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Enantioselective Conjugate Addition of Hydroxylamines to Pyrazolidinone Acrylamides

Mukund P. Sibi* and Mei Liu

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58015

Mukund.Sibi@ndsu.nodak.edu

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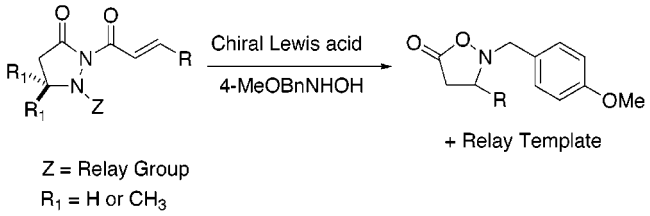
ABSTRACT



Chiral relay templates provide amplification of selectivity in conjugate addition reactions. Reversal of stereochemistry of the product isoxazolidinones has also been demonstrated by a simple change of the Lewis acid.

Chiral Lewis acid catalysis has become one of the most attractive and efficient methods for the synthesis of enantiomerically pure compounds.[1] Until now, much attention has been focused on the design of complex ligands or chiral auxiliaries that are often necessary for obtaining high selectivities. We have developed a novel protocol termed "chiral relay"[2,3] in which functional groups in the achiral templates play a crucial role in enantioselective transformations. An application of this concept was recently illustrated in enantioselective Diels−Alder reactions.[4] We present here an extension of the chiral relay methodology to enantioselective conjugate amine additions.[5]

We have recently shown that conjugate addition of *N*-benzylhydroxylamine to enoates is a convenient enantioselective method for the synthesis of β-amino acid derivatives.[6] To investigate whether our newly developed chiral relay strategy is applicable in other enantioselective transformations, we have examined the addition of *N*-benzylhydroxylamine to crotonates. The formation of the same

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(2) For examples of chiral relay in diastereoselective transformations, see: (a) Bull, S. D.; Davies, S. G.; Fox, D. J.; Garner, A. C.; Sellers, T. G. R. *Pure Appl. Chem.* **1998**, *70*, 1501. (b) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Ouzman, J. V. A. *J. Chem. Soc. Chem. Commun.* **1998**, 659. (c) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Leech, M. A.; Ouzman, J. V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2321.

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isoxazolidinone irrespective of different achiral templates would simplify product analysis. At the onset, we had two goals in mind: (1) the use of a simple, readily available chiral ligand which only minimally controls the chiral environment such that the relay group affects on selectivity and (2) optimization of the conjugate additions at practical temperatures (−25 °C and higher). Results from these studies are presented here.

Two different types of pyrazolidinones were selected as relay templates for evaluation in conjugate addition reactions. One series of templates contained *gem*-dimethyl substitution[7] at C-5 with variation of the relay Z group (R_1 = Me, see structure **1**, Figure 1). The second template contained a large

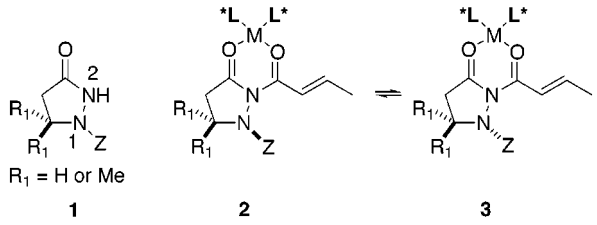
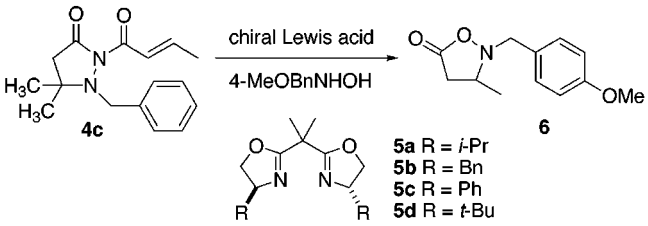


Figure 1.

diphenylmethyl relay group but lacks C-5 substitution (R_1 = H; Z = $CHPh_2$, structure **1**, Figure 1). The templates had the following characteristics: (1) ready availability, (2) easy attachment and detachment, (3) easy variation of the relay group Z, (4) carbonyl group as a donor site for Lewis acid coordination.

