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# Copper(II)-Catalyzed Exo and Enantioselective Cycloadditions of Azomethine Imines

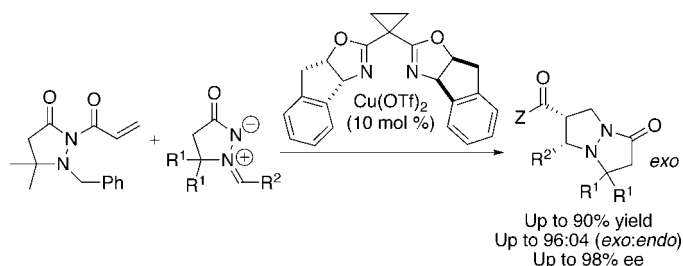
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## ABSTRACT



A strategy for exo and enantioselective 1,3-dipolar cycloaddition of azomethine imines to 2-acryloyl-3-pyrazolidinone is described. The corresponding cycloadducts are isolated with high diastereoselectivities (up to >96:4 exo/endo) and enantioselectivities (up to 98% ee).

Catalytic, enantioselective cycloaddition of 1,3-dipoles to olefins has become a premier method for the preparation of optically active, five-membered nitrogen-containing heterocycles.<sup>1</sup> Advances in the fields of chiral Lewis acid catalysis and organocatalysis have led to the development of highly enantioselective cycloadditions of a variety of nitrogen-containing 1,3-dipoles, including azomethine,<sup>2</sup> nitrilium,<sup>3</sup> and diazonium betaines.<sup>4</sup> To date, the azomethine betaines represent the most thoroughly studied class of 1,3-dipoles in enantioselective cycloadditions. Highly enantioselective

cycloadditions of nitrones, azomethine ylides, and azomethine imines have all been reported. A variety of azomethine ylide cycloadditions with olefins have been developed to access pyrrolidine derivatives as either the endo or exo isomer with high diastereo- and enantioselectivity.<sup>5</sup> Likewise, endo and enantioselective cycloadditions of nitrones with olefins are well established,<sup>2b,6</sup> while endo and enantioselective cycloadditions of azomethine imines with electron-

(1) For a comprehensive review of 1,3-dipolar cycloadditions, see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003. For a recent review on asymmetric 1,3-dipolar cycloadditions, see: (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.

(2) For a highlight on enantioselective cycloadditions of azomethine ylides, see: (a) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272. For selected recent examples of enantioselective cycloadditions of nitrones, see: (b) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351. (c) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. For selected recent examples of enantioselective cycloadditions of azomethine imines, see: (d) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (e) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97. (f) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244. (g) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778.

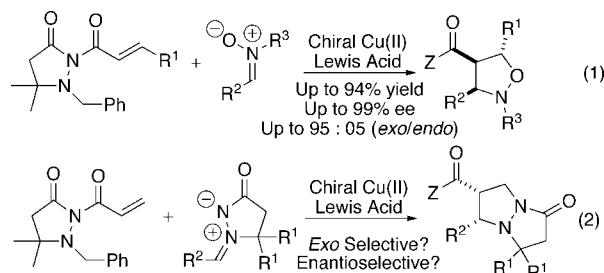
(3) For enantioselective cycloaddition of nitrile oxides, see: (a) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366. For enantioselective cycloaddition of nitrile imines, see: (b) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276.

(4) For enantioselective cycloadditions of diazoalkanes and diazoacetates, see: (a) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710. (b) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174. (c) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553.

(5) For selected endo and enantioselective azomethine ylide cycloadditions, see: (a) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J. Am. Chem. Soc.* **2007**, *129*, 750. (b) Zhang, X.; Wang, B.; Longmire, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 13400. For selected exo and enantioselective azomethine ylide cycloadditions, see: (c) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1799. (d) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795.

(6) (a) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (b) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840.

