</sup> Determined by chiral HPLC. <sup>e</sup> Reaction with **1b** at -50 °C gave **3a** in 84% yield and 75% ee (**3a/4a** = 98:2).

use of 3,5-dimethylpyrazole as an achiral template (**1c**) did not lead to improved selectivity (entry 8). In contrast, imide templates proved to be very effective in the conjugate additions (entries 9–15). The benzimide **1e** gave high levels of selectivity for the major isomer at room temperature (entry 10). A significant improvement in isomer ratio could be realized by cooling the reaction to -30 °C (entry

**Table 2.** Examination of Substrate and Reagent Scope

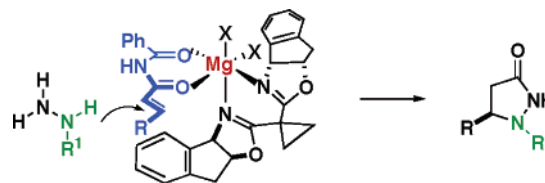
entry	R <sub>1</sub>	R <sub>2</sub>	product	yield (%) <sup>a</sup>	3/4 <sup>b</sup>	ee % <sup>c</sup>
1	Me ( <b>1e</b> )	Bn	<b>3a</b>	92	98:2	84
2	Et ( <b>1i</b> )	Bn	<b>3b</b>	93	99:1	80
3	<i>i</i> -Pr ( <b>1j</b> )	Bn	<b>3c</b>	69	95:5	77
4	CH <sub>2</sub> - <i>c</i> Hex ( <b>1k</b> )	Bn	<b>3d</b>	67	98:2	80
5	CH <sub>2</sub> Ph ( <b>1l</b> )	Bn	<b>3e</b>	74	98:2	89
6	CH <sub>2</sub> OBn ( <b>1m</b> )	Bn	<b>3f</b>	70	98:2	95
7	Ph ( <b>1n</b> )	Bn	<b>3g</b>	43	90:10	37
8	CO <sub>2</sub> <i>t</i> -Bu ( <b>1o</b> )	Bn	<b>3h</b>	80	99:1	67
9	Me ( <b>1e</b> )	Me	<b>3i</b>	88	99:1	80
10	Me ( <b>1e</b> )	<i>c</i> -Hex	<b>3j</b>	83	99:1	67
11	Me ( <b>1e</b> )	<i>i</i> -Pr	<b>3k</b>	79	99:1	87
12	CH <sub>2</sub> OBn ( <b>1m</b> )	Me	<b>3l</b>	84	99:1	90
13	CH <sub>2</sub> OBn ( <b>1m</b> )	<i>c</i> -Hex	<b>3m</b>	61	99:1	79
14	CH <sub>2</sub> OBn ( <b>1m</b> )	<i>i</i> -Pr	<b>3n</b>	67	99:1	99

<sup>a</sup> Isolated yield. <sup>b</sup> Isomer ratio determined by <sup>1</sup>H NMR (400 MHz). <sup>c</sup> Determined by chiral HPLC. The minor products were not characterized.

11), and the highest level of selectivity of 84% was obtained by conducting the reaction at  $-50\text{ }^{\circ}\text{C}$  (entry 12).<sup>13</sup> It is interesting to note that at lower temperature the reaction is better able to discriminate between the nucleophilicity of the hydrazine nitrogens. Thus the more nucleophilic and bulky nitrogen adds selectively to the  $\beta$ -carbon. As can be expected, lower temperature also provides improved enantioselectivity. Other structural changes to the imide template did not provide improved enantioselectivity (entries 13–15).

Having established that a highly selective method for conjugate hydrazine addition was at hand, we explored the scope of substrate and the reagent and these results are tabulated in Table 2. For these reactions, the optimal benzimide template and the chiral Lewis acid prepared from **5** and magnesium perchlorate were used. Changing the methyl substituent in **1e** to an ethyl group (**1i**) gave the pyrazolidinone product with similar yields and selectivity (compare entry 1 with 2). Reaction efficiency with a bulky isopropyl group on the  $\beta$ -carbon (**1j**) was lowered; however, the isomer ratio and enantioselectivity remained nearly the same (entry 3). Other substituents on the  $\beta$ -carbon were also competent substrates in the conjugate addition (entries 4–6) with a protected hydroxymethyl substituent providing a very high level of enantioselectivity (entry 6). The reactivity of cinnamate **1n** was low and gave product in low yield and enantioselectivity (entry 7). The fumarate **1o** gave the product in good yield and moderate selectivity (entry 8). The reaction of substrates **1e** and **1m** with different hydrazines was investigated (entries 9–14). Of these, reactions with methyl and isopropyl hydrazine were very selective. The addition of isopropyl hydrazine **2d** to **1m** gave pyrazolidinone with 99% enantioselectivity (entry 14). The data in Table 2 clearly demonstrates that there is good substrate and reagent scope for the conjugate addition of hydrazines to  $\alpha,\beta$ -unsaturated imides.

The absolute stereochemistry for the major isomer of the pyrazolidinone product was established by comparison of its optical rotation with that reported in the literature.<sup>6b</sup> The *R* stereochemistry for the product(s) is consistent with hydrazine addition to an *s*-cis

**Figure 1.** Stereochemical model for hydrazine addition.

rotamer of the imide substrate with magnesium in a *cis*-octahedral geometry (Figure 1).<sup>14</sup>

In conclusion, we have developed a novel enantioselective method for the preparation of pyrazolidinones in highly enantioenriched form. The utilization of these products as chiral auxiliaries and ligands is being pursued in our laboratory.

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**Supporting Information Available:** Characterization data for compounds **1–4** and experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) The identity of the isomers was established by comparing their spectral characteristics with known compounds and/or by spectroscopic analysis (see Supporting Information for details).
- (10) We have examined other amines and solvents in the conjugate addition. A variety of Lewis acid/box ligand combinations have also been investigated using both **1a** and **1e**. These reactions showed either low reactivity and/or selectivity and results in Table 1 proved to be optimal.
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