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The Role of Achiral Pyrazolidinone Templates in Enantioselective Diels−Alder Reactions: Scope, Limitations, and Conformational Insights

Mukund P. Sibi,* Levi M. Stanley, Xiaoping Nie, Lakshmanan Venkatraman, Mei Liu, and Craig P. Jasperse

Contribution from the Department of Chemistry and Molecular Biology, North Dakota State University, Fargo, North Dakota 58105

Received September 5, 2006; E-mail: mukund.sibi@ndsu.edu

Abstract: We have evaluated the role of achiral pyrazolidinone templates in conjunction with chiral Lewis acids in room temperature, enantioselective Diels−Alder cycloadditions. The role of the fluxional N(1) substituent was examined, with the bulky 1-naphthylmethyl group providing enantioselectivities up to 99% ee, while templates with smaller fluxional groups gave lower selectivities. High selectivities were also observed in reactions of **7d** with chiral Lewis acids derived from relatively small chiral ligands, suggesting the pyrazolidinone templates are capable of relaying stereochemical information from the ligand to the reaction center. Lewis acids capable of adapting square planar geometries, such as $Cu(OTf)_2$, $Cu(ClO_4)_2$, and $Pd(ClO_4)_2$, were found to be particularly effective at providing high selectivities. Additionally, substitution at the C-5 position of the pyrazolidinone templates has been shown to be critical for optimal selectivity. Reactions of the optimal pyrazolidinone appended with a number of common dienophiles and various dienes demonstrate the utility of this achiral template. Furthermore, catalytic loadings could be lowered to 2.5 mol % with essentially no loss in selectivity. $\pi-\pi$ interactions were evaluated as a means to explain the unusually high selectivity observed at room temperature. Finally, non-C_2-symmetric ligands were employed as a test to determine if chiral relay was operative.

Introduction

Chiral Lewis acid catalysis continues to be an effective way to access enantiomerically pure compounds.[1] A wealth of research has been dedicated to the development of efficient chiral Lewis acid catalysts.[2] Much of this effort has focused on the design of superior ligands capable of shielding distant reactive centers when combined with an appropriate Lewis acid.[3] Although this approach continues to provide unique solutions in terms of asymmetric synthesis, the preparation of many of the necessary ligands involves significant effort. An additional limitation in many enantioselective reactions is the requirement for low temperatures to achieve high levels of selectivity.

We have considered an approach involving improving the design of achiral templates utilized for asymmetric transformations. Can modified templates amplify the enantioselectivity afforded by existing chiral Lewis acids? If so, amplification of enantioselectivity might enable simpler, less elaborate, and more accessible chiral ligands to induce high enantioselectivity for reactions in which relatively inaccessible or expensive ligands are currently required. The ability to amplify enantioselectivity might also make room-temperature reactions practical.

Our approach focused on the use of pyrazolidinone templates 1 (Figure 1). Pyrazolidinones 1 are readily available and are attractive because the R group can be easily varied and they have no static (permanent) chirality. However, the fluxional N(1) nitrogen does provide a chiral center. Following coordination to a chiral Lewis acid, conformations 2 and 3 become diastereotopic. We reasoned the reaction might proceed preferentially through one of these two fluxional configurations, with the chirality of the reactive configuration controlled by the chiral Lewis acid. If so, the pyrazolidinone with induced chirality might function much like a chiral auxiliary such as 4. Chiral oxazolidinones 4 are effective in numerous diastereoselective reactions[4] and, when used in conjunction with matched chiral Lewis acids, give strongly amplified stereoselectivity (double

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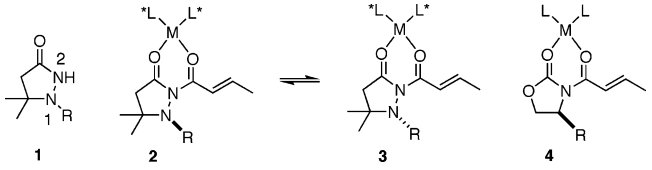
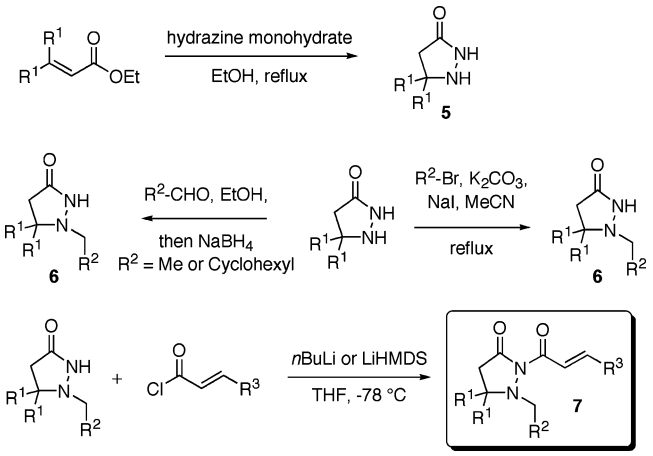


Figure 1. Rationale for increased enantioselectivity with pyrazolidinone substrates.

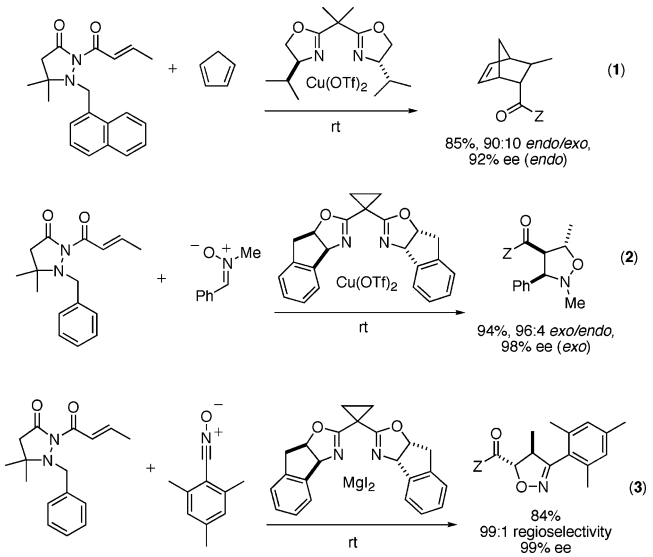
diastereoselection).[5] We thought that if the pyrazolidinone R group were to act in a consonant fashion with a chiral Lewis acid, it could provide similar amplification of enantioselectivity. However, unlike permanently chiral substrates such as 4, the pyrazolidinone substrates need not be synthesized from chiral pool precursors. Thus, we hoped to establish a "chiral relay" situation in which the chiral Lewis acid would bias the fluxional nitrogen, establish the pyrazolidinone as an effective chiral auxiliary where the nitrogen substituent (the "relay group") could participate in face shielding, and if possible have the chiral ligand with static chirality and the relay group work synergistically to amplify enantioselectivity.[6]

Davies introduced a related concept for relaying stereochemical information using a chiral auxiliary to install asymmetry.[7] Similar approaches have also been evaluated in other laboratories, most notably by Clayden[8] and Hitchcock.[9] Our approach differs in that chirality is not inherent to our substrate but is indirectly relayed from a chiral Lewis acid through the template to the reaction centers.[10−13]

Scheme 1. Synthesis of Pyrazolidinone Dienophiles



Scheme 2. Enantioselective Reactions Utilizing Pyrazolidinone Substrates



The pyrazolidinone templates of interest to this study were prepared in a straightforward manner from the corresponding β,β-disubstituted enoates (Scheme 1). Condensation of the enoates with hydrazine hydrate gave the desired N(1) unsubstituted pyrazolidinones **5** in high yields. N(1) substitution was accomplished by either reductive amination or selective alkylation of the more nucleophilic N(1) nitrogen. Finally, acylation of **6** at N-2 occurs upon deprotonation with *n*-BuLi or LiHMDS and subsequent addition of the appropriate α,β-unsaturated acid chloride.

