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Enantioselective diethylzinc additions to aldehydes catalyzed by chiral relay ligands

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Abstract—A new pyrazole ligand system incorporating fluxional chirality was found to catalyze the addition of diethylzinc to aldehydes giving rise to the corresponding secondary alcohol products in excellent yields (74–99%) with moderate to high enantioselectivities (46–93%). The size of the fluxional group on the ligand correlated with the level of enantioselectivity of the product.

1. Introduction

Development of modular ligand systems that are applicable in a broad set of enantioselective transformations is important.[1] We have recently introduced a new class of ligands containing fluxional groups[2,3] that show promise in Diels–Alder cycloadditions[4] and radical reactions.[5] Addition of dialkyl zinc reagents to aldehydes has become a primary reaction sequence to evaluate the efficiency of new ligand systems.[6,7] In the previous Diels–Alder study using chiral relay ligands, zinc Lewis acids were found to be optimal for selectivity. Herein we report the utility of chiral relay ligands in diethylzinc addition to aldehydes and show that the size of the fluxional group on the ligand correlates with the level of enantioselectivity of the product.

2. Results and discussion

The chiral relay ligand system contains a dihydropyrazole moiety with chirality residing remotely to the fluxional group R^1 as shown in Figure 1. The ligand design incorporates the following features: (1) it has two nitrogen atoms, which can form a five-membered chelate with Lewis acids; (2) the permanent stereogenic center could indirectly control the orientation of the fluxional N^1 substituent in a metal complex; (3) the fluxional N^1 substituent R^1 plays a major role in face shielding. The permanent stereogenic center need not necessarily serve a face-shielding role, as long as it dictates the conformation of R^1 (**2** or **3**); (4) the stereocontrol element R^1 can be varied simply by alkylation; (5) the chiral portion of the molecule is derived from various chiral amines, which can be obtained commercially or synthesized independently, and (6) when an amino alcohol is used as the chiral source, the ligands are potentially tridentate. One advantage inherent to these ligands is the presence of multiple sites for facile diversification. Of particular interest to the current study is the effect of the size of the fluxional group on enantioselectivity.

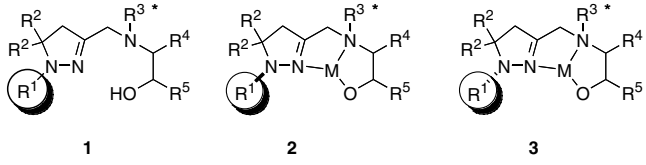

Figure 1.

The chiral relay ligands **7a**–**g** were synthesized as shown in Scheme 1. Mesityl oxide was converted to the bromide **4** using a literature procedure.[8] *N*-Alkylation of (1*R*,2*R*)-(−)-pseudoephedrine **5** with bromide **4** gave amino ketone **6** in good yield. Reaction of **6** with hydrazine followed by alkylation with the corresponding alkyl bromide provided ligands **7a**–**g**. The overall yields for the ligand synthesis ranged from 24% to 72% over three steps.

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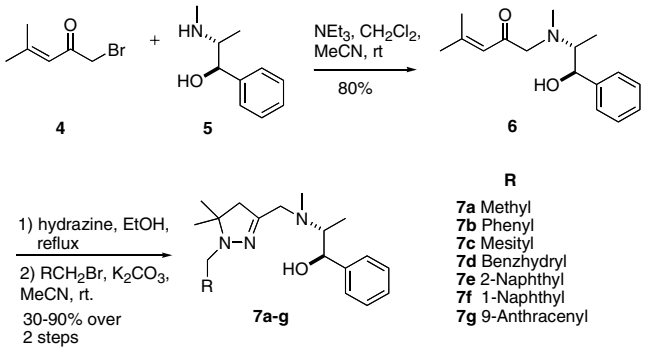
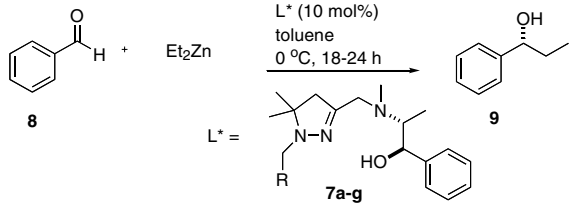


Scheme 1.

