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Evaluation of Achiral Templates with Fluxional Brønsted Basic Substituents in Enantioselective Conjugate Additions

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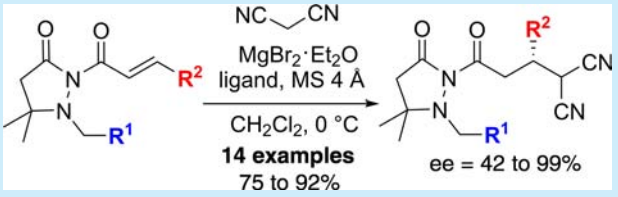
Supporting Information

ABSTRACT: Enantioselective conjugate addition of malononitrile to pyrazolidinone-derived enoates proceeds in excellent yields and high enantioselectivities. A comparison of fluxional substituents with and without a Brønsted basic site and their impact on selectivity is detailed. Molecular sieves as an additive were found to be essential to achieve high enantioselectivity.



Achiral templates play an important role in a wide variety of asymmetric transformations.[1] In this context, we have developed a class of templates, 3-pyrazolidinones, which incorporate a fluxional substituent to provide enhanced selectivity in enantioselective transformations.[2] We have shown that templates containing fluxional substituents were highly effective in cycloaddition,[3] addition of hydroxylamine to enoates,[4] and radical reactions.[5] Suga and co-workers have adapted our templates and have demonstrated their utility in dipolar cycloadditions.[6] We have extended the concept of fluxional chirality and designed ligands,[7] additives,[8] and organocatalysts.[9] In this work we report the utility of achiral templates with fluxional substituents in conjugate addition of carbon nucleophiles to enoates.[10]

The N-1 fluxional substituent in 3-pyrazolidinones is easily varied, and its steric size has been shown to correlate with enantioselectivity in chiral Lewis acid mediated transformations. In an effort to extend the role of the fluxional substituent, we were interested in incorporating a Brønsted basic site into the fluxional substituent. We hypothesized that the fluxional substituent with a Brønsted basic site could play several roles: (1) provide steric shielding, (2) act as a base and generate a nucleophile, (3) potentially deliver the nucleophile, and (4) impact the chiral Lewis acid substrate complex. Four fluxional substituents containing pyridine and quinoline rings were chosen for the study. Malononitrile was the reagent of choice for the conjugate additions to evaluate the effect of fluxional substituent with a Brønsted basic site. The study also included fluxional substituents lacking the Brønsted basic site as controls. Results from conjugate addition of malononitrile to 3-acylpyrazolidinones mediated by chiral Lewis acids are detailed here.

We began our work using an acceptor derived from 3-pyrazolidinone with a 2-pyridylmethyl substituent.[11] Optimization of reaction conditions for the addition of malononitrile **2** to pyrazolidinone derived enoate **1a** (R = 2-pyridylmethyl) using different chiral Lewis acids was undertaken initially (Table 1). Ligands **4**−**7** were evaluated in combination with different Lewis acids. Chiral Lewis acids derived from ligands **4**−**6** were not effective (Table 1, entries 1−4). Among the several chiral Lewis acid complexes examined, the best result was obtained with $MgBr_2{\cdot}Et_2O$ and indanol-derived ligand **7** (Table 1, entry 5, 36% ee). We carried out further optimization studies using ligand **7** for enantioselective malononitrile addition. Remarkably, the addition of molecular sieves (MS 4 Å) led to a substantial increase in enantioselectivity (Table 1, entry 5 versus 6). Three alternate Mg^{2+} Lewis acids were screened for the conjugate addition. $Mg(ClO_4)_2{\cdot}6H_2O$ as a Lewis acid was not effective and gave the product in low yield and selectivity (Table 1 entry 7). However, addition of MS 4 Å gave a huge increase in yield as well as selectivity (Table 1, entry 7 versus 8). Similar trends of improved selectivity with MS 4 Å were also observed with $Mg(NTf_2)_2$ (Table 1, entry 9 versus 10) and MgI_2 (compare entries with 11 and 12). In the absence of MS 4 Å, $Zn(NTf_2)_2$ as a Lewis acid gave no product (Table 1, entry 13). In contrast, addition of MS 4 Å led to a good yield of the product with no selectivity (Table 1, entry 14).

