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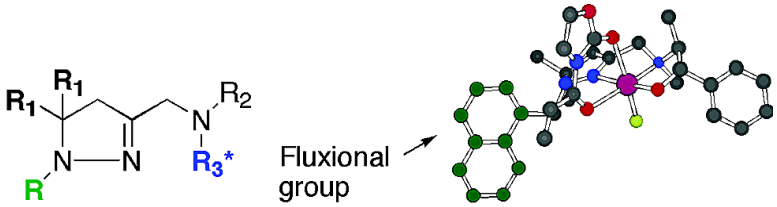

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A New Class of Modular Chiral Ligands with Fluxional Groups

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Ligand design and synthesis is a central challenge in asymmetric catalysis.[1] In developing chiral ligands, their design should allow for tuning through easy modification of substituents. Often, synthesis of a modified ligand requires a new chiral source. An alternative approach is one in which a fluxional blocking group is incorporated into a parent chiral ligand.[2,3] This would obviate the need for multiple chiral sources and would allow the synthesis of a family of ligands with steric groups of varying size from a single chiral source.

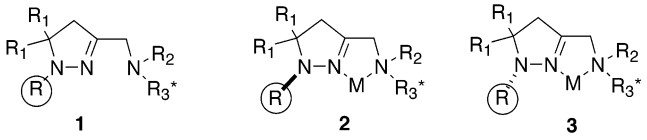
We have been interested in the design of chiral ligands for use in a variety of asymmetric transformations. Thus, we needed a flexible ligand design so that ligands with structural diversity would be readily available. This work reports the synthesis and proof of principle for a new class of modular ligands that incorporate fluxional groups to control face selectivity.

We have designed a new ligand system **1** containing a core dihydropyrazole moiety with chirality (R_3) residing remotely to the fluxional group R as shown in Scheme 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 chirality (R_3) indirectly controls the orientation of the fluxional N1 substituent in a metal complex (structure **2** or **3**). (3) The fluxional N1 substituent R plays a major role in face shielding. The permanent chiral center need not necessarily serve a face shielding role, so long as it dictates the conformation of R. (4) The stereocontrol element (R) can be varied simply by alkylation. (5) The chiral portion (R_3) of the molecule is derived from various chiral amines which can be obtained commercially or synthesized independently. (6) When an amino alcohol is used as the chiral source, then R_3 contains a hydroxyl group. In this case, the ligands are potentially tridentate. (7) A modular synthesis provides diverse ligands (four diversity points: variation in R, R_1, R_2, and R_3).

The synthesis of the new ligands was achieved in a straightforward manner from the known[4] bromomethyl mesityloxide **4** in three steps (Scheme 2). Treatment of the bromide with a chiral amine followed by reaction with hydrazine gave the parent dihydropyrazole compound. We chose three commercially available chiral amines to prepare the ligands, and the fourth was prepared in two steps from proline methyl ester. The parent compound was then alkylated with the appropriate fluxional group to furnish ligands **6**−**13**. The unoptimized overall yields for the ligand synthesis ranged from 30% to 45%.[5]

With the ligands at hand, we evaluated their effectiveness in the Diels−Alder reaction between acrylate **14** and cyclopentadiene using copper and zinc triflate as the Lewis acids (eq 1 and Table 1).[5] Reactions with the chiral Lewis acid derived from copper and zinc triflates and prolinol ligands **6**−**9** were initially evaluated (entries 1−4). Of the two Lewis acids, $Cu(OTf)_2$ gave higher selectivity. The size of the substituent R_1 on the remote proline ring (methyl vs phenyl **6** vs **7**) had an impact on selectivity with the larger phenyl group leading to a higher ee for endo **16** (compare entry 2 to entry 1). In the proline series, the size of the fluxional group (Me < Ph < 1-Naph; **7**−**9**) had an inverse relationship with selectivity: as the size of the group increased, the ee for endo adduct decreased (entries 2−4). These results suggest that there may be dissonance between the permanent and fluxional chiral groups. A simple change in the chiral amine portion to pseudoephedrine (ligands **10**−**12**), a ring-unconstrained analogue of the proline ligands, gave more gratifying results (entries 5−7). In this series, both Cu and $Zn(OTf)_2$ gave high selectivity for the endo adduct. More interestingly, the level of selectivity was dependent on the size of the fluxional group (ethyl < benzyl < naphthylmethyl: **10** < **11** < **12**): the larger the size, the higher the selectivity for both

Scheme 1



Scheme 2

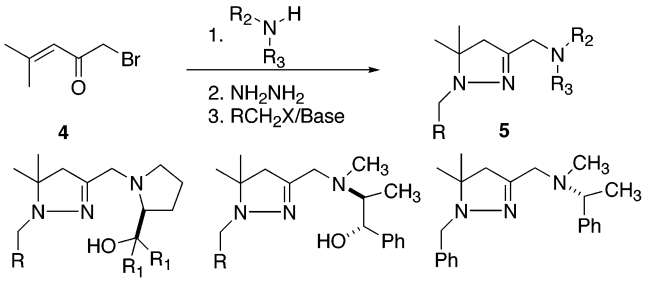
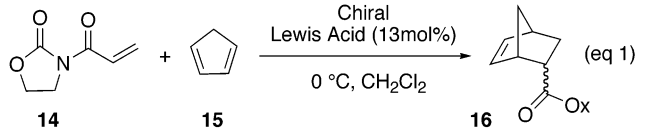


Table 1. Ligands with Fluxional Groups in Diels−Alder Reactions



		$Cu(OTf)_2$			$Zn(OTf)_2$		
entry	ligand	yield (%)[a,b]	endo/exo[c]	ee endo (exo)[d]	yield (%)[a,b]	endo/exo[c]	ee endo (exo)[d]
1	**6**	93	4.6	51 (46)	87	2.8	23 (19)
2	**7**	87	5.8	78 (61)	92	4.9	32 (12)
3	**8**	96	4.5	76 (71)	90	4.0	41 (02)
4	**9**	77	3.7	62 (75)	94	3.0	18 (14)
5	**10**	83	4.6	59 (60)	95	3.9	54 (41)
6	**11**	90	3.2	82 (92)	85	3.4	89 (87)
7	**12**	90	2.4	92 (97)	83	3.8	96 (95)
8	**13**	77	5.2	08 (04)	77	18.5	0 (0)

[a] For reaction conditions, see the Supporting Information. [b] Isolated yield. [c] Diastereomer ratio determined by ^1H NMR (500 MHz). [d] Determined by chiral HPLC.

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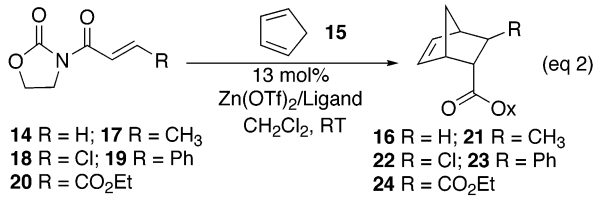