With ligands **7a**–**g** in hand, diethylzinc addition to benzaldehyde was examined as shown in Scheme 2. A catalytic loading of 10 mol% of the ligand and reaction at 0 °C was used as the standard conditions.[9] Our initial goal was to evaluate the effect of the size of the N^1-fluxional group on the level of enantioselectivity. The results from these experiments are shown in Table 1. From these results it is evident that ethyl group addition proceeds in high yield using all the different ligands (entries 1–7). Furthermore, the size of the group on the fluxional nitrogen plays an important role in determining the levels of enantioselectivity. For example, reaction with ligand **7a** with a small ethyl substituent is less selective (entry 1, 50% ee) than with **7b** containing a benzyl group (entry 2, 77% ee). This trend holds true for all the ligands except for **7d** (entry 4) with a benzhydryl group. Ligand **7g** with a bulky 9-anthracenyl substituent gave the highest selectivity (entry 7, 93% ee, reaction at 25 °C). Lowering the reaction temperature or increasing the ligand loading did not lead to substantial increase in enantioselectivity. The above results demonstrate that enantioselectivity is highly dependent on the size of the fluxional group R on the N^1 nitrogen with large groups producing the highest enantioselectivity.



Scheme 2.

Table 1. Evaluation of chiral relay ligands in diethylzinc addition to benzaldehyde

Entry	Ligand	Yield[a] (%)	Ee[b] (%)	Config.[c]
1	**7a**	96	50	*R*
2	**7b**	97	77	*R*
3	**7c**	88	81	*R*
4	**7d**	98	76	*R*
5	**7e**	99	81	*R*
6	**7f**	99	89	*R*
7[d]	**7g**	99	93	*R*

[a] Isolated yield after column chromatography.
[b] Ee was determined by GC analysis using a chiral column (Supelco β-dex 120).
[c] Determined by comparison of retention times with literature values.[10]
[d] Reaction was carried out at room temperature.

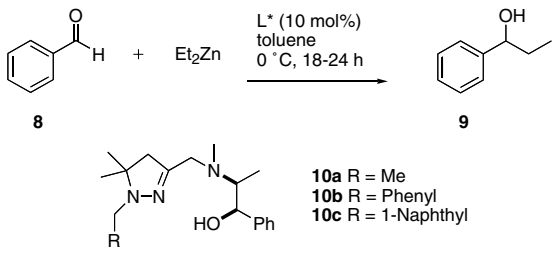
We then undertook a breadth and scope study using the best ligand **7f** (Table 2). Ligand **7f** catalyzed diethylzinc addition to a variety of aromatic aldehydes in moderate to good enantioselectivities and excellent yields (entries 1–7).[10] One exception was the addition to *o*-anisaldehyde (entry 4). The lower selectivity observed in this reaction is likely due to steric crowding due to the *ortho* substitution. Reactions with aliphatic aldehydes proceeded in high yields and the products obtained in good selectivities (entries 8–10). This is encouraging as a number of ligand systems suffer from poor yields in the addition of diethylzinc to aliphatic aldehydes. As is common with many other ligand systems, **9f** catalyzed the addition of diethylzinc to *trans*-cinnamaldehyde in moderate yield and poor enantioselectivity (entry 11).

Table 2. Scope study using various aldehydes[a]

Entry	Aldehyde	Yield[b] (%)	Ee[c] (%)	Config.[d]
1	Benzaldehyde	99	89	*R*
2	2-Naphthaldehyde	95	93	*R*
3	1-Naphthaldehyde	96	92	*R*
4	*o*-Anisaldehyde	97	69	*R*
5	*m*-Anisaldehyde	95	80	*R*
6	*p*-Anisaldehyde	97	84	*R*
7	*p*-Chlorobenzaldehyde	99	87	*R*
8	Isovaleraldehyde	99	81	*R*
9	Hexanal	96	75	*R*
10	Heptanal	93	77	*R*
11	*trans*-Cinnamaldehyde	74	46	*R*

[a] For reaction conditions, see footnotes.
[b] Isolated yield after column chromatography.
[c] Ee was determined by GC analysis using a chiral column (Supelco β-dex 120).
[d] Determined by comparison of retention times with literature values.[10]

We carried out control experiments to assess the role of the fluxional group and the permanent chirality in determining the level of enantioselectivity. In the first set of experiments, we set out to examine the effect of the permanent chirality on selectivity in diethylzinc addition to benzaldehyde (Scheme 3). Three ligands derived from (1*R*,2*S*)-(−)-ephedrine **10a**–**c** were prepared using the procedure outlined in Scheme 1. The results from addition experiments using ligands **10a**–**c** are tabulated in Table 3. In these experiments, the enantioselectivity



Scheme 3.