The conjugate amine addition to the *N*-benzyl-substituted relay template **4c** was assessed first (Scheme 1 and Table

Scheme 1



1). Chiral Lewis acids derived from simple and readily available bisoxazolines in combination with $Mg(ClO_4)_2$ and $Zn(OTf)_2$ were evaluated by conducting the reactions at 0 °C and using a catalyst loading of 30 mol %. These results are tabulated in Table 1. Conjugate additions were not selective when magnesium perchlorate was used as the Lewis

(7) *gem*-Dialkyl substitution has been effectively used to control rotamers in the design of chiral auxiliaries. For relevant contributions, see: Onimura, K.; Kanemasa, S. *Tetrahedron* **1992**, *48*, 8631. (a) Bull, S. D.; Davies, S. G.; Hones, S.; Sanganee, H. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 387. (b) Bull, S. D.; Davies, S. G.; Key, M.-S.; Nicholson, R. L.; Savory, E. D. *Chem. Commun.* **2000**, 1721.

Table 1. Effect of Ligand and Lewis Acid on Enantioselectivity[a,b]

		yield (%), ee (%)			
entry	ligand	$Mg(ClO_4)_2$		$Zn(OTf)_2$	
1	**5a**	71	10 (S)	80	70 (S)
2	**5b**	73	4 (S)	84	50 (S)
3	**5c**	71	14 (S)	80	41 (S)
4	**5d**	69	1 (−)	73	17 (S)

[a] For reaction details see Supporting Information. Ee's were determined using chiral HPLC. [b]The configuration of **6** was established by converting it to known 3-aminobutyric acid comparing the sign of rotation of the product acid with that reported in the literature.

acid irrespective of the nature of the ligand (entries 1−4). This may suggest that the chiral ligand and the *N*(1)-benzyl group are shielding opposite faces of the double bond. In contrast, higher levels of enantioselectivities were achieved when zinc triflate was used in conjunction with the same box-ligands. The chemical efficiency was good in all cases. Another trend is noteworthy. The C-4 isopropyl substituent of bisoxazoline **5a** is relatively small and often provides poor face shielding.[8] We were delighted to see that much higher selectivity was obtained using the same ligand with the relay substrate, indicating that there is chiral amplification (entry 1). The absolute stereochemistry for the conjugate addition product **6** was determined by converting it to a known compound.[9] The large difference in selectivity in reactions with the two different Lewis acids may indicate that geometry around the metal affects whether there is consonance or dissonance between the relay group and the substituent in the chiral ligand.

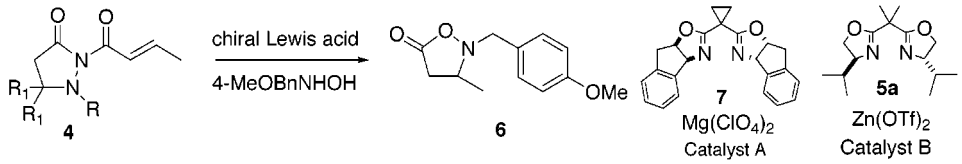
In our previous work, the bisoxazoline derived from amino indanol **7** in combination with Mg Lewis acids provided high selectivity in conjugate amine additions.[6a,b] In light of this result, we undertook a more detailed study on the effect of different relay substituents and chiral Lewis acids on selectivity in the conjugate additions (Scheme 2). Two catalysts: magnesium perchlorate with ligand **7** (catalyst A) and zinc triflate with ligand **5a** (catalyst B) were tested, and these results are tabulated in Table 2. For the series of substrates with C(5) *gem*-dimethyls, as size of the relay group

Table 2. Effect of Relay Substituents on Enantioselectivity[a]

		catalyst A		catalyst B	
entry	substrate	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee (%)[c]
1	**4a** R_1 = Me, R = H	75	76 (*R*)[11]	74	28 (*S*)
2	**4b** R_1 = Me, R = ethyl	70	52 (*R*)	74	49 (*S*)
3	**4c** R_1 = Me, R = benzyl	67	78 (*R*)	71	68 (*S*)
4	**4d** R_1 = Me, R = 2-CH_2naphthyl	75	78 (*R*)	73	70 (*S*)
5	**4e** R_1 = Me, R = 1-CH_2naphthyl	77	81 (*R*)	75	75 (*S*)
6	**4f** R_1 = H, R = $CH(Ph)_2$	71	84 (*R*)	72	57 (*S*)

[a] All reactions were carried out at 0 °C and using 30 mol % of the chiral Lewis acid. [b]Isolated yields. [c]Ee's were determined using chiral HPLC.