Prior reports from our laboratory have demonstrated the utility of α,β-unsaturated pyrazolidinone imides in several asymmetric transformations (Scheme 2). Pyrazolidinone substrates have proven to be very effective for bisoxazoline/Lewis acid-catalyzed Diels−Alder cycloadditions (eq 1),[14] 1,3-dipolar cycloadditions of nitrones (eq 2),[15] and nitrile oxides (eq 3) at ambient temperature.[16] Pyrazolidinone templates have also

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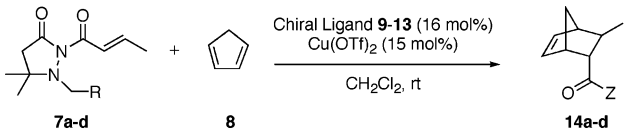
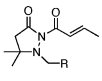
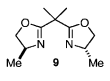
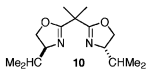
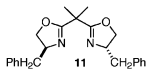
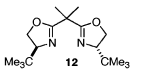
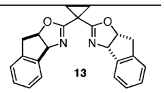
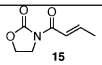
Table 1. Diels−Alder Reactions with Pyrazolidinone Templates Using Chiral Bisoxazolines[a]



										
Entry	Substrate	%ee	endo/ exo	%ee	endo/ exo	%ee	endo/ exo	%ee	endo/ exo	%ee	endo/ exo
1		38	88:12	23	87:13	17	86:14	54[b]	81:19	83	89:11
2	**7a** R = Me	64	91:09	56	96:04	55	88:12	77	93:07	96	92:08
3	**7b** R = Ph	71	93:07	84	92:08	71	91:09	97	92:08	95	91:09
4	**7c** R = 2-Naphthyl	79	93:07	65	91:09	69	90:10	99	93:07	96	93:07
5	**7d** R = 1-Naphthyl	86	90:10	95	93:07	85	87:13	99	90:10	96	90:10

[a] For reaction details see Supporting Information. Endo/exo ratios were determined by ^{1}H NMR, and ee determination was carried out after conversion to the known benzyl ester using chiral HPLC. Absolute configuration was determined to be (1*S*,2*S*,3*R*,4*R*) by comparison of retention times of the known benzyl ester. Yields for isolated column-purified material were 85−90%. [b] This experiment was carried out using $Cu(SbF6)_2$ as the Lewis acid.

amplified enantioselectivity in the conjugate additions of hydroxylamines[17] and radicals.[18]

In this study, we report a detailed investigation on the use of pyrazolidinone templates in enantioselective Diels−Alder reactions.[14] The importance of the R group on the pyrazolidinone nitrogen in reactions catalyzed by Cu(II)/bisoxazoline complexes of varying size was further examined. A variety of different Lewis acids were screened, and the study suggests that interplay of the chiral ligand and the pyrazolidinone R group is most cooperative for metals with pseudo-square-planar geometries. In addition, the effect of substitution at C-5 has also been evaluated.[19] Optimal pyrazolidinone templates and chiral Lewis acids have been employed to evaluate the scope of substrates and dienes amenable to effective cycloaddition. Some insights are provided by X-ray structures of the pyrazolidinones. Finally, mechanistic and conformational possibilities have been addressed by: (1) employing non-C_2-symmetric ligands and (2) screening for the possibility of $\pi-\pi$ interactions between aromatic relay groups and the olefin of the dienophile.

Results and Discussion

Proof of Principle Experiments. The role of the relay group substituents on the fluxional N(1) nitrogen was initially evaluated in $Cu(OTf)_2$/bisoxazoline-catalyzed Diels−Alder reactions.[20] Cu(II)/bisoxazoline catalysts were chosen because of the abundance of literature data for their catalysis of Diels−Alder reactions involving oxazolidinones and related substrates.[2e] Ready availability of various bisoxazoline ligands with differing steric volumes allowed for the possibility to assess the importance of the chiral ligand size relative to the pyrazolidinone R group in controlling enantioselection.

Diels−Alder reactions with substrates **7a**−**d** were carried out at room temperature using 15 mol % of the appropriate catalyst and excess cyclopentadiene (Table 1).[21] In each case the reaction was also conducted using oxazolidinone substrate **15** for comparison.

Initial experiments were conducted using Me-box ligand **9**, whose C-4 methyl substituents were expected to be too small to afford high enantioselection without amplification from the pyrazolidinone auxiliaries. Selectivity was low when oxazolidinone **15** was used (38% ee, entry 1). However, when pyrazolidinone auxiliaries were used, a systematic increase in

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(21) For detailed reaction conditions and substrate preparation procedures, see Supporting Information.

enantioselectivity correlated increasing size of the R group (Me, 64% ee < Ph, 71% ee < 2-naphthyl, 79% ee < 1-naphthyl, 86% ee, entries 2−5). These results suggested that even when a weak ligand was used at room temperature, good enantioselectivity was possible. The results also suggested that in this case the pyrazolidinone R group played a major, perhaps dominant, role in face shielding. The results with **7d** represent a 3-fold enhancement of enantioselectivity relative to those with smaller pyrazolidinone **7a**, (13.1:1 vs 4.6:1 er) and a 6-fold amplification relative to those with oxazolidinone **15** (13.1:1 vs 2.2:1 er).

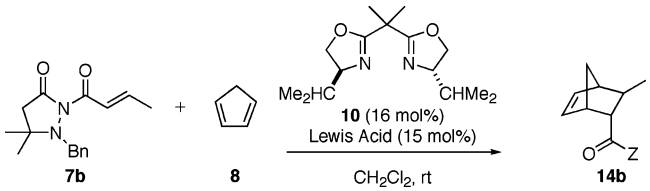
Diels−Alder reactions using ligands **10** and **11**, which have medium-sized C-4 substituents (*i*-Pr **10**, Bn **11**), followed a similar trend (entries 2−5) with the exception that **7c** gave lower enantioselectivities than **7b** (entries 3, 4).[22] Comparison of results with pyrazolidinone substrate **7d** and oxazolidinone substrate **15** using ligand **10** was particularly interesting. In analogous room-temperature experiments the pyrazolidinone substrate gave 95% ee (entry 5) while the oxazolidinone substrate gave only 23% ee (entry 1), which represents a 24-fold increase in enantioselection (39:1 vs 1.6:1 er). These results again supported the principle that pyrazolidinone templates can amplify enantioselectivity to useful levels at room temperature, using ordinary chiral ligands of modest steric bulk.

Ligands **12** and **13** are relatively strong ligands in terms of steric demand. When ligand **12** was used, the pyrazolidinone templates again amplified enantioselectivity relative to oxazolidinone **15** (77−99% ee versus 54% ee), and again selectivity increased with the size of the R group. Compounds **7a** and **7b** gave 77% ee and 97% ee respectively, while **7c** and **7d** both gave 99% ee (entries 2−5). The increase in enantioselectivity between experiments with **7a** and **7b** where R = Et and R = Ph illustrated the pyrazolidinone R group still played a critical role in enhancing enantioselectivity, but consistently high enantioselectivity when R = Ph, 2-naphthyl, and 1-naphthyl indicated that the face-shielding ability of the chiral ligand in conjunction with the pyrazolidinone R group was nearly complete even with medium sized pyrazolidinone R groups.

This was even more apparent when the bisoxazoline ligand **13** derived from amino indanol was employed. Enantioselectivities were uniformly high (95−96% ee) regardless of the size of the pyrazolidinone R group (entries 2−5). From this data it appeared that ligand **13** was the primary controller of enantioselection; but there was still significant amplification in enantioselectivity when pyrazolidinone substrates were employed (95−96% ee) versus the non-relay substrate **15** (83% ee, entry 1). These results suggest the relay group on nitrogen still played a critical role in enhancing selectivity, even though the correlation between size of the pyrazolidinone R group and selectivity was not observed in this series of experiments. The principle that combination of an excellent ligand with a pyrazolidinone auxiliary/template can lead to very high enantioselectivities was supported.

Screening of Lewis Acids and Metal Geometries. Having established that pyrazolidinones amplify the enantioselectivity induced by $Cu(OTf)_2$/bisoxazoline complexes, we screened a series of additional Lewis acids (Table 2). We expected the impact of the pyrazolidinone group might be dependent on whether a chiral Lewis acid has a square planar, tetrahedral, octahedral, or higher coordination environment. Some chiral Lewis acids might induce chirality such that the pyrazolidinone chirality works in concert with the chiral Lewis acid (matched case) and amplify enantioselectivity. In other cases, the induced chirality might display a mismatched, dissonant effect. It is also possible that both configurations of the fluxional pyrazolidinone might be present and reactive in other instances (see **2** and **3** in Figure 1).