**Scheme 1.** Exo-Selective Cycloadditions of Azomethine Betaines with  $\alpha,\beta$ -Unsaturated Pyrazolidinone Imides

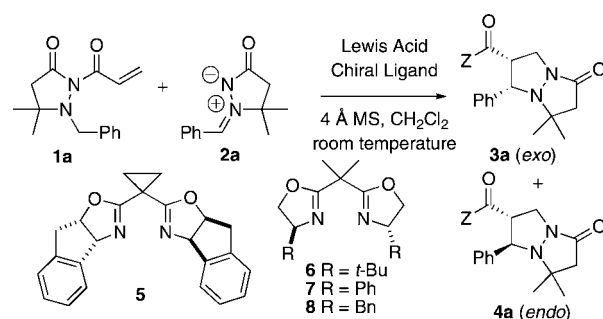


deficient olefins have recently begun to appear in the literature.<sup>2d,e</sup> However, reports of exo and enantioselective cycloadditions of nitrones or azomethine imines are relatively scarce.<sup>7,8</sup> We and others have previously reported approaches for exo and enantioselective cycloadditions of nitrones to electron-deficient alkenes,<sup>7a-c</sup> but to date, none of these methods have proven general for exo-selective cycloadditions of both nitrones and azomethine imines. The lack of general methods for exo-selective cycloadditions of azomethine betaines led us to investigate whether our strategy for exo and enantioselective cycloaddition of nitrones<sup>7a</sup> with  $\alpha,\beta$ -unsaturated pyrazolidinone imides (Scheme 1, eq 1) could be applied to azomethine imine cycloadditions (eq 2).

We began by optimizing reaction conditions for the cycloaddition of azomethine imine **2a** with pyrazolidinone acrylate **1a**. The optimal chiral Lewis acid from our study of exo-selective nitron cycloadditions, Cu(OTf)<sub>2</sub>/bis(oxazoline) **5**, was also an effective catalyst for exo-selective azomethine imine cycloadditions. Cu(OTf)<sub>2</sub>/**5**-catalyzed cycloaddition of **2a** with **1a** gave the cycloadducts **3a** and **4a** in 81% yield as a 90:10 mixture of exo and endo isomers (Table 1, entry 1).<sup>9</sup> Furthermore, the desired exo cycloadduct was formed with 98% enantiomeric excess. Chiral Lewis acids prepared from additional bis(oxazoline) ligands and Cu(OTf)<sub>2</sub> were employed as catalysts in an attempt to improve the diastereo- and/or enantioselectivity of the cycloaddition (entries 2–4). When Cu(OTf)<sub>2</sub>/*t*-Bu-BOX **6** was used as the chiral Lewis acid, *exo*-**3a** was isolated in excellent ee, but the ratio of **3a**:**4a** was decreased to 83:17 (entry 2). The results of reactions employing Ph-BOX **7** and Bn-BOX **8** as the chiral ligand were very similar. The *exo*/endo ratio was 84:16 with both ligands, and cycloadduct **3a** was isolated in –82% ee with ligand **7** (entry 3) and –84% ee with ligand **8** (entry 4).

The use of additional chiral Lewis acid complexes prepared from ligand **5** and Mg(II), Zn(II), or Ni(II) salts

**Table 1.** Optimization of Chiral Lewis Acid-Catalyzed Exo- and Enantioselective Cycloadditions of Azomethine Imine **1a**<sup>a</sup>