Scheme 2



increases (from H to 1-naphthylmethyl), so does the enantioselectivity in reactions with either of the two catalyst systems (entries 1−5). This is consistent with our proposed chiral relay model operating to amplify the stereochemical information from the chiral ligand to the reaction center. The use of bulky 1-naphthylmethyl as the relay group gave the highest selectivity of 81% ee (*R*) using catalyst A (entry 5). In contrast, reactions with **4e** using catalyst B gave the enantiomeric (*S*) product in 75% ee. It is important to note that ligand **5a** and **7** have the same configuration at C-4. *Thus a simple change in the Lewis acid reverses the enantioselectivity, allowing either (R) or (S) enantiomers to be formed with similarly high selectivities.*[10]

The effectiveness of template **4f** with a bulky diphenylmethyl substituent at the *N*(1) position but without C(5) *gem*-dimethyl groups was also explored. This template was found to be the most selective (84% *R*, entry 6, Table 2) when catalyst A was used and only moderately selective in the catalyst B mediated reaction (57%, *S*).

The effect of temperature on conjugate addition using the two best relay templates was examined next. When magnesium perchlorate in conjunction with ligand **7** was used as the chiral Lewis acid (CLA), the complex formed between the CLA and substrate **4f** was relatively stable even at elevated temperatures. Good selectivity was obtained when reaction was carried out at room temperature (entry 1, Table 3). Decreasing the reaction temperature, further increased the ee to as high as 96% at −60 °C (entry 4, Table 3). On the other hand, enantioselectivities of zinc and *i*-Pr-box (**5a**) catalyzed reactions were not temperature dependent; moderate ee's were observed at all temperatures but with reversal of product configuration. Similar temperature study was also performed with the 1-naphthylmethyl template **4e**. We were able to obtain both enantiomers of the product with high selectivities, 96% and 83%, respectively, when using magnesium or zinc Lewis acid and at moderate temperature (−25 °C). In addition, substrate **4e** is less reactive than **4f** but often more selective.

Figure 2 summarizes the results of *p*-methoxybenzylhydroxylamine conjugate additions to different templates: pyrrolidinone **8** (nonrelay template) and two pyrazolidinone relay templates **4e**,**f**. Significant enantioselectivity enhancement was observed with the relay templates over pyrrolidinone (nonrelay template) at different reaction temperatures and using different catalyst. In addition, a reversal of stereochemistry was obtained when magnesium or zinc Lewis acid was employed. Control experiments with nonrelay template **8** clearly indicate the advantages of using the readily prepared relay templates in enantioselective transformations. These results exemplify the use of achiral templates to relay

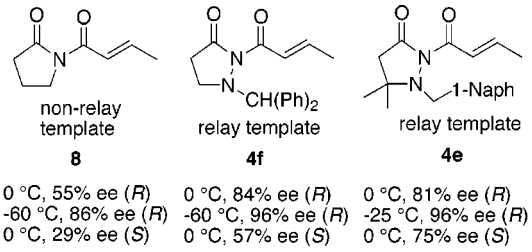
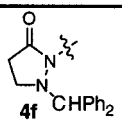
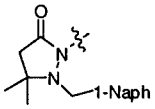


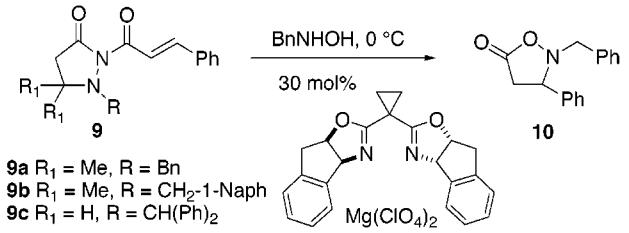
Figure 2.