Table 2. Screening of Metal Geometries with *i*-Pr-bisoxazoline[a]



7b 8 14b

entry	Lewis acid	yield (%)[b]	endo/exo[c]	ee (%)[d]
1	$Cu(OTf)_2$	90	92:08	84
2	$Cu(ClO_4)_2$	92	92:08	85
3	$Pd(ClO_4)_2$	94	93:07	96
4	$Ni(ClO_4)_2$	85	85:15	60
5	$NiBr_2$	23	81:19	05
6	$Mg(ClO_4)_2$	81	91:09	23
7	$Mg(NTf_2)_2$	92	91:09	07
8	$Mg(OTf)_2$	95	84:16	07
9	MgI_2	68	90:10	07
10	$Zn(OTf)_2$	73	90:10	45
11	$Zn(ClO_4)_2$	87	91:09	66
12	$Zn(NTf_2)_2$	87	93:07	02
13	ZnI_2	24	90:10	03
14	$Fe(ClO_4)_3$	39	81:19	14
15	$Fe(ClO_4)_2$	29	84:16	08
16	$Sm(OTf)_3$	73	82:18	03
17	$Sc(OTf)_3$	81	83:17	03
18	$Yb(OTf)_3$	89	77:23	03
19	$Yb(NTf_2)_3$	62	83:17	05
20	$Au(ClO_4)_3$	41	89:11	02

[a] For reaction details see Supporting Information. [b] Yields are for column-purified products. [c] Endo/exo ratios were determined by ^1H NMR. [d] Enantioselectivities were determined after conversion to the known benzyl ester using chiral HPLC. Absolute configuration was determined to be (1*S*,2*S*,3*R*,4*R*) by comparison of retention times of the known benzyl ester.

Our standard screening reaction used substrate **7b** and ligand **10** with cycloaddition conducted at room temperature. These were conditions not designed for optimal enantioselectivity; we intentionally avoided low temperature and chose a ligand with only a medium-sized substituent so that high enantioselectivity would be possible only if strong amplification from the pyrazolidinone was a contributing factor.

As shown in Table 2, maximal enantioselectivity resulted when $Cu(OTf)_2$, $Cu(ClO_4)_2$, and especially $Pd(ClO_4)_2$ were used as Lewis acids (84%, 85%, and 96% ee, entries 1−3). The improvement from $Cu(ClO_4)_2$ to $Pd(ClO_4)_2$ reflects a 4-fold increase in enantioselectivity (12:1 vs 50:1 er). The 96% ee observed with $Pd(ClO_4)_2$ was quite remarkable given the reaction temperature and the unexceptional size of the ligand.

(22) Analogous experiments corresponding to entries 2, 3, and 5 (substrates **7a**, **7b**, and **7d**, respectively) in Table 1 employing $Cu(OTf)_2$/(*S*,*S*)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) as the chiral Lewis acid were also conducted. Although a similar trend of increasing enantioselectivity with increasing size of the fluxional group was observed, the enantioselectivities were significantly lower in each case. The following enantioselectivities and *endo*:*exo* ratios were obtained with this ligand: (1) for substrate **7a**, 28% ee, 88:12 *endo*:*exo*; (2) for substrate **7b**, 38% ee, 91:09 *endo*:*exo*; and (3) for substrate **7d**, 46% ee, 86:14 *endo*:*exo*. The sense of absolute stereochemistry of the cycloadducts was identical to that obtained with ligands **9**−**13**.

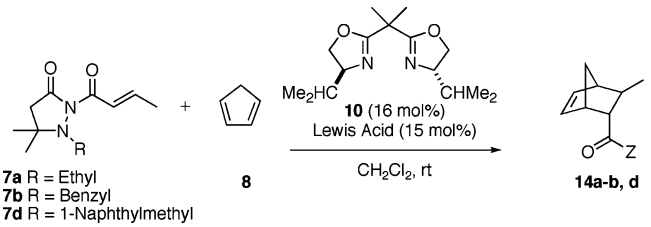
The results with the copper and palladium Lewis acids suggested that amplification of enantioselectivity was excellent for Lewis acids with square planar geometry. It is well established that Cu(II)/bisoxazoline catalysts react via distorted square planar geometries upon complexation to bidentate substrates.[5c] There are a number of instances of high selectivity in Diels−Alder reactions catalyzed by square planar palladium(II) complexes.[23] However, the degree to which Pd(II) was superior to Cu(II) in this case is noteworthy.

On the basis of literature reports of Ni(II) complexes with both square planar and octahedral geometries, $Ni(ClO_4)_2$ and $NiBr_2$ were subsequently screened.[24] $Ni(ClO_4)_2$ gave 60% ee (entry 4), while reactivity and selectivity were poor for $NiBr_2$-catalyzed reactions (entry 5). The reactivity and selectivity differences may be explained by the strongly dissociating nature of the perchlorate counterion. The ClO_4^- counterions are likely dissociated, leading to a cationic square planar complex, while the Br^- counterions should not be dissociated, leading to a neutral, less reactive octahedral complex.

We then chose to examine Lewis acids that have been reported to give tetrahedral or octahedral metal geometries. Of the Mg(II) Lewis acids[25] screened, only $Mg(ClO_4)_2$ provided any significant level of enantioselection (23% ee, entry 6), while $Mg(NTf_2)_2$, $Mg(OTf)_2$, and MgI_2 all gave nearly racemic product (entries 7−9). $Zn(ClO_4)_2$ gave the best results of the Zn(II) salts screened (66% ee, entry 11). $Zn(OTf)_2$ gave cycloadduct in 45% ee (entry 10). $Zn(NTf_2)_2$ provided nearly racemic product in good yield (entry 12), while reactivity and selectivity for ZnI_2 were poor (24% yield, 3% ee, entry 13). Fe(III) and Fe(II) Lewis acids were then screened on the basis of previous reports of success when combined with bisoxazoline ligands.[26] However, reactivities and selectivities were poor when $Fe(ClO_4)_3$ and $Fe(ClO_4)_2$ (entries 14 and 15) were used. On the basis of these results it was determined that tetrahedral or octahedral complexes were not optimal for enantioselective Diels−Alder reactions with pyrazolidinone substrates.

Entries 16−19 show results from a number of Lewis acids capable of providing higher-coordinate complexes. Although reactivities were moderate to good (62−89% yield) with $Sm(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Yb(NTf_2)_3$, enantioselectivities were negligible (entries 16−19). Finally, a Au(III) salt was used on the basis of reports of square planar Au(III) complexes, but $Au(ClO_4)_3$ gave essentially racemic product in 41% yield (entry 20).[27] This result is likely due to poor solubility of the Au(III)/ligand complex in dichloromethane.

Table 3. Size Effects of Chiral Relay Groups with Various Lewis Acids[a]



entry	substrate	Lewis acid	yield (%)[b]	endo/exo[c]	ee (%)[d]
1	**7a**	$Cu(OTf)_2$	90	96:04	56
2	**7b**	$Cu(OTf)_2$	90	92:08	84
3	**7d**	$Cu(OTf)_2$	85	93:07	95
4	**7a**	$Cu(ClO_4)_2$	86	92:08	78
5	**7b**	$Cu(ClO_4)_2$	92	92:08	85
6	**7d**	$Cu(ClO_4)_2$	93	93:07	92
7	**7a**	$Pd(ClO_4)_2$	54	91:09	45
8	**7b**	$Pd(ClO_4)_2$	94	93:07	96
9	**7d**	$Pd(ClO_4)_2$	97	95:05	99
10	**7a**	$Ni(ClO_4)_2$	96	87:13	56
11	**7b**	$Ni(ClO_4)_2$	85	85:15	62
12	**7d**	$Ni(ClO_4)_2$	93	83:17	60
13	**7a**	$Mg(ClO_4)_2$	79	87:13	20
14	**7b**	$Mg(ClO_4)_2$	81	91:09	23
15	**7d**	$Mg(ClO_4)_2$	86	91:09	20
16	**7a**	$Zn(ClO_4)_2$	70	88:12	54
17	**7b**	$Zn(ClO_4)_2$	87	91:09	66
18	**7d**	$Zn(ClO_4)_2$	84	92:08	74
19	**7a**	$Fe(ClO_4)_3$	19	87:13	23
20	**7b**	$Fe(ClO_4)_3$	39	81:19	14
21	**7d**	$Fe(ClO_4)_3$	12	80:20	00
22	**7a**	$Fe(ClO_4)_2$	33	81:19	21
23	**7b**	$Fe(ClO_4)_2$	29	84:16	08
24	**7d**	$Fe(ClO_4)_2$	44	86:14	04

[a] For reaction details see Supporting Information. [b] Yields are for column-purified products. [c] Endo/exo ratios were determined by ^{1}H NMR. [d] Enantioselectivities were determined after conversion to the known benzyl ester using chiral HPLC. Absolute configuration was determined to be (1*S*,2*S*,3*R*,4*R*) by comparison of retention times of the known benzyl ester.

