A New Approach to Enantiocontrol and Enantioselectivity Amplification: Chiral Relay in Diels−Alder Reactions

Mukund P. Sibi,* Lakshmanan Venkatraman, Mei Liu, and Craig P. Jasperse

Department of Chemistry
North Dakota State University
Fargo, North Dakota 58105-5516

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Development of new strategies to access enantiomerically pure compounds is at the forefront of synthetic organic chemistry.[1] In this context, chiral Lewis acid catalysis has emerged as one of the premiere methods to control stereochemistry. Much effort has gone into the design of superior ligands with increased steric extension, to shield distant reactive sites.[2] We have instead considered a "chiral relay" approach, focusing on the improved design of achiral templates which may indirectly relay and amplify stereoselectivity from ligands, including ligands with minimal steric bias.

Davies has recently introduced the relay concept, using a chiral auxiliary to install asymmetry.[3,4] Our approach differs from Davies in that in our relay network, asymmetry originates with a chiral Lewis acid but is then relayed/amplified via an achiral template.[5] There are no reports in the literature in which an achiral template has been applied for stereocontrol in a systematic way. The design of our achiral template took into consideration several requirements: (1) easy variation of the relay group R, (2) ready accessibility, (3) easy attachment of the appropriate reaction fragment, and (4) the presence of donor sites suitable for rotamer and Lewis acid coordination control.

A novel class of achiral templates which met the above criteria were the pyrazolidinones **1** (Figure 1).[6] The parent (**1** R = H) is readily available by conjugate addition of hydrazine to 3,3-dimethylacrylate.[7] The relay group R was installed either by simple S_N2 alkylation or by reductive amination of aldehydes, taking advantage of the higher reactivity of the N-1 nitrogen. We reasoned that in the presence of a chiral Lewis acid, the tetrahedral N(1)-nitrogen would undergo inversion (**2**→**3**) and preferentially equilibrate to an asymmetric conformation **2** or **3**. With the N(1) conformation determined by the Lewis acid, the substituent R (shown as a circle) should in turn provide shielding. In essence, the chiral Lewis acid would effectively convert an achiral auxiliary into a chiral auxiliary. It should be emphasized that if chiral relay

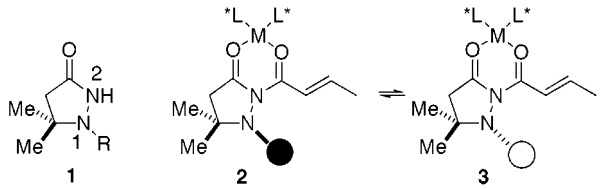
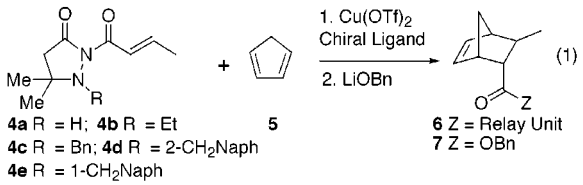


Figure 1.

is effective, the chiral ligand is only required to bias the conformation of the N(1) substituent, which in turn controls face selectivity; the ligand itself need not shield the reaction center. But any inherent bias of the chiral Lewis acid could be either consonant or dissonant with the relay group. Consonant chiral relay would be an attractive approach to amplify selectivity.

To examine if our chiral relay design is operative, Diels−Alder cycloaddition of cyclopentadiene to crotonates was undertaken using $Cu(OTf)_2$/bisoxazolines as the chiral Lewis acid (eq 1).[8] The reaction choice was based on two key factors: (1) the well-established square planar-like geometry for Cu(II) complexes with bisoxazoline ligands[9] and bidentate substrates and (2) literature data for DA reactions with nonrelay substrates for easy comparison.