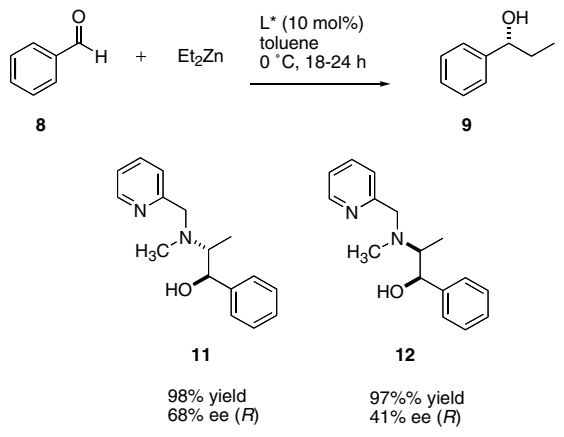
for the product correlated with the size of the fluxional group: the larger the fluxional group, the higher the selectivity (Table 3, entries 1–3). This is the same trend as observed with the pseudoephedrine ligand series **7** (see Table 1). However, the level of selectivity with ligand **7** was much higher than that obtained from ligand **10**. For example, pseudoephedrine ligand **7f** with a naphthylmethyl fluxional group gave 89% ee (Table 1, entry 6) whereas the corresponding ephedrine ligand **10c** gave only 50% ee (Table 3, entry 3). This was surprising since literature reports demonstrate that tridentate ligands (1*R*,2*S*)-*N*-[2-(dimethylamino)ethyl]-ephedrine and (1*S*,2*S*)-*N*-[2-(dimethylamino)ethyl]pseudoephedrine both catalyzed the addition of diethylzinc to benzaldehyde in high enantioselectivities.[11] This was also the case when the tridentate lithium salts of (*S*)-*N*-[1-methylpyrrolidin-2-yl)methyl] derivatives of ephedrine and pseudoephedrine were employed as chiral catalysts.[12,13] The absolute stereochemistry for the product using **7f** or **10c** was *R*. This suggests that the secondary hydroxyl group is the primary controller of product stereochemistry.

Table 3. Diethylzinc addition to benzaldehyde using ephedrine derived ligands[a]

Entry	Ligand	Yield[b] (%)	Ee[c] (%)	Config.[d]
1	**10a**	60	15	*R*
2	**10b**	90	40	*R*
3	**10c**	94	50	*R*

[a] For reaction conditions see Ref. 9.
[b] Isolated yield after column chromatography.
[c] Ee was determined by GC analysis using a chiral column (Supelco β-dex 120).
[d] Determined by comparison of retention times with literature values.[10]

To understand further the role of the pyrazole substituent incorporating the fluxional group, we prepared two pyridine derived ligands that mimic the basic structure present in **7** or **10** and evaluated them in diethylzinc additions (Scheme 4). Reaction with the pseudoephedrine derived ligand **11** was more selective than that with **12** derived from ephedrine (68% ee for **11** compared to 41% ee with **12**). The trend in level of enantioselectivity for ligands **11** and **12** is the same as that for **7f** and **10c** in



Scheme 4.

that the pseudoephedrine derived ligands are more selective. Furthermore, the absolute stereochemistry was the same regardless of the ligand used (**7f**, **10c**, **11**, or **12**).

The results we have obtained so far suggest that the role of the fluxional group in **7** and **10** in determining face selectivity is still not very clear.[14] It is evident that the size of the fluxional group impacts selectivity. However, the data also suggests that the pyrazole containing the fluxional may only function as a bulky group and thus the correlation between size and enantioselectivity.

3. Conclusion

In conclusion, a new modular ligand system has been shown to catalyze the addition of diethylzinc to various aldehydes in excellent yields with moderate to high selectivity. The efficiency of the ligand system was found to be highly dependent on both the size of the substituent on the fluxional nitrogen and the permanent chirality employed. At this point it is not clear if the fluxional group is the major contributor to face selectivity by adapting a preferred conformation or the ligand as a whole is responsible. A new series of ligands with chirality adjacent to the fluxional nitrogen in question will be developed in the future to more clearly answer this question.

Acknowledgements

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References

1. (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999.
2. For a mini review on chiral relay, see: (a) Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, M.; Jasperse, C. P.; Sibi, M. P. *Chem. Eur. J.* **2003**, *9*, 28; Chiral relay in diastereoselective transformations, see: (b) Bull, S. D.; Davies, S. G.; Fox, D. J.; Garner, A. C.; Sellers, T. G. R. *Pure Appl. Chem.* **1998**, *70*, 1501; Selected examples of chiral relay in enantioselective transformations: (c) Watanabe, Y.; Mase, N.; Furue, R.; Toru, T. *Tetrahedron Lett.* **2001**, *42*, 2981; (d) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 2161; (e) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1802; (f) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905; (g) Hiroi, K.; Ishii, M. *Tetrahedron Lett.* **2000**, *41*, 7071; (h) Wada, E.; Pei, W.; Kanemasa, S. *Chem. Lett.* **1994**, 2345; (i) Quaranta, L.; Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 39.
3. For work from our laboratory on chiral relay, see: (a) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444; (b) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718; (c) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366; (d) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181.