Dependence of Enantioselectivity on the Size of the Pyrazolidinone R Group with Various Lewis Acids. Our initial experiments with $Cu(OTf)_2$/*i*-Pr bisoxazoline complex demonstrated the dramatic effects of increasing the size of the pyrazolidinone R group (Table 3, entries 1−3). It was thus desirable to see whether this size dependence would be observed with other Lewis acid/metal geometries. Not surprisingly, a similarly strong size effect was observed with $Cu(ClO_4)_2$ as the Lewis acid (entries 4−6). For $Pd(ClO_4)_2$ the effect was even more dramatic. Reactions with **7a**, where R = Et, gave 45% ee (entry 7). However, substrates **7b** and **7d** with R = Ph and 1-naphthyl, respectively, gave 96% ee and 99% ee (entries 8 and 9).

Two possibilities exist for the increased enhancements observed with $Pd(ClO_4)_2$ versus $Cu(ClO_4)_2$ (compare entries 5 and 6 with entries 8 and 9). One possible explanation is that the reactive Pd(II) complex may be a less distorted square planar complex than the analogous Cu(II) complex, leading to more efficient shielding by the pyrazolidinone R group and/or the C-4 isopropyl group.[5c,28] Alternatively, the N−Pd−O bond lengths in the Pd(II) complex are likely significantly longer than the N−Cu−O bond lengths in the Cu(II) complex.[29] This

(23) (a) Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157. (b) Nakano, H.; Takahashi, K.; Okuyama, Y.; Senoo, C.; Tsugawa, N.; Suzuki, Y.; Fujita, R.; Sasaki, K.; Kabuto, C. *J. Org. Chem.* **2004**, *69*, 7092. (c) Nakano, H.; Okuyama, Y.; Suzuki, Y.; Fujita, R.; Kabuto, C. *Chem. Commun.* **2002**, 1146. (d) Nakano, H.; Suzuki, Y.; Kabuto, C.; Fujita, R.; Hongo, H. *J. Org. Chem.* **2002**, *67*, 5011. (e) Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C. *Organometallics*, **2005**, *24*, 557. (f) Nakano, H.; Tsugawa, N.; Fujita, R. *Tetrahedron Lett.* **2005**, *46*, 5677.

(24) (a) Venkataraman, D.; Du, Y.; Wilson, S. R.; Hirsch, K. A.; Zhang, P.; Moore, J. S. *J. Chem. Educ.* **1997**, *74*, 915. (b) Kanemasa, S.; Adachi, K.; Yamamoto, H.; Wada, E. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 681. (c) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706.

(25) (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. (b) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099.

(26) (a) Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2879. (B) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387. (c) Bromidge, S.; Wilson, P. C.; Whiting, A. *Tetrahedron Lett.* **1998**, *39*, 8905. (d) Bart, S. C.; Hawrelak, E. J.; Schmisseur, A. K.; Lobkovsky, E.; Chirick, P. J. *Organometallics* **2004**, *23*, 237.

(27) (a) Yanagisawa, A. In *Lewis Acids in Organic Synthesis*; Yamamoto, H.; Ed., Wiley-VCH: Weinheim, 2000; Vol. 2, p 575. (b) Mansour, M. A.; Lachicotte, R. J.; Gysling, H. J.; Eisenberg, R. *Inorg. Chem.* **1998**, *37*, 4625. (c) Ortner, K.; Abram, U. *Polyhedron* **1999**, 749.

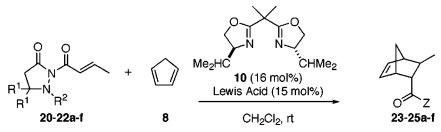
increase in bond length may in turn result in more efficient shielding by the pyrazolidinone R group. While it is possible that the C-4 isopropyl group provides improved face shielding with Pd(II), this seems unlikely since an increase in N−Pd−O bond lengths effectively moves the C-4 substituent further from the reaction center.

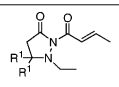
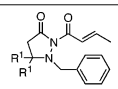
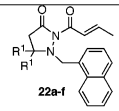
While reactions involving Cu(II) and Pd(II) showed a strong correlation between enantioselectivity and the size of the pyrazolidinone R group, this pattern was not shared by Ni(II). Substrates **7a**, **7b**, and **7d** gave 56%, 62%, and 60% ee, respectively (entries 10−12). These results suggested that the reactions proceed through a metal geometry significantly different from that for Cu(II) and Pd(II), such that the pyrazolidinone R group provides very little face shielding.

The dependence of enantioselectivity on the size of the R group varied widely for Lewis acids that probably involve tetrahedral or octahedral complexes. There was no apparent dependence on size of the R group when $Mg(ClO_4)_2$ was employed as the Lewis acid (entries 13−15). With $Zn(ClO_4)_2$, a systematic increase in enantioselectivity correlated with increasing size of R, with **7a**, **7b**, and **7d** giving 54%, 66%, and 74% ee, respectively (entries 16−18). On the other hand, both $Fe(ClO_4)_3$ and $Fe(ClO_4)_2$ gave diminishing selectivity on the already negligible enantioselectivity as the R group increased from ethyl to 1-methylnaphthyl (entries 19−21 for $Fe(ClO_4)_3$ and 22−24 for $Fe(ClO_4)_2$).

Several generalizations can be drawn from these results. First, it appears that for bisoxazoline/Lewis acid complexes with square-planar-type geometries, pyrazolidinone auxiliaries tend to amplify enantioselectivity to a large degree, and the degree of amplification is maximized as the size of the pyrazolidinone R group increases. Second, even with non-square planar geometries, there appears to be a significant dependence on the size of the pyrazolidinone group, although not always in a predictable way. Many of the less selective Lewis acids included in our survey are not well matched with the isopropyl bisoxazoline ligand, so both the overall enantioselectivity and the dependence on the pyrazolidinone size are muted. It does not necessarily follow that pyrazolidinones might not provide meaningful amplification of enantioselectivity when more effective chiral Lewis acids involving Mg(II), Zn(II), Ni(II), and other metals are used.[15−18]

Table 4. Diels−Alder Reactions on Templates with C-5 Variation[a]



	Dienophile	 20a-f		 21a-f		 22a-f	
Entry	R^1	endo/exo	ee (%)	endo/exo	ee (%)	endo/exo	ee (%)
1	H (**20-22a**)	81:19	50	79:21	65	71:29	63
2	Methyl (**20-22b**)	96:04	56	92:08	84	93:07	95
3	Ethyl (**20-22c**)	88:12	75	93:07	87	88:12	95
4	-$(CH_2)_3$- (**20-22d**)	88:12	73	95:05	88	88:12	94
5	-$(CH_2)_4$- (**20-22e**)	88:12	74	91:09	92	88:12	97
6	Benzyl (**20-22f**)	85:15	79	91:09	95	87:13	96

[a] For reaction details see Supporting Information. Endo/exo ratios were determined by ^{1}H NMR, and ee determination was carried out after conversion to the known benzyl ester using chiral HPLC. Absolute configuration was determined to be (1*S*,2*S*,3*R*,4*R*) by comparison of retention times of the known benzyl ester. Yields for isolated column-purified material averaged 85−95%, except for R^1 = Bn (yields around 65%).

C-5 Variation Effects. With a greater understanding of the importance of metal geometry and of the size of the pyrazolidinone nitrogen substituent, the effect of C-5 substitution was investigated (Table 4). We had previously demonstrated that the nitrogen substituent plays an important face-shielding role when C-5 was dimethyl substituted (Table 1), but questions remained as to whether this substitution was necessary in order to place the chiral relay substituent on nitrogen into close proximity to the reaction center. Thus, substrates **20**−**22a** where R^1 = H were prepared. Diastereoselectivities and enantioselectivities were markedly lower for substrates where R^1 = H (50% ee for **20a**, 65% ee for **21a**, and 63% ee for **22a**) when compared with substrates where R^1 = Me (56% ee for **20b**, 84% ee for **21b**, and 95% ee for **22b**).