We next examined $MgBr_2{\cdot}Et_2O$/**7**-catalyzed reactions using substrates **1a**−**d** that contained the basic nitrogen atom at different locations (Table 2). As noted previously, reaction with **1a** showed a significant improvement in selectivity in the presence of MS 4 Å (Table 2, entry 1 versus entry 2). Template **1b** containing a 3-pyridylmethyl fluxional group gave the product in low selectivity (Table 2, entry 3). Addition of MS 4 Å led to a significant improvement in selectivity (Table 2, entry 4). More notably, the sense of stereoinduction was opposite to that obtained in the absence of molecular sieves.[12] Reaction of **1c** showed a trend similar to that of reaction with **1a** in the presence and absence of MS 4 Å (entries 5 and 6, no change in the sense of stereoinduction). Substrate **1d** with a 4-isoquinolinylmethyl fluxional substituent behaved similar to **1b** in that the sense of stereoinduction changed with the addition of MS 4 Å (Table 2, entry 7 versus entry 8). Furthermore, **1d** with a bigger fluxional group than **1b** gave higher level of selectivity for both enantiomers (Table 2, entry 3 versus entry 7 and entry 4 versus entry 8). These results indicate that the nature of the fluxional

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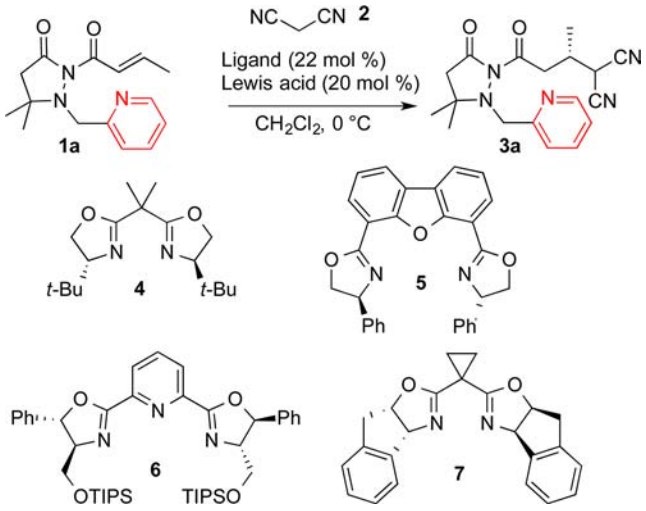
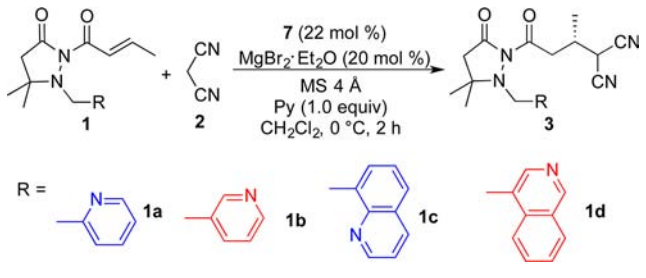
Table 1. Screening of Chiral Lewis Acids and Additives[a]



entry	Lewis acid	ligand	MS 4 Å	yield[b] (%)	ee[c] (%)
1	$MgBr_2{\cdot}Et_2O$	**4**	–	73	0
2	$Ni(ClO_4)_2{\cdot}6H_2O$	**5**	–	80	7
3	$Co(ClO_4)_2{\cdot}6H_2O$	**5**	–	80	14
4	$Sc(OTf)_3$	**6**	–	0	0
5	$MgBr_2{\cdot}Et_2O$	**7**	–	88	36
6	$MgBr_2{\cdot}Et_2O$	**7**	+	92	79
7	$Mg(ClO_4)_2$	**7**	–	18	5
8	$Mg(ClO_4)_2$	**7**	+	91	78
9	$Mg(NTf_2)_2$	**7**	–	87	16[d]
10	$Mg(NTf_2)_2$	**7**	+	93	82
11	MgI_2	**7**	–	88	12[d]
12	MgI_2	**7**	+	82	80
13	$Zn(NTf_2)_2$	**7**	–	0	0
14	$Zn(NTf_2)_2$	**7**	+	79	5

[a]4.0 equiv of malononitrile was used. [b]Isolated yields after purification by column chromatography. [c]ee values were determined by chiral HPLC. [d]Enriched with the opposite enantiomer.