The DA reactions were carried out at room temperature with substrates **4a**−**e** and excess cyclopentadiene using 15 mol % of the catalyst (equation 1, Table 1). On the average, the DA reactions took 24 h for completion, and yields ranged from 85 to 90%. The endo selectivity was generally good. For ease of ee determination and absolute stereochemistry analysis, the DA adducts **6** were converted to the known benzyl ester **7**. For our initial experiments, we chose bisoxazoline **8** whose C-4 methyl substituent is too small to provide high selectivity in the absence of chiral relay. As the effective size of the relay group increases (H < Et < Bn < CH_2-2-naphthyl, CH_2-1-naphthyl), so does the enantioselectivity (entries 1−5). Use of the bulky 1-naphthylmethyl relay group (compound **4e**) gave 86% ee (entry 5). Decreasing the reaction temperature to −23 °C further increased the ee to 96% (entry 6). *The data presented in the table suggests that enantioselectivity for the major endo adduct correlates directly with the size of the relay group. The high ee for reaction with **4e** clearly indicates that chiral relay is operative.* This high selectivity with ligand **8** is very impressive since one requires the bulky chiral Lewis acid *tert*-butylbisoxazoline/$Cu(OTf)_2$ to obtain high selectivity in DA reactions with nonrelay oxazolidinone crotonate **11**.[9] The absolute stereochemistry of the major adduct of **6e** was determined to be (2*S*,3*R*).[9] That the stereochemical outcome with substrates **4a**−**e** is identical to that obtained using oxazolidinone crotonate **11** suggests similar coordination geometries in the two series. The DA reactions with ligands **9** and **10**, which have medium-sized substituents (*i*-Pr, **9** and Bn, **10**), follow the same trend as with ligand **8**. Once again, substrate **4e** gave the highest selectivity: *92 and 85% ee at room temperature and 99 and 96% ee at −23 °C respectively. The results with **4e** are in stark contrast to the low selectivities*

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(2) For recent monographs see: *Catalytic Asymmetric Synthesis*, Ojima, I. Ed.; Wiley-VCH: New York; 2000. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York; 1999.
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(4) Clayden, J.; Pink, J. H.; Yasin, S. A. *Tetrahedron Lett.* **1998**, *39*, 105.
(5) Only a few examples have been reported to date that apply this concept in enantioselective reactions. (a) Quaranta, L.; Renaud, P. *Chimia* **1999**, *53*, 364. (b) Quaranta, L.; Ph. D thesis, University of Fribourg, Switzerland, **2000.** (c) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1802. (d) Hiroi, K.; Ishii, M. *Tetrahedron Lett.* **2000**, *41*, 7071. (e) Wada, E.; Pei, W.; Kanemasa, S. *Chem. Lett.* **1994**, 2345. (f) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637. (g) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905.
(6) For detailed procedures of synthesis and characterization data see Supporting Information.
(7) For the effect of gem alkyl substitution on conformation control see: (a) Onimura, K.; Kanemasa, S. *Tetrahedron* **1992**, *48*, 8631. (b) Bull, S. D.; Davies, S. G.; Key, M.-S.; Nicholson, R. L.; Savory, E. D. *Chem. Commun.* **2000**, 1721.
(8) (a) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289**.** (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
(9) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559.

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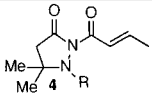
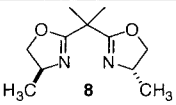
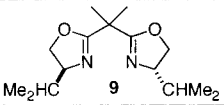
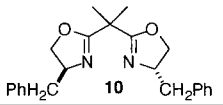
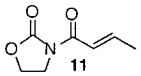
Table 1. Diels-Alder Reactions with Relay Templates Using C_2 Chiral Bisoxazolines[a]





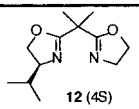


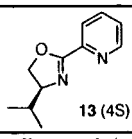


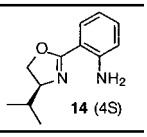
Entry	Substrate	%ee	endo/exo	%ee	endo/exo	%ee	endo/exo
1	**4a** R = H	29	91:09	08	95:05	03	86:14
2	**4b** R = Et	64	91:09	56	96:04	55	88:12
3	**4c** R = Bn	71	93:07	71	93:07	71	91:09
4	**4d** R = 2-CH_2Naph	79	93:07	65	91:09	69	90:10
5	**4e** R = 1-CH_2Naph	86	90:10	92	90:10	85	87:13
6	**4e** R = 1-CH_2Naph	96[b]	94:06	99[b]	80:20	96[b]	81:19
7		38	88:12	23	87:13	17	86:14[c]

[a] For reaction details see Supporting Information. Endo/exo ratios were determined by NMR, and ee determination was carried out using chiral HPLC. Yields for isolated column purified material averaged around 85−90%. [b] Reaction at −23 °C using 50 mol % chiral Lewis acid. [c] 8% ee was reported in ref 10 for this adduct.