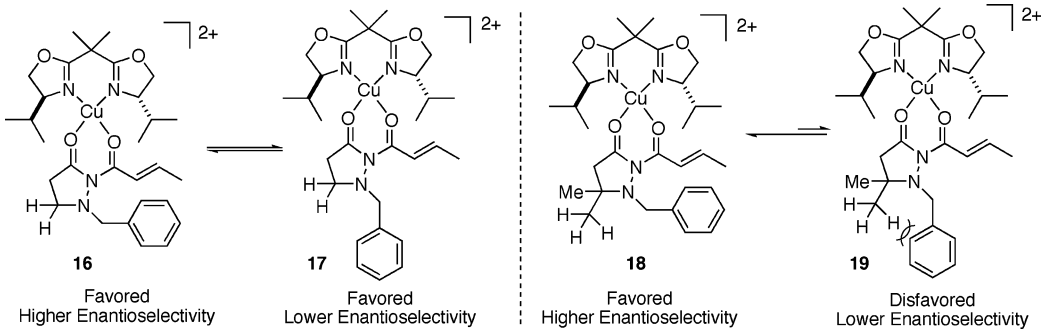
The lack of relay group effect was evident upon examination of entry 1, where increasing the size of the nitrogen substituent R^2 from benzyl (65% ee) to 1-naphthylmethyl (63% ee) did not amplify the enantioselectivity. This was in stark contrast to entry 2 where a significant positive effect on enantioselectivity was observed when the size of the pyrazolidinone R^2 group was increased. This difference can be explained by the lack of steric interaction between R^1 substituents and the R^2 relay group when R^1 = H, which allows a favored conformation in which the nitrogen substituent is rotated away from the reaction center (Scheme 3). In the case where R^1 = Me, the conformation in which the N(1) substituent is rotated away from the reaction center is likely disfavored by an adverse interaction between the benzyl group and the C5-methyl hydrogen atoms. Thus, the conformation in which the relay group is positioned near the reaction center is favored, leading to enhanced face shielding.

On the basis of these results an investigation of additional C-5 substituents was undertaken to evaluate whether increased steric volume at this position would lead to increased enantioselectivity. Additional substrates with R^1 = Et, -$(CH_2)_4$-,

(28) For examples of distorted square planar Cu(II)/bisoxazoline complexes, see: (a) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, D. A. *J. Org. Chem.* **1998**, *63*, 4541. (b) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407. (c) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879. (d) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (e) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888. (f) Evans, D. A.; Miller, S. J.; Lectka, T.; Von, Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (g) Evans, D. A.; Scheidt, K. A.; Johnson, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (h) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134. (i) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487. (j) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692. For examples of pseudo-square-planar Pd(II)/bisoxazoline complexes, see: (k) Von, Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rüegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265. (l) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (m) Hoarau, O.; Aït-Haddou, H.; Daran, J. C.; Cramailère, D.; Balavoine, G. G. A. *Organometallics* **1999**, *18*, 4718.

(29) For Cu−N and Cu−O bond lengths in Cu(II)/bisoxazoline/bidentate oxygen donor complexes, see: (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. For a representative Pd−N bond length in a Pd(II)/bisoxazoline complex, see reference 27(l). For a representative PdlO bond length, see: (b) Bugarcic, Z. D.; Nandibewoor, S. T.; Hamza, M. S. A.; Heinemann, F.; van Eldik, R. *Dalton Trans.* **2006**, 2984.

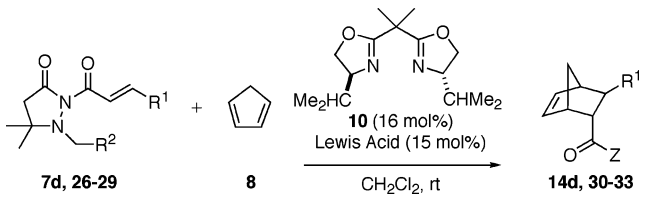
Scheme 3. Role of C-5 Substitution in Determining Enantioselectivity



-$(CH_2)_5$-, and Bn were prepared with R^2 = Et (**20c**−**f**), Bn (**21c**−**f**), and 1-CH_2naphthyl (**22c**−**f**). Although enantioselectivities increased as the size of the R^1 substituents was increased irrespective of the identity of the R^2 relay group, the trend was quite apparent with substrates where R^2 = Bn (see the **21a**−**f** column, Table 4). In this case the baseline selectivity for R^1 = Me was 84% ee (entry 2). When substrate **21c** with R^1 = Et was used, the enantioselectivity increased to 87% (entry 3). Enantioselectivity was further increased when the R^1 groups were cyclopentyl (88% ee, entry 4) or cyclohexyl (92% ee, entry 5). When substrate **21f** with R^1 = Bn was employed, the enantioselectivity rose to 95% even with the medium sized benzyl R^2 relay group (entry 6). These results clearly indicated that the nature of C-5 substitution was critical for optimal selectivity in reactions involving pyrazolidinone templates.

Study of the Scope of Pyrazolidinone Dienophiles in Diels−**Alder Reactions.** Knowledge of the elements necessary for high selectivity with pyrazolidinone templates was then applied to templates with a number of common dienophiles appended. Although we had determined that relay substrates containing bulkier C-5 substituents provided optimal enantioselectivity, substrates with C-5 methyl groups were chosen as most practical for further evaluation due to the commercial availability of ethyl 3,3-dimethyl acrylate, which is the starting material necessary for preparation of the pyrazolidinone core. The N(1)-CH_2naphthyl substituent was determined to be the pyrazolidinone substituent of choice based on previous results (Tables 1 and 3). $Cu(OTf)_2$-catalyzed reactions with acrylate **26** gave 85% ee (Table 5, entry 1). However, the enantioselectivity of this reaction was improved to 90% ee upon lowering the reaction temperature to 0 °C (entry 3). $Pd(ClO_4)_2$ was also an effective Lewis acid for **26**, providing product in 87% ee at room temperature (entry 2). As reported previously, $Cu(OTf)_2$ and $Pd(ClO_4)_2$ both proved excellent for crotonate **7d**, giving 95% ee and 99% ee, respectively (entries 4 and 5). When cinnamate substrate **28** bearing the 1-naphthlylmethyl group was employed under standard $Cu(OTf)_2$-catalyzed conditions, reactivity was very poor. Reactivity was increased marginally by using cinnamate **27**, which contains the benzyl R group (entry 6). Yields were still poor (35%), and enantioselectivity was moderate (70% ee). However, moderate yields were obtained with **28** with $Pd(ClO_4)_2$ (entry 7). In this case the Diels−Alder adduct was isolated in 57% yield with 88% ee. Fumarate substrate **29** gave only 76% ee in the $Cu(OTf)_2$-catalyzed reactions (entry 8). This result was improved with $Pd(ClO_4)_2$, which resulted in product isolated in 91% ee (entry 9). $Cu(OTf)_2$-catalyzed reaction of **29** was further improved to give 96% ee when the reaction was performed at −20 °C (entry 10).

Table 5. Evaluation of Substrate Scope[a]



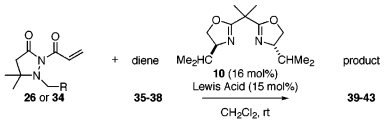
entry	R^1	R^2	temp	Lewis acid	yield (%)	endo/exo	ee (%)
1	H (**26**)	1-Naph	rt	$Cu(OTf)_2$	93	91:09	85
2	H (**26**)	1-Naph	rt	$Pd(ClO_4)_2$	89	95:05	87
3	H (**26**)	1-Naph	0 °C	$Cu(OTf)_2$	93	93:07	90
4	Me (**7d**)	1-Naph	rt	$Cu(OTf)_2$	85	93:07	95
5	Me (**7d**)	1-Naph	rt	$Pd(ClO_4)_2$	97	95:05	99
6	Ph (**27**)	Ph	rt	$Cu(OTf)_2$	35	85:15	70
7	Ph (**28**)	1-Naph	rt	$Pd(ClO_4)_2$	57	83:17	88
8	CO_2Et (**29**)	1-Naph	rt	$Cu(OTf)_2$	94	86:14	76
9	CO_2Et (**29**)	1-Naph	rt	$Pd(ClO_4)_2$	80	93:07	91
10	CO_2Et (**29**)	1-Naph	−20 °C	$Cu(OTf)_2$	99	93:07	96

[a] For reaction details see Supporting Information. Endo/exo ratios were determined by ^{1}H NMR, and ee determination was carried out using chiral HPLC.

It again bears mention that these selectivities were induced using only the modest isopropyl bisoxazoline ligand **10**; most likely a stronger ligand would provide higher enantioselectivities.