Table 3. Effect of Temperature on Enantioselectivity[a]

entry	substrate	temp, °C	time, h	catalyst A		catalyst B	
				yield (%)	ee (%)	yield (%)	ee (%)
1		rt	2	71	74 (*R*)	69	51 (*S*)
2		0	3	71	84 (*R*)	72	57 (*S*)
3		-25	7	75	90 (*R*)	69	52 (*S*)
4		-60	14	77	96 (*R*)	71[b]	54 (*S*)
5		rt	3	76	76 (*R*)	72	45 (*S*)
6		0	5	77	81 (*R*)	75	75 (*S*)
7		-25	24	76	96 (*R*)	74	83 (*S*)

[a] 30 mol % of the chiral Lewis acid was used in all reactions. Ee's were determined using chiral HPLC. [b] Reaction at −40 °C for 22 h.

Scheme 3

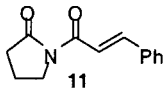


and amplify the chiral information from chiral Lewis acid to the reaction center.

Taking advantage of the practical aspects (high selectivity and moderate temperature) of the relay strategy, we then explored the conjugate addition reactions to cinnamates (Scheme 3). Once again, ee's with all relay substrates are considerably higher than the low selectivity obtained with the nonrelay substrate pyrrolidinone cinnamate **11** (Table 4). Substrate **4f** gave the highest selectivity: 88% ee at 0 °C, this is comparable with the selectivity obtained with the nonrelay substrate **11** at much lower temperature.[6b]

At the present time we do not have definitive stereochemical models for the sense of stereoinduction observed in the conjugate addition experiments. The formation of enantiomeric products using catalyst A and B suggests different geometries around the metal.[12,13]

Table 4. Conjugate Additions to Cinnamates

entry	substrate	time (h)	yield (%)[a]	ee (%)[b]
1	**9a**	4	79	71 (*S*)
2	**9b**	4	91	80 (*S*)
3	**9c**	5	82	88 (*S*)
4	 **11**	3	90	57 (*S*)

[a] Isolated yields. 30 mol % of the Lewis acid was used. [b]Ee's determined by HPLC analysis.

In conclusion, we have demonstrated the use of a novel class of achiral templates, pyrazolidinones, to perform chiral relay in enantioselective conjugate amine additions. Both enantiomers of the product may be obtained in high enantiomeric purity at moderate reaction temperatures. Experiments to determine the crystal structure of these templates and a better understanding of the architecture of the ligand−metal−substrate complex are underway.

Acknowledgment. This work was supported in part by a grant from the National Science Foundation (CHE-9983680). Mei Liu thanks ND-EPSCoR for a doctoral dissertation fellowship.

Supporting Information Available: Characterization data for compounds **1**−**10** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Only 29% ee was obtained with pyrrolidinone crotonate (nonrelay substrate) in *i*-Pr-box ligand catalyzed conjugate addition of *p*-methoxybenzyl hydroxylamine.

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(10) For a review on reversal of stereochemistry, see: Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719. (a) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879. (b) Sibi, P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200.

(11) Reasons for the high selectivity in this case are not clear at the present time. It may reflect a different chelation with *N*(1) nitrogen and the Lewis acid.

(12) Penta- and hexacoordinated zinc complexes are well-known and used for understanding reaction mechanisms of zinc enzymes: (a) Bock, C. W.; Katz, A. K.; Glusker, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3754. (b) Bhattacharya, S.; Kumar, S. B.; Dutta, S. K.; Tiekink, E. T. T.; Chaudhury. M. *Inorg. Chem.* **1996**, *35*, 1967.

(13) For issues related to metal geometry in chiral Lewis acid catalysis, see: (a) ref 10. (b) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955. (c) Porter, N. A.; Feng, H.; Kavrakova, I. K. *Tetrahedron Lett.* **1999**, *40*, 6713. (d) Murakata, M.; Tsutsui, H.; Hoshino, O. *Org. Lett.* **2001**, *3*, 299. (e) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481. (f) Yao, S.; Johannsen, M.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2345.