Table 2. Reactions with Relay Templates Using C_1 Chiral Ligands[a]







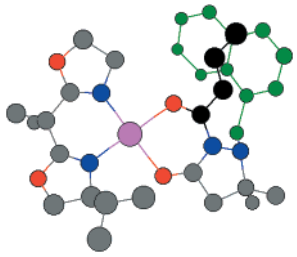
Entry	Sub	%ee	endo/exo	%ee	endo/exo	%ee	endo/exo
1	**4a**	04	86:14	01	88:12	01	87:13
2	**4b**	29	85:15	12	86:14	26	84:16
3	**4c**	47	88:12	21	87:13	51	84:16
4	**4d**	56	88:12	38	88:12	58	84:16
5	**4e**	69	85:15	59	88:12	71	83:17
6	**4e**	88[b]	91:09	66[b]	92:08	85[b]	88:12
7	**11**	06	85:15	03	84:16	00	83:17

[a] Endo/exo ratios were determined by NMR and ee determination was carried out using chiral HPLC. Yields for isolated column purified material averaged around 90%. [b] Reaction at −23 °C using 50 mol % chiral Lewis acid.

observed with oxazolidinone crotonate ***11****, a nonrelay substrate (entry 7).*[10] These results exemplify chiral amplification between the chiral ligand and the relay group.

A more stringent test for demonstrating chiral relay was devised using non-C_2 symmetric ligands **12**−**14**, which afford almost no enantioselectivity in the absence of chiral relay (Table 2).[11] We surmised that ligand **12**, like **9**, should provide a square planar complex, but should now force the relay group to occupy an opposite quadrant relative to the ligand's isopropyl group. Reaction using **12** showed the same trend as was observed with the C_2 symmetric ligands: larger relay groups gave higher selectivity (entries 1−5) with **4e** again being the best (entry 5). Lowering the temperature (compare entry 5 with 6) gave selectivity as high as 88% at −23 °C. The stereochemical outcome for reaction using ligand **12** was the same as with ligand **9** (2*S*,3*R*). *DA reactions with oxazolidinone crotonate* ***11*** *using ligands* **12**−**14** *were nearly racemic (entry 7).* The high selectivity observed with ligand **12** clearly establishes that the relay group primarily provides the face shielding, not the ligand, and that chiral relay is indeed operative. Cycloadditions using chiral Lewis acids derived from ligands **13** and **14** showed the same trend as with **12**.

The results detailed in Tables 1 and 2 can be explained using a square planar geometry model relative to Cu,[9] with the bisoxazoline occupying two sites, and with bidentate coordination by the template in an *s-cis* conformation (complex with **12** is shown). The ligand isopropyl group in the lower left front quadrant orients the relay group to the upper right rear quadrant, where the relay group 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 chiral bisoxazoline **9**, the additional ligand isopropyl group would occupy the upper left rear quadrant and reinforce shielding of the back face of the crotonate. Thus in reactions with



the C_2 ligands both the relay group and the C-4 substituent act in concert to mutually amplify the selectivity. These observations are similar to double diastereoselection experiments described by Evans[9] involving both chiral Lewis acids and chiral auxiliaries.[12]

In conclusion, we have demonstrated that chiral relay is a novel and promising strategy for obtaining high selectivity in enantioselective transformations using simple ligands. This approach should also find utility in situations where one requires enhancement of enantioselectivity for synthetic applications. Experiments are underway to evaluate chiral relay in other enantioselective transformations of general interest.

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Supporting Information Available: Characterization data for compounds **1**−**14** and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016396B

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(12) With both symmetric and nonsymmetric ligands, minor enantiomers may result from imperfect shielding within the indicated model or if the relay group partially populates the upper right front quadrant. In reactions with nonsymmetric ligands **12**−**14**, alternate ligand coordination such that the isopropyl group is in the upper left rear quadrant could further erode selectivity.