Evaluation of Dienes with Pyrazolidinone Acrylates. A sample of common dienes was then evaluated using acrylate substrate **26** with the 1-naphthylmethyl relay group (Table 6). Room-temperature $Cu(OTf)_2$-catalyzed reaction of isoprene (**35**) with **26** gave cycloadduct in 87% ee (entry 1). Enantioselectivity increased moderately when the reaction temperature was lowered to 0 °C with product obtained in 90% ee (entry 3). A more dramatic increase in enantioselectivity was observed using $Pd(ClO_4)_2$ (entry 2), which boosted the selectivity for isoprene addition to 97% ee and also improved the yield to 92%. A similar trend was observed for reaction of 2,3-dimethylbutadiene (**36**) and cyclohexadiene (**37**) with **26**. $Cu(OTf)_2$-catalyzed reactions of 2,3-dimethylbutadiene at room temperature and 0 °C gave 88% ee and 92% ee (entries 4 and 6), respectively, while the corresponding experiments with cyclohexadiene gave 85% ee and 90% ee (entries 7 and 9). But when $Pd(ClO_4)_2$−**10** was used at room temperature, both 2,3-dimethylbutadiene and cyclohexadiene provided cycloadducts in 98% ee (entries 5 and 8). The superiority of Pd(II) over Cu(II) in terms of both reactivity and enantioselectivity was even more pronounced for cycloaddition of 1-(phenoxycarbonyl)-1,2-dihydropyridine (**38**) to pyrazolidinone acrylates **34** and **26**. Pd(II)-catalyzed cycloaddition to *N*-benzyl substrate **34** gave product in 77% yield and 92% ee (entry 11), while product was isolated in only 38% yield

Table 6. Diene Study with Acrylate **26** or **34**[a]



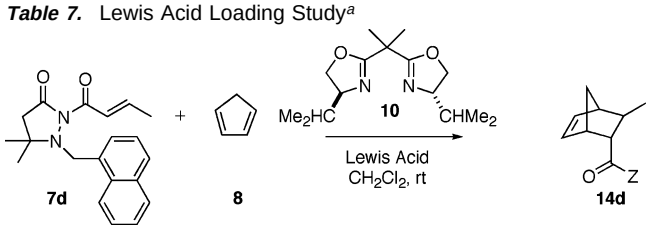
Diene	Entry	R	Temp	Lewis Acid	Yield (%)	endo/exo	ee (%)
	1	1-Naph (**26**)	rt	$Cu(OTf)_2$	83	98:02	87
35	2	1-Naph (**26**)	rt	$Pd(ClO_4)_2$	92	98:02	97
	3	1-Naph (**26**)	0 °C	$Cu(OTf)_2$	80	97:03	90
	4	1-Naph (**26**)	rt	$Cu(OTf)_2$	74	NA	88
36	5	1-Naph (**26**)	rt	$Pd(ClO_4)_2$	96	NA	98
	6	1-Naph (**26**)	0 °C	$Cu(OTf)_2$	77	NA	92
	7	1-Naph (**26**)	rt	$Cu(OTf)_2$	77	97:03	85
37	8	1-Naph (**26**)	rt	$Pd(ClO_4)_2$	78	98:02	98
	9	1-Naph (**26**)	0 °C	$Cu(OTf)_2$	81	92:02	90
	10	Ph (**34**)	rt	$Cu(OTf)_2$	38	>99:01	72
	11	Ph (**34**)	rt	$Pd(ClO_4)_2$	77	>99:01	92
38	12	1-Naph (**26**)	rt	$Cu(OTf)_2$	49	>99:01	77
	13	1-Naph (**26**)	rt	$Pd(ClO_4)_2$	83	>99:01	98

[a] For reaction details see Supporting Information. Endo/exo ratios were determined by ^{1}H NMR, and ee determination was carried out using chiral HPLC.

and 72% ee in the corresponding Cu(II)-catalyzed experiment (entry 10). Yield and enantioselectivities were likewise improved when N(1)-naphthylmethyl substrate **26** was employed. Pd(II)-catalyzed cycloaddition gave product in 83% yield and 98% ee (entry 13), while product was isolated in only 49% yield and 77% yield in the corresponding Cu(II)-catalyzed experiment (entries 11 and 12). Entry 13 represents the best enantioselectivity reported to date for Diels−Alder cycloaddition of 1-(aryloxycarbonyl)- or 1-(alkoxycarbonyl)-1,2-dihydropyridines.[14b] Related isoquinuclidines have been proposed as key intermediates in the synthesis of a number of natural products, which continue to be of interest.[30]

Lewis Acid Loading Study. Upon determining that the reactivity and selectivity of the template/catalyst systems were sufficient to be of interest, we recognized the need for catalysts loadings below the 15 mol % loadings reported to this point. As such, cycloaddition of cyclopentadiene to substrate **7d** was chosen to evaluate if catalyst loadings could be decreased in $Cu(OTf)_2$- and $Pd(ClO_4)_2$-catalyzed reactions (Table 7). The baseline 15 mol % catalyst loading experiment for $Cu(OTf)_2$ provided product in 85% yield and 95% ee (entry 4). We were pleased to observe no loss in enantioselectivity upon lowering the catalytic loading from 15 to 2.5 mol % (entries 1−4). This trend was also seen in $Pd(ClO_4)_2$-catalyzed experiments. Catalyst loadings of 2.5, 5, 10, and 15 mol % all gave high yields of cycloadducts (91−97% yield) in 99% ee (entries 5−8). Although results from room-temperature catalyst loading experiments with crotonate **7d** may not correlate to all relay substrate/diene combinations, they do suggest that high selectivities at low

Table 7. Lewis Acid Loading Study[a]



entry	mol % CLA	Lewis acid	yield (%)[b]	endo/exo[c]	ee (%)[d]
1	2.5	$Cu(OTf)_2$	75	93:07	95
2	5	$Cu(OTf)_2$	86	93:07	95
3	10	$Cu(OTf)_2$	90	93:07	95
4	15	$Cu(OTf)_2$	85	93:07	95
5	2.5	$Pd(ClO_4)_2$	91	96:04	99
6	5	$Pd(ClO_4)_2$	97	95:05	99
7	10	$Pd(ClO_4)_2$	94	95:05	99
8	15	$Pd(ClO_4)_2$	97	95:05	99

[a] For reaction details see Supporting Information. [b] Yields are for column-purified products. [c] Endo/exo ratios were determined by ^{1}H NMR. [d] Enantioselectivities were determined after conversion to the known benzyl ester using chiral HPLC. Absolute configuration was determined to be (1*S*,2*S*,3*R*,4*R*) by comparison of retention times of the know benzyl ester.

ligand loadings are possible in systems in which the rate of uncatalyzed background cycloaddition is low.

Conformational Insights Based on the Crystal Structure for 7d. Although indirect evidence for the role of the pyrazolidinone R group was strong at this point, additional insights were provided by the crystal structure of substrate **7d** (Figure 2). The carbonyls in this crystal structure have an interesting *syn* orientation. Other pyrazolidinone substrates such as **44** crystallize with the carbonyls *anti*; thus, the structure for **7d** may reflect crystal packing effects. Nevertheless, the structure for **7d** provides an interesting image of how the naphthylmethyl substituent might position itself when the carbonyls are locked into *syn* alignment, as would be expected following Lewis acid coordination. It is easy to envision from structure **7d** how the aryl portion of the N(1) substituent might block the bottom face of the enoyl group.

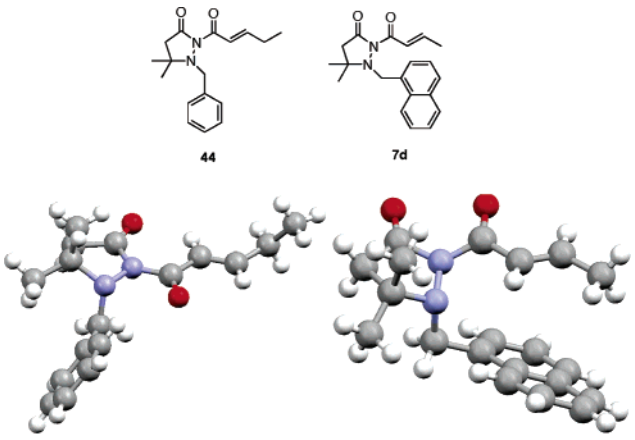


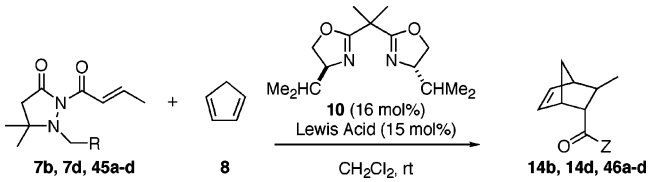
Figure 2. Crystal structures of **44** and **7d**.

π-Stacking Studies. The crystal structure for **7d** suggested the possibility that π-stacking might play a role in the amplification of enantioselectivity afforded by pyrazolidinones.[31] We have conducted several studies to address this possibility (Table 8).