entry	Lewis acid	L*	CLA (mol %)	yield (%) <sup>b</sup>	exo/endo <sup>c</sup>	exo ee <sup>d</sup> (%)
1	Cu(OTf) <sub>2</sub>	<b>5</b>	30	81	90:10	98
2	Cu(OTf) <sub>2</sub>	<b>6</b>	30	85	83:17	–98
3	Cu(OTf) <sub>2</sub>	<b>7</b>	30	88	84:16	–82
4	Cu(OTf) <sub>2</sub>	<b>8</b>	30	75	84:16	–84
5	Mg(OTf) <sub>2</sub>	<b>5</b>	30	38	4:96	46 (47) <sup>e</sup>
6	Zn(OTf) <sub>2</sub>	<b>5</b>	30	84	33:67	60 (–59) <sup>e</sup>
7	Ni(ClO <sub>4</sub> ) <sub>2</sub>	<b>5</b>	30	80	7:93	55 (85) <sup>e</sup>
8	Cu(OTf) <sub>2</sub>	<b>5</b>	20	83	89:11	98
9	Cu(OTf) <sub>2</sub>	<b>5</b>	10	90	88:12	94

<sup>a</sup> For experimental details, see the Supporting Information. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by chiral HPLC. <sup>e</sup> Values in parentheses are for the endo adduct.

led to endo-selective cycloadditions of azomethine imine **2a** (entries 5–7). The Mg(OTf)<sub>2</sub>/**5**- and Zn(OTf)<sub>2</sub>/**5**-catalyzed cycloaddition gave *endo*-**4a** as the major diastereomer with modest enantioselectivity (entries 3 and 4). However, the Ni(ClO<sub>4</sub>)<sub>2</sub>/**5**-catalyzed cycloaddition was highly endo selective and gave *endo*-**4a** with good ee (entry 5). The results for the Ni(II)-catalyzed reaction were not surprising given the excellent endo selectivities and enantioselectivities reported in Suga's Ni(II)/binaphthylidene-catalyzed azomethine imine cycloadditions.<sup>2e</sup> The difference in the diastereoselectivity between Cu(II)- and Ni(II)-catalyzed cycloadditions can be explained by alternate approach of the azomethine imine depending on the metal geometry of the chiral Lewis acid complex. The Cu(II)-catalyzed cycloadditions likely proceed through distorted square planar complexes, which favor *exo* approach of **1a**. On the other hand, the Ni(II)-catalyzed cycloadditions likely proceed through an octahedral complex, which leads to *endo* approach of **1a**.

With a reasonable study of chiral Lewis acids in hand, we chose Cu(OTf)<sub>2</sub>/**5** as the optimal choice for further exo-selective azomethine imine cycloadditions. Our next goal was to lower the loading of Cu(OTf)<sub>2</sub>/**5**. We were quite pleased to observe essentially no loss of diastereo- or enantioselectivity when the catalyst loading was decreased to 20 mol % (compare entry 8 with entry 1). Furthermore, the loading of Cu(OTf)<sub>2</sub>/**5** could be decreased to 10 mol % with minimal impact on the *exo*- and enantioselectivity (compare entry 9 with entries 1 and 8).

(7) For exo and enantioselective nitron cycloadditions, see: (a) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (b) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431. (c) Desimoni, G.; Faita, G.; Mella, M. Boiocchi, M. *Eur. J. Org. Chem.* **2005**, 1020.

(8) For an example of exo and enantioselective azomethine imine cycloaddition, see: Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818.

(9) An analogous experiment to entry 1, Table 1, employing Cu(ClO<sub>4</sub>)<sub>2</sub> as the Lewis acid led to 91% yield of **3a** and **4a** as a 90:10 *exo*/*endo* mixture with 98% ee for the *exo* adduct **3a**.

**Table 2.** Effect Pyrazolidinone N-1 Substitution<sup>a</sup>

entry	SM	<i>T</i> (°C)	yield <sup>b</sup> (%)	exo/endo <sup>c</sup>	exo ee <sup>d</sup> (%)
1	<b>1a</b>	rt	90	88:12	94
2 <sup>e</sup>	<b>1b</b>	40	86	92:08	98
3	<b>1c</b>	rt	79	95:05	98

<sup>a</sup> For experimental details, see the Supporting Information. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by chiral HPLC. <sup>e</sup> Reaction performed at 40 °C in sealed, heavy wall pressure vessel.