Table 2. Effect of Fluxional Substituent[a]



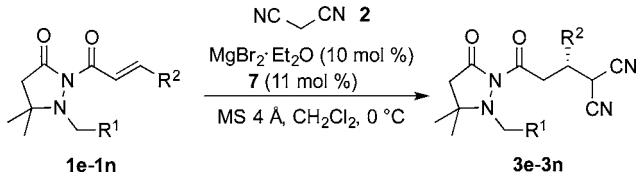
entry	R	MS 4 Å	yield[b] (%)	ee[c] (%)
1	**1a**	–	88	(+) 36
2		+	92	(+) 78
3	**1b**	–	73	(−) 27
4		+	73	(+) 76
5	**1c**	–	83	(+) 39
6		+	76	(+) 79
7	**1d**	–	82	(−) 59
8		+	87	(+) 88

[a]Unless otherwise noted, 0.20 equiv of $MgBr_2{\cdot}Et_2O$, 0.22 equiv of **7**, and 4.0 equiv of **2** were used. [b]Isolated yields after purification by column chromatography. [c]ee values were determined by chiral HPLC.

substituent with Brønsted site significantly impacts the enantioselectivity. In all cases, molecular sieves were effective, and the best result was obtained when **1d** was used (Table 2, entry 8, ee = 88%).

Next, reactions with **1e** and **1f**, substrates devoid of any Brønsted basic site in the fluxional group were examined (Table 3). Additionally, reaction with pyridine as an additive to mimic

Table 3. Control Reactions with Benzyl and Naphthyl Fluxional Groups[a]



entry	substrate	MS 4 Å	Py	yield[b] (%)	ee[c] (%)
1	**1e**	–	–	69	(+) 44
2		–	+	87	(−) 02
3		+	–	75	(+) 90
4		+	+	84	(+) 80
5	**1f**	–	–	22	(+) 36
6		–	+	61	(−) 15
7		+	–	83	(+) 96
8[d]		+	–	89	(+) 97
9		+	+	85	(+) 94

[a]Unless otherwise noted, 0.20 equiv of $MgBr_2{\cdot}Et_2O$, 0.22 equiv of **7**, and 4.0 equiv of **2** was used. [b]Isolated yields after purification by column chromatography. [c]ee values were determined by chiral HPLC. [d]0.10 equiv of $MgBr_2{\cdot}Et_2O$, 0.11 equiv of **7**, and 1.5 equiv of **2** were used.

reactions with **1a**–**d** was also carried out. Reaction of **1e** with a benzyl fluxional group in the absence of both MS 4 Å and pyridine gave the product in good yield and modest selectivity (Table 3, entry 1). Addition of 1 equiv of pyridine increased chemical efficiency, but the selectivity decreased (Table 3. entry 2). Reaction in the presence of MS 4 Å led to a higher yield and very high selectivity (Table 3, entry 1 versus entry 3).[13] A combination of MS 4 Å and pyridine led to a slight decrease in selectivity (Table 3, entry 4). Compound **1f** with a bulky naphthyl fluxional substituent was evaluated next by conducting reactions with and without additives (Table 3, entries 5–9). The trend was similar to that observed for **1e** in that the optimal results were obtained in the presence of MS 4 Å. Notably, we obtained the highest selectivity (Table 3, entry 7, ee = 96%) for **3f**. These results clearly demonstrate that the size of the fluxional group has a significant impact on selectivity. The catalyst loading could be reduced to 10 mol % without loss of selectivity (Table 3, entry 8, ee = 97%). The above results demonstrate that enantioselectivity is highly dependent on the structure of the fluxional group R on the N-1 nitrogen.

Control experiments to assess the role of additives using **1e** as a substrate were undertaken (Table 4). Reaction in the presence of $MgBr_2$ only (no ligand or additive) gave none of the conjugate addition product (Table 4, entry 1) suggesting a base is required for the generation of the nucleophile. Reaction with MS 4 Å resulted in low yield of the product (Table 4, entry 2), indicating that MS 4 Å could deprotonate malononitrile, but the process is not efficient.[14] Reaction using pyridine as an additive gave good yield of the product (Table 4, entry 3) suggesting that deprotonation by pyridine is efficient. As noted previously,

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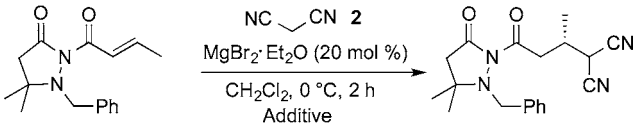
Table 4. Control Experiments To Assess Impact of Additives[a]



1e 3e

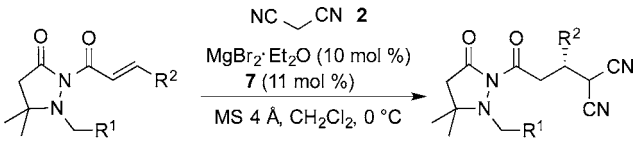
entry	ligand 7	MS 4 Å	additive (equiv)	yield[b] (%)	ee[c] (%)
1	–	–		0	0
2	–	+		20	0
3	–	–	Py (1 equiv)	75	0
4	+	–		69	44
5	+	–	H_2O (0.5 equiv)	66	46
6	+	–	2-picoline (1 equiv)	80	65
7	+	+	2-picoline (1 equiv)	89	90
8	+	–	3-picoline (1 equiv)	82	42
9	+	+	3-picoline (1 equiv)	80	80
10	+	–	2,6-di-*t*-Bu-pyridine (1 equiv)	51	41
11	+	+	2,6-di-*t*-Bu-pyridine (1 equiv)	92	88

[a]Unless otherwise noted, 0.20 equiv of $MgBr_2{\cdot}Et_2O$, 0.22 equiv of **7**, and 4.0 equiv of **2** were used. [b]Isolated yields after purification by column chromatography. [c]ee values were determined by chiral HPLC.

enantioselective reaction in the absence of MS 4 Å gave the addition product in modest selectivity (Table 4, entry 4). Addition of water did not lead to a decrease of enantioselectivity (Table 4, entry 5). Pyridine derivatives were explored next as additives. These additives showed a similar trend to the reactions with pyridine in that MS 4 Å was essential for obtaining high selectivity (Table 4, entries 6–11).

We carried out a small breadth and scope study by varying the enoyl substrate, and these results are tabulated in Table 5. As demonstrated previously, substrate **1f** with a naphthylmethyl fluxional group gave higher selectivity than **1e** with a benzyl fluxional group (Table 5, entry 1 versus entry 2). Thus, our initial

Table 5. Substrate Scope[a]



1e-1n 3e-3n

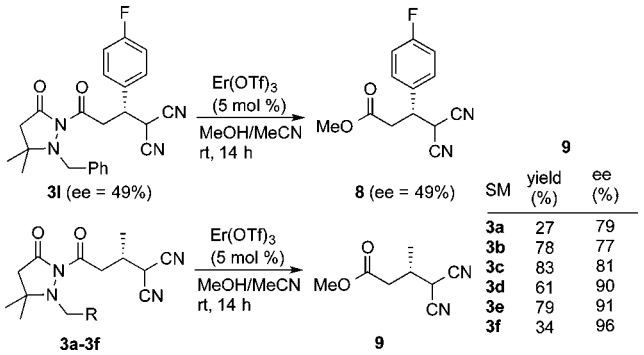
	substrate					
entry	1	R^1	R^2	time (h)	yield[b] (%)	ee[c] (%)
1[d]	**1e**	Ph	Me	2	75	90
2	**1f**	1-Naph	Me	2	89	97
3	**1g**	1-Naph	Et	21	88	99
4	**1h**	1-Naph	CH_2*i*Pr	21	88	94
5	**1i**	1-Naph	CH_2OBn	21	80	95
6	**1j**	1-Naph	Ph	21	86	71
7	**1k**	Ph	Ph	21	86	93
8	**1l**	Ph	*p*-FC_6H_4	21	87	49
9	**1m**	Ph	*p*-ClC_6H_4	21	86	53
10	**1n**	Ph	*p*-$MeOC_6H_4$	68	77	42

[a]Unless otherwise noted, 0.10 equiv of $MgBr_2{\cdot}Et_2O$, 0.11 equiv of **7**, and 1.5 equiv of **2** were used. [b]Isolated yields after purification by column chromatography. [c]ee values were determined by chiral HPLC. [d]0.20 equiv of $MgBr_2{\cdot}Et_2O$, 0.22 equiv of **7**, and 4.0 equiv of **2** were used.

breadth and scope studies used the template with a naphthylmethyl group. Increasing the size of the β-substituent from a methyl (**1f**) to an ethyl group (**1g**) resulted in diminished reactivity (2 h versus 21 h for completion of reaction, Table 5, entry 2 and 3). Remarkably, the enantioselectivity for the product **3g** was the highest for the all the reactions (Table 5, entry 3, ee = 99%). Compounds **1h** and **1i** with a β-CH_2-*i*-Pr and CH_2OBn substituent, respectively, also gave high enantioselectivity (Table 5, entries 4 and 5, ee = 94 and 95%). In contrast to these β-alkyl substrates, cinnamate (**1j**) was somewhat less selective (Table 5, entry 6). Interestingly, the use of template with a benzyl fluxional group was effective, and the product was obtained with 93% ee (Table 5, entry 7). In contrast, substrates with a *p*-substituent on the phenyl ring (**1l**, **1m**, and **1n**) gave low selectivities (Table 5, entries 8–10).

To gain an understanding of the differences in selectivity with changes in the template as well as the role of MS 4 Å, compound **3l** was converted to a known compound **8** by a Lewis acid mediated transesterification (Scheme 1). This established that **3l**

Scheme 1. Determination of Absolute Stereochemistry



has the (*S*)-configuration.[10a−c] Similarly, compounds **3a**–**f** were also converted to a single methyl ester **9** by transesterfication. Interestingly, regardless of the nature of the fluxional substituent, the face selectivity of the conjugate addition was identical as evidenced by the formation of the ester **9** with (*S*)-configuration.

We propose two tentative models to account for reactions using different templates and the reversal of selectivity in the presence and absence of MS 4 Å. In the presence of MS 4 Å, reactions occur from a tetrahedral or cis octahedral organization of the Lewis acid/ligand/substrate complex (Figure 1A). On the basis of control experiments, either MS 4 Å, basic nitrogen in the template, or bromide counterion[15] assists in the formation of the nucleophile. The ligand is the major contributor of face shielding with some reinforcement by the fluxional group, and since the basic fluxional groups gave predominantly the same enantiomer, this suggests that ion-pair directed addition was not occurring,

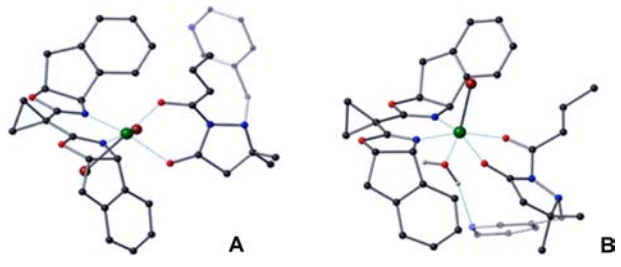


Figure 1. Stereochemical models.

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contrary to our original hypothesis. This accounts for the observed stereochemical outcome of the reaction and the impact of the size of the fluxional group on selectivity: the larger the substituent the higher the selectivity. In the absence of MS 4 Å, reactions occur from both a cis octahedral and trans octahedral organization of the reactive complex with interstitial water molecules still coordinated to the metal ion (Figure 1B). Since these two organizations shield opposite faces, the selectivity is modest. In the case of substrates **1b** and **1d**, the Brønsted base has the potential to form a H-bond with water and leading to a higher proportion of the trans octahedral complex and thus leading to an inversion in stereochemistry. Geometrical constraints may make this type of interaction less effective for compounds **1a** and **1c**.

In summary, we have developed enantioselective conjugate addition of malononitrile to pyrazolidinone-derived enoates. The efficiency of this reaction was found to be highly dependent on both the structure of the substituent on the fluxional nitrogen and additives such as MS. The results suggest that inclusion of donor atom in the fluxional group may allow for interesting organization of chiral Lewis acid/substrate complex and ensuing selectivity issues.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new compounds. 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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(11) For details on synthesis, experimental conditions, and characterization data, see the Supporting Information.

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(13) Use of MS 3 Å or MS 5 Å instead of MS 4 Å gave nearly identical results.

(14) Molecular sieves can act as a base. See: (a) Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal.* **2006**, *348*, 1161. (b) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583. (c) Hasegawa, M.; Ono, F.; Kanemasa. *Tetrahedron Lett.* **2008**, *49*, 5220. (d) García, J. M.; Maestro, M. A.; Oiarbide, M.; Odriozola, J. M.; Razkin, J.; Palomo, C. *Org. Lett.* **2009**, *11*, 3826.

(15) The bromide counterion may be formed after the substrate coordinates the chiral Lewis acid.