(30) (a) Kuehne, M. E.; Marko, I. In *Syntheses of Vinblastine-type Alkaloids. The Alkaloids. Antitumor Bisindole Alkaloids from Catharanthus roseus (L.)*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. 37, pp 77. (b) Popik, P.; Skolnick, P. In *Pharmacology of Ibogain and Ibogaine-related Alkaloids. The Alkaloids. Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: Sand Diego, 1999; Vol. 52, p 197. (c) Redding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973. (d) Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124.

(31) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

Table 8. $\pi-\pi$ Interaction Study[a]



entry	R	Lewis acid	yield (%)[b]	endo/exo[c]	ee (%)[d]
1	Ph (**7b**)	$Cu(OTf)_2$	90	92:08	84
2	Ph (**7b**)	$Pd(ClO_4)_2$	94	93:07	96
3	1-Naph (**7d**)	$Cu(OTf)_2$	85	93:07	95
4	1-Naph (**7d**)	$Pd(ClO_4)_2$	97	95:05	99
5	cyclohexyl (**45a**)	$Cu(OTf)_2$	92	91:09	66
6	cyclohexyl (**45a**)	$Pd(ClO_4)_2$	91	96:04	97
7	4-MeO-C_6H_4 (**45b**)	$Cu(OTf)_2$	91	89:11	88
8	4-MeO-C_6H_4 (**45b**)	$Pd(ClO_4)_2$	89	94:06	98
9	4-F-C_6H_4 (**45c**)	$Cu(OTf)_2$	92	90:10	86
10	4-F-C_6H_4 (**45c**)	$Pd(ClO_4)_2$	88	94:06	97
11	4-MeO_2C-C_6H_4 (**45d**)	$Cu(OTf)_2$	91	92:08	86
12	4-MeO_2C-C_6H_4 (**45d**)	$Pd(ClO_4)_2$	85	93:07	99

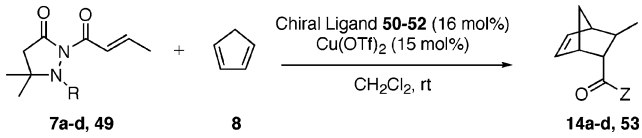
[a] For reaction details see Supporting Information. [b] Yields are for column-purified products. [c] Endo/exo ratios were determined by ^1H NMR. [d] Enantioselectivities were determined after conversion to the known benzyl ester using chiral HPLC. Absolute configuration was determined to be (1*S*,2*S*,3*R*,4*R*) by comparison of retention times of the know benzyl ester.

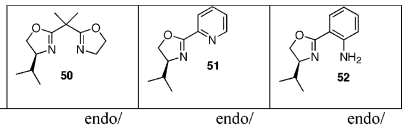
We prepared substrate **45a** with a cyclohexylmethyl substituent that lacks a π-system for comparison to the N(1)-benzyl substrate **7b**. Initial results with $Cu(OTf)_2$-catalyzed reaction of **45a** gave 66% ee (entry 5), which is significantly lower than the values of 84% ee achieved with **7b** where R = Ph (entry 1) and 95% with **7d** where R = 1-naphthyl (entry 3). This result initially suggested that $\pi-\pi$ interaction may be important. However, analogous experiments catalyzed by $Pd(ClO_4)_2$ gave 97% ee with cyclohexyl substrate **45a** (entry 6), a selectivity which is comparable to those observed with phenyl and 1-naphthyl substrates **7b** and **7d** (96% and 99% ee, entries 2 and 4). These results suggest that $\pi-\pi$ interaction is not essential for high enantioselectivity.

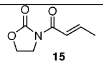
We also prepared additional substrates **45b**−**d**, which incorporate electron-donating or -withdrawing groups onto the *N*-benzyl group. We reasoned the 4-MeO-C_6H_4 π-system would be more electron rich relative to the Ph π-system, which could enhance a π-stacking interaction with the electron-deficient crotonate group. On the other hand, the 4-F-C_6H_4 and 4-MeO_2C-C_6H_4 π-systems would be less electron rich relative to the Ph π-system, leading to less interaction with the crotonate. On the basis of this proposal, increased enantioselectivity was expected with **45b**, whereas decreased enantioselectivity was expected with **45c** and **45d**. This reasoning proved to be false as electron-rich **45b** gave 88% ee (entry 7), while electron-poor **45c** and **45d** both gave 86% ee (entries 9 and 11) in $Cu(OTf)_2$ experiments. The parent benzyl **7b** gave 84% ee (entry 1). These results point to the insignificance of $\pi-\pi$ interactions in determining enantioselectivity. Steric volume appears to be the foremost factor responsible for enhanced selectivity. This conclusion is further supported by the similar trend observed in Pd(II)-catalyzed experiments (compare entries 2, 8, 10, and 12).

Evaluation of Pyrazolidinone Templates When Using Non-C_2 Symmetric Ligands. An even more stringent test for

Table 9. Reactions with Relay Templates Using C_1 Chiral Ligands[a]

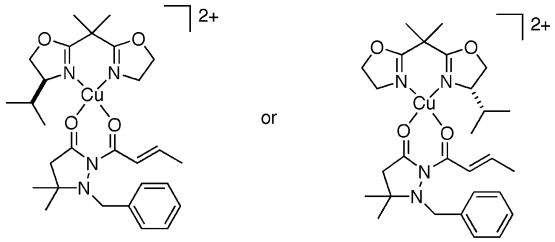




Entry	Substrate	ee (%)	endo/exo	ee (%)	endo/exo	ee (%)	endo/exo
1	 **15**	06	85:15	03	84:16	00	83:17
2	R = H (**49**)	04	86:14	01	88:12	01	87:13
3	R = Et (**7a**)	29	85:15	12	86:14	26	84:16
4	R = Bn (**7b**)	47	88:12	21	87:13	51	84:16
5	R = 2-CH_2Naph (**7c**)	56	88:12	38	88:12	58	84:16
6	R = 1-CH_2Naph (**7d**)	69	85:15	59	88:12	71	83:17
7	R = 1-CH_2Naph (**7d**)	88[b]	91:09	66[b]	92:08	85[b]	88:12

[a] Endo/exo ratios were determined by ^1H NMR. Enantioselectivities were determined after conversion to the known benzyl ester using chiral HPLC. Absolute configuration was determined to be (1*S*,2*S*,3*R*,4*R*) by comparison of retention times of the known benzyl ester. Yields for isolated column-purified material averaged 85−90%. [b] Reaction at −23 °C using 50 mol % chiral Lewis acid.

demonstrating chiral relay was devised using non-C_2-symmetric ligands **50**−**52** (Table 9), which afford almost no enantioselectivity when applied to oxazolidinone substrate **15** (entry 1). Use of a non-C_2-symmetric ligand such as **50** most likely provides a square planar complex, but two distinctly different complexes are possible (Figure 3). The most probable complex **47** has the ligand's isopropyl group occupying an opposite quadrant that is remote relative to both the reactive crotonate center and the pyrazolidinone benzyl group. That the isopropyl group is too distant to provide any meaningful face shielding is reflected by the negligible enantioselectivities observed using achiral oxazolidinone **15** and substrate **49** (entries 1 and 2).



47 **48**

Figure 3. Possible square planar complexes with non-C_2-symmetric ligands.

For reactions occurring through complex **47** (Figure 3), appreciable enantioselectivity seems likely only if the pyrazolidinone benzyl group provides the actual face shielding at the reactive center. This would then be evidence of the "chiral relay" concept, in which a permanently chiral center (in this case a rather remote one) is able to bias the configuration of the fluxional nitrogen, and it is the substituent on the fluxional nitrogen that actually shields the reactive center. The chirality

at the fluxional nitrogen controls enantioselectivity, but the chirality at the fluxional nitrogen is induced or "relayed" from the fixed chiral center.