Previously, our group has shown that the size of the fluxional *N*-1 substituent in the pyrazolidinone auxiliary can impact the level of enantioselectivity in Cu(II)-catalyzed Diels–Alder<sup>10</sup> and nitrone cycloadditions.<sup>7a</sup> We prepared  $\alpha,\beta$ -unsaturated pyrazolidinone imides **1b** and **1c** to test whether a similar correlation between the size of the fluxional group (*R*) and the enantioselectivity was present in azomethine imine cycloadditions (Table 2). Unfortunately, a clear correlation between *R* group size and enantioselectivity was not apparent. Both smaller and larger *R* groups led to moderate improvement in enantioselectivity when compared to the standard *N*-benzyl auxiliary (compare entries 2 and 3 with entry 1). The limited impact of the fluxional group size likely occurs because the sterically bulky ligands, such as **5** and **6**, override any participation by the fluxional *R* group in face shielding of the dipolarophile.<sup>10b</sup> Given the modest impact of the *N*-1 substituent, we chose to conduct breadth and scope studies with **1a** since its reactivity is greater than **1b** and **1c**.

Enantioselective 1,3-dipolar cycloadditions of pyrazolidinone-derived azomethine imines with electron-deficient alkenes are often limited to C-5 unsubstituted or in one case C-5 dimethyl-substituted azomethine imines. Therefore, we sought to expand the scope of C-5 substitution in exo-selective cycloadditions of pyrazolidinone-derived azomethine imines (Table 3). As shown above, cycloaddition of C-5 dimethyl-substituted **2a** proceeds in high diastereo- and enantioselectivity (entry 1).

When C-5-unsubstituted azomethine imine **2b** was used as the dipole, the cycloadducts were isolated as a >96:04 ratio of exo and endo isomers and the enantiomeric excess for the desired exo adduct **3d** was 95% (entry 2). Interestingly, an increase in the steric volume of the C-5 substituents in **2c** relative to **2a** (*R* = Et for **2c**, *R* = Me for **2a**) led to a decrease in the exo/endo ratio (compare entry 3 with entry 1). We were quite surprised to find that the cycloaddition of

**Table 3.** Effect of Azomethine Imine C-5 Substitution<sup>a</sup>

entry	dipole	product	4 Å MS	yield (%) <sup>b</sup>	exo/endo <sup>c</sup>	exo ee (%) <sup>d</sup>
1	<b>2a</b>	<b>3a</b>	yes	90	88:12	94
2	<b>2b</b>	<b>3d</b>	yes	79	>96:04	95
3	<b>2c</b>	<b>3e</b>	yes	69	72:28	91
4	<b>2c</b>	<b>3e</b>	no	33	88:12	94
5 <sup>e</sup>	<b>2c</b>	<b>3e</b>	no	75	81:19	98
6	<b>2d</b>	<b>3f</b>	yes	77	73:27	95
7	<b>2d</b>	<b>3f</b>	no	65	86:14	95

<sup>a</sup> For experimental details, see the Supporting Information. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by chiral HPLC. <sup>e</sup> Reaction performed at 40 °C in sealed, heavy wall pressure vessel.

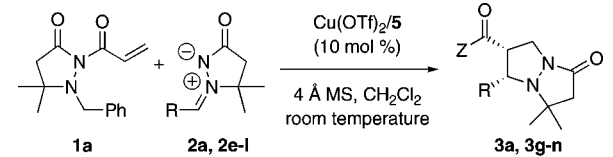
**2c** with **1a** in the absence of 4 Å MS led to significant increase in the diastereomeric ratio (compare entry 4 with entry 3). However, the reaction in the absence of 4 Å MS was sluggish and the yield of the cycloadducts was low. A compromise between reactivity and diastereoselectivity could be achieved by performing the cycloaddition at 40 °C in the absence of 4 Å MS. Under these reaction conditions, the cycloadducts are isolated in 75% yield as an 81:19 mixture of exo and endo isomers (exo ee = 98%).

Two issues arise from the results of these experiments. First, the enantioselectivity for the cycloaddition performed at 40 °C is greater than that for the corresponding cycloadditions performed at room temperature (compare entry 5 with entries 3 and 4). These results remain contrary to the trends commonly observed in enantioselective catalysis but are not unprecedented. We have reported similar increases in enantioselectivity with increasing reaction temperature in Mg(NTf<sub>2</sub>)<sub>2</sub>/5-catalyzed cycloadditions of diazoacetates with  $\alpha,\beta$ -unsaturated pyrazolidinone imides.<sup>4c</sup> Second, the increase in exo selectivity when 4 Å MS are excluded from the reaction is not well understood at this time but is clearly relevant since a similar trend is observed for cycloadditions of azomethine imine **2d** with and without 4 Å MS (compare entries 6 and 7).<sup>11</sup>

After demonstrating that good diastereo- and enantioselectivities were possible from cycloadditions with both C-5-substituted and unsubstituted azomethine imines, we set out to explore the scope of azomethine imines derived from 5,5-dimethylpyrazolidin-3-one and a variety of aldehydes (Table 4). Cycloadditions of azomethine imines (**2e** and **2f**) derived from electron-rich aromatic aldehydes gave the desired cycloadducts with high exo and enantioselectivities

(10) (a) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444. (b) Sibi, M. P.; Stanley, L. M.; Nie, X.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2007**, *129*, 395.

(11) The 4 Å MS lead to increased reactivity by preventing adventitious water molecules from binding to the Lewis acid, the enhanced diastereoselectivity in the absence of 4 Å MS may result from cycloaddition onto a chiral copper complex with a copper-bound water molecule.

**Table 4.** Survey of Additional Azomethine Imines<sup>a</sup>


entry	R	product	4 Å MS	yield <sup>b</sup> (%)	exo/endo <sup>c</sup>	exo ee <sup>d</sup> (%)
1	Ph ( <b>2a</b> )	<b>3a</b>	yes	90	88:12	94
2	<i>p</i> MeOC <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	<b>3g</b>	yes	81	96:04	98
3	<i>p</i> MeC <sub>6</sub> H <sub>4</sub> ( <b>2f</b> )	<b>3h</b>	yes	83	91:09	98
4	<i>p</i> BrC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	<b>3i</b>	yes	83	93:07	98
5	<i>p</i> ClC <sub>6</sub> H <sub>4</sub> ( <b>2h</b> )	<b>3j</b>	yes	82	92:08	98
6	<i>p</i> CNC <sub>6</sub> H <sub>4</sub> ( <b>2i</b> )	<b>3k</b>	yes	80	82:18	93
7	<i>p</i> CNC <sub>6</sub> H <sub>4</sub> ( <b>2i</b> )	<b>3k</b>	no	81	87:13	96
8	<i>o</i> ClC <sub>6</sub> H <sub>4</sub> ( <b>2j</b> )	<b>3l</b>	yes	89	94:06	98
9	<i>o</i> FC <sub>6</sub> H <sub>4</sub> ( <b>2k</b> )	<b>3m</b>	yes	81	79:21	93
10	<i>o</i> FC <sub>6</sub> H <sub>4</sub> ( <b>2k</b> )	<b>3m</b>	no	74	93:07	93
11 <sup>e</sup>	<i>i</i> -Pr ( <b>2l</b> )	<b>3n</b>	yes	72	88:12	78

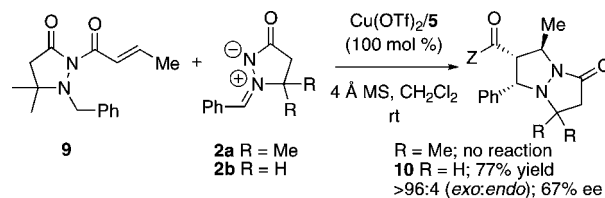
<sup>a</sup> For experimental details, see the Supporting Information. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by chiral HPLC. <sup>e</sup> 20 mol % of Cu(OTf)<sub>2</sub> and 22 mol % of **5** was used to prepare the catalyst.

(entries 2 and 3). Azomethine imines derived from *p*-halogenated benzaldehydes were also well tolerated (entries 4 and 5). In fact, cycloadditions of **2g** and **2h** gave the desired exo diastereomers in 98% ee and ≥92:08 exo/endo ratio. A crystal structure was obtained for exo cycloadduct **3i** (see Table 4, entry 3). The absolute stereochemistry was found to be (5*S*,6*R*).<sup>12</sup> This observation is consistent with the stereochemical model proposed for our previously published exo and enantioselective nitron cycloadditions.<sup>7a,13</sup> Cycloaddition of **1a** with an azomethine imine **2i**, which is derived from an aldehyde bearing a strong electron-withdrawing group in the para position, led to a slightly lower exo/endo ratio and a modest decrease in enantioselectivity (entry 6). However, the diastereomeric ratio and enantiomeric excess could be improved from 82:18 to 87:13 and 93% ee to 96% ee, respectively, when the reaction was run in the absence of 4 Å MS (compare entry 7 with entry 6).

Azomethine imines derived from ortho-substituted benzaldehydes are also competent dipoles. Cycloaddition of *o*-chlorobenzaldehyde-derived **2j** occurred with excellent exo selectivity to give the desired exo cycloadduct **3l** in 98% ee (entry 8). The enantioselectivity remained high when *o*-fluorobenzaldehyde-derived azomethine imine **2k** was employed as the dipole, but the exo/endo ratio was moderate (79:21, entry 9). A remarkable improvement in exo selectiv-

(12) See the Supporting Information for details and a crystal structure of **3i**. NOE experiments demonstrated that the exo cycloadduct was the major diastereomer.

(13) The opposite enantiomer of ligand **5** was used for the exo-selective nitron cycloadditions in reference 7a.

**Scheme 2.** Cycloadditions of Azomethine Imines with Pyrazolidinone Crotonate **9**

ity was once again observed when the cycloaddition of **2k** with **1a** was conducted in the absence of 4 Å MS (compare entry 10 with entry entry 9, 93:07 vs 79:21 exo/endo). Finally, we have demonstrated that an azomethine imine derived from an aliphatic aldehyde can be used without a significant loss of diastereoselectivity and a modest decrease in enantioselectivity (entry 11).

We have made attempts to expand the scope of dipolarophiles in exo and enantioselective cycloadditions of azomethine imines. Specifically, we sought to apply this methodology to  $\beta$ -substituted  $\alpha,\beta$ -unsaturated pyrazolidinone imides. Unfortunately, the cycloaddition of azomethine imine **2a** with pyrazolidinone crotonate **9** does not proceed in the presence of 100 mol % of Cu(OTf)<sub>2</sub>/5. Acceptable yields could be achieved by using azomethine imine **2b** as the dipole in Cu(OTf)<sub>2</sub>/5-catalyzed cycloadditions with **9**. The cycloaddition yielded exo-**10** as a single isomer in 77% yield with 67% ee. Further attempts to improve the enantioselectivity by lowering the reaction temperature led to low yields of **10**.

In conclusion, we have illustrated an efficient method for exo and enantioselective cycloaddition of azomethine imines with pyrazolidinone acrylates. Cycloadducts derived from a variety of azomethine imines were prepared in good to high yields with moderate to good exo selectivity and high enantioselectivity. Furthermore, this methodology represents the first general strategy for exo and enantioselective cycloaddition of azomethine betaines that tolerates both nitrones and azomethine imines as dipoles. At present, the dipolarophile scope for this azomethine imine cycloaddition methodology is limited, and work to address this limitation is ongoing in our laboratory.

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**Supporting Information Available:** Experimental procedures, characterization data, CIF file, and proof of stereochemistry. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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