4. Sibi, M. P.; Zhang, R.; Manyem, S. *J. Am. Chem. Soc.* **2003**, *125*, 9306.
5. Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *15*, 2879.
6. For reviews on diethylzinc addition to aldehydes, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757; (b) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739.
7. For selected reports on diethylzinc additions to aldehydes, see: (a) Zhu, H. J.; Zhao, B. T.; Zuo, G. Y.; Pittman, C. U., Jr.; Dai, W. M.; Hao, X. J. *Tetrahedron: Asymmetry* **2001**, *12*, 2613; (b) Bauer, T.; Tarasiuk, J.; Pasániczek, K. *Tetrahedron: Asymmetry* **2002**, *13*, 77; (c) Braga, A. L.; Rubim, R. M.; Schrekker, H. S.; Wessjohann, L. A.; de Bolster, M. W. G.; Zeni, G.; Sehnem, J. A. *Tetrahedron: Asymmetry* **2003**, *14*, 3291; (d) Fonseca, M. H.; Eibler, E.; Zabel, M.; König, B. *Tetrahedron: Asymmetry* **2003**, *14*, 1989; (e) Fu, B.; Du, D.-M.; Wang, J. *Tetrahedron: Asymmetry* **2004**, *15*, 119; (f) Scarpi, D.; Galbo, F. L.; Occhiato, E. G.; Guarna, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1319; (g) Hermsen, P. J.; Cremers, J. G. O.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **2001**, *42*, 4243; (h) Dahmen, S.; Bräse, S. *Chem. Commun.* **2002**, 26; (i) Sarvary, I.; Wan, Y.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 645; (j) Joshi, N. N.; Srebnik, M.; Brown, H. C. *Tetrahedron Lett.* **1989**, *30*, 5551; (k) Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 7505; (l) Wipf, P.; Wang, X. *Org. Lett.* **2002**, *4*, 1197; (m) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 3053; (n) Huang W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364; (o) Sibi, M. P.; Chen, J.; Cook, G. R. *Tetrahedron Lett.* **1999**, *40*, 3301; (p) Long, J.; Ding, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 544.
8. (a) Bloch, R. *Synthesis* **1978**, 140; (b) Babadjamian, A.; Kessat, A. *Synth. Commun.* **1995**, *25*, 2203.
9. The reaction was carried out at 0 °C for 18–24 h after addition of a 1.0 M solution of diethylzinc in hexanes (2.2 mmol) to a solution of the appropriate aldehyde (1.0 mmol) and ligand (0.10 mmol) in toluene. The reaction was quenched with ammonium chloride and after work-up the product was purified by column chromatography. The ee for the product was determined by using chiral GC or HPLC.
10. The absolute stereochemistry was assigned by comparison of retention times with those reported in the literature: Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J. *J. Org. Chem.* **1998**, *63*, 7078.
11. Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233.
12. Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5237.
13. For other reactions with ephedrine based ligands, see: (a) Abramson, S.; Lasperas, M.; Brunel, D. *Tetrahedron: Asymmetry* **2002**, *13*, 357; (b) Jimeno, C.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synlett* **2001**, 1155; (c) Chung, Y.-M.; Rhee, H.-K. *Chem. Commun.* **2002**, 238; (d) Nakamura, Y.; Takeuchi, S.; Okumura, K.; Ohgo, Y. *Tetrahedron* **2001**, *57*, 5565; (e) Sung, D. W. L.; Hodge, P.; Stratford, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1463; (f) Fitzpatrick, K.; Hulst, R.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1861; (g) Chaloner, P. A.; Langadianou, E.; Perera, S. A.; Renuka *J. Chem. Soc., Perkin Trans. 1* **1991**, 2731; (h) Soai, K.; Niwa, S.; Watanabe, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 109; (i) Soai, K.; Nishi, M.; Ito, Y. *Chem. Lett.* **1987**, 2405; (j) Chaloner, P. A.; Perera, S. A.; Renuka *Tetrahedron Lett.* **1987**, *28*, 3013.
14. Hitchcock et al. have reported chiral relay in auxiliaries derived from ephedrine and pseudoephedrine. See: (a) Casper, D. M.; Blackburn, J. R.; Maroules, C. D.; Brady, T.; Esken, J. M.; Ferrence, G. M.; Standard, J. M.; Hitchcock, S. R. *J. Org. Chem.* **2002**, *67*, 8871; (b) Hitchcock, S. R.; Nora, G. P.; Casper, D. M.; Squire, M. D.; Maroules, C. D.; Ferrence, G. M.; Szczepura, L. F.; Standard, J. M. *Tetrahedron* **2001**, *57*, 9789.