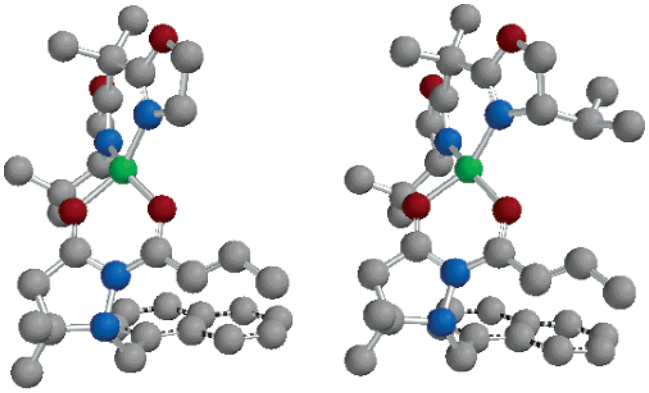
Reactions using ligand **50** and a series of pyrazolidinones showed a clear correlation between the size of the pyrazolidinone R group and enantioselectivity. Substrates **49** and **7a** with small pyrazolidinone R groups (H and Et) gave 4 and 29% ee (Table 9, entries 2 and 3). Enantioselectivities increased to 47 and 56% ee using benzyl and 1-naphthylmethyl pyrazolidinones **7b** and **7d** (entries 4 and 5). Optimal enantioselectivity was once again observed with 1-naphthylmethyl pyrazolidinones **7d** (69% ee, entry 6), and could be increased to 88% at −23 °C (entry 7). This increase in enantioselectivity with increasing size of the pyrazolidinone relay group R followed the same trend as was observed with C_2-symmetric bisoxazoline ligands (Table 1), and gave the same absolute configuration as when isopropyl bisoxazoline ligand **10** was used. While the magnitude of the enantioselectivity was diminished using ligand **50** versus ligand **10**, it is actually rather surprising how modest the diminishment of selectivity was.

Analogous trends were observed using nonsymmetric and readily accessible ligands **51** and **52**. In each case, there was no selectivity using oxazolidinone **15** or N−H pyrazolidinone **49** (entries 1 and 2), but as the pyrazolidinone R groups got larger, increasing levels of enantioselectivity resulted. All of these results seem to demonstrate that chiral relay was operative when the pyrazolidinone R group is sufficiently large and that the pyrazolidinone R groups provide the actual face shielding when ligands such as **50**−**52** are used. It is interesting to note that similar results were obtained with ligands **50** and **52**, capable of forming six-membered chelates versus ligand **51**, which forms a five-membered chelate.

NMR Data, Model, and Discussion. As a means to further evaluate the location and/or configuration of the fluxional group in solution, an extensive 1D nOe NMR study was conducted on a complex of $Pd(OTf)_2$/ligand **12**/substrate **7d**.[32] Although this study was not conclusive due to the small enhancements observed, it suggested C-5 substitution was critical for orientation of the fluxional group near the olefin. In fact a small enhancement was observed at the C-8 proton of the naphthyl ring upon irradiation of the proton α to the carbonyl at 5.37 ppm. This observation is consistent with the fluxional group in near proximity to the olefin.

The results in Tables 1 and 9 can be rationalized using a distorted square-planar-geometry model relative to Cu(II) or Pd(II), with the ligand occupying two sites while the template is coordinated in a bidentate fashion in an *s-cis* conformation (the complex with non-C_2 **50** is shown in Figure 4). The ligand isopropyl group in the upper left quadrant orients the pyrazolidinone R group to the rear of the lower right quadrant, where it blocks the back face of the crotonate. Thus, the 1-naphthylmethyl group "relays" chirality from the ligand's isopropyl group to the reactive centers in the substrate.

In reactions with the C_2-symmetric chiral bisoxazoline **10** (Figure 4), the additional ligand isopropyl group would occupy the upper right rear quadrant and actually reinforce shielding of the back face of the crotonate. Thus, in reactions with the C_2 ligands both the pyrazolidinone R group and the C-4 substituent act in concert (matched double stereoselection) to mutually amplify the selectivity. In both non-C_2 and C_2-symmetric cases the proposed models suggest approach of the diene to the *re* face, resulting in the observed (1*S*,2*S*,3*R*,4*R*) configuration.



$[Cu(\mathbf{50})(\mathbf{7d})]^{2+}$ $[Cu(\mathbf{10})(\mathbf{7d})]^{2+}$

Figure 4. Distorted square planar models with ligands **50** and **10**.

For C_2-symmetric chiral bisoxazolines, a question is why the pyrazolidinone substituent would occupy the lower right rear quadrant rather than the front quadrant. The fluxional substituent can either be cis to the upper right bisoxazoline substituent and trans to the upper left substituent, or trans to the upper right bisoxazoline substituent and cis to the upper left substituent. The first situation would seemingly be a matched situation resulting in amplified enantioselectivity (as is observed), the second situation would result in a mismatch leading to reduced enantioselectivity. While the latter situation seems intuitively more likely, it obviously does not conform to the actual experimental observations.

We do not have a complete explanation for the underlying organizational factors. Unfortunately we have been unable to obtain crystal structures for any Cu(II)/bisoxazoline/pyrazolidinone complexes or for the Pd(II) analogues. One possibility is that, when the fluxional substituent is in the front quadrant, then neither face of the dienophile is accessible, with the chiral ligand blocking the back and the fluxional substituent blocking the front. If so, then reaction might be preferable via the conformation in which the fluxional group is on the same side as the ligand substituent, so that the back face is very well blocked but the front face is completely exposed. Thus, a Curtin-Hammett situation might be involved in which both configurations are in rapid equilibrium, but reaction via the matched configuration is much faster than reaction via the mismatched configuration.

Other factors may also impact the location of the fluxional group: (1) the copper complexes are probably significantly distorted from planarity; (2) the energy differential between having the fluxional group in the front versus the back is relatively small, and actually favors the matched configuration in which the fluxional substituent is in the back; and (3) the

(32) Experimental details, analysis, and spectra for nOe experiments are provided in the Supporting Information.

(33) Variable-temperature NMR experiments on the complex derived from $Pd(ClO_4)_2$, bisoxazoline **10**, and pyrazolidinone substrate **7d** showed no line broadening with lower temperature (from room temperature to −35 °C), suggesting nitrogen inversion is sufficiently rapid that it is not observed on the NMR time scale.

barrier to nitrogen inversion appears to be very small, such that rapid interconversion of the fluxional substituent is likely.[33]

The above discussion has focused on how pyrazolidinone groups can amplify enantioselectivity via matched double enantioselection, in which the fluxional substituent provides active face shielding at the reactive center. This certainly seems to be operative with some of the weak ligands investigated, such as methyl bisoxazoline **6** and nonsymmetric ligands **50**−**52**.

However, it is also likely that pyrazolidinone templates may both amplify enantioselection and provide other benefits in situations where the fluxional substituent is not the primary face-shielding element. The pyrazolidinone templates in structures **7a**−**d** are significantly larger than traditional auxiliaries like oxazolidinone, and with adjustable size. By simply occupying more space in a metal complex, other elements in an array may be pushed closer together. If a chiral ligand and a reactive center are squeezed closer together, amplification of enantioselectivity may result, even if the pyrazolidinone substituent is not itself directly shielding the face of a reactive center. The bulky pyrazolidinone may simply be pushing the ligand nearer to the reactive center so that the chiral ligand itself provides more effective face shielding. This effect may be operative when strong ligands such as **13** are used, and this basis for amplified enantioselectivity need not be limited to square planar Lewis acids. While the effect was not entirely clear in this Diels−Alder study using Mg(II)/**7** (Table 3), we have elsewhere documented that the use of pyrazolidinone auxiliaries amplify enantioselectivity for Mg(II)/**13**-catalyzed additions of hydroxylamines and radicals, and do so to an increasing degree as the fluxional group gets larger.[17,18] The large size of the pyrazolidinone template may also benefit regioselectivity as we have observed for enantioselective nitrile oxide cycloadditions. One other attractive feature of pyrazolidinone substrates that we have observed in other studies is that they have relatively strong coordinating abilities toward many Lewis acids (relative to oxazolidinone analogues). As a result Lewis-acid-catalyzed processes involving pyrazolidinones may be more tolerant of a wider range of functionalilty in both reactants and solvents, since the Lewis acid is less likely to be sequestered from the pyrazolidinone substrate by the other functional groups.

Conclusion

We have further demonstrated utility of pyrazolidinone templates in enantioselective Diels−Alder reactions. Enantioselectivities in room-temperature reactions were found to be highly dependent on the size of the dienophile's pyrazolidinone R group. High selectivities were observed in reactions with chiral Lewis acids capable of providing square planar metal geometries. Cu(II) and Pd(II) complexes provided excellent enantioselectivities when substrates with the 1-naphthylmethyl group were employed, with Pd(II) normally being superior. Substitution at the C-5 position of the pyrazolidinone core was found to play a significant role in enhancing selectivity. Reactions with common dienophiles and dienes were performed to demonstrate the utility of pyrazolidinone substrates. Studies indicated that $\pi-\pi$ interactions were not an important component of the high selectivities obtained. Some weak ligands and non-C_2-symmetric ligands were used to further demonstrate that chiral relay is indeed operative, in which actual face shielding is probably provided by the pyrazolidinone fluxional group rather than the ligand itself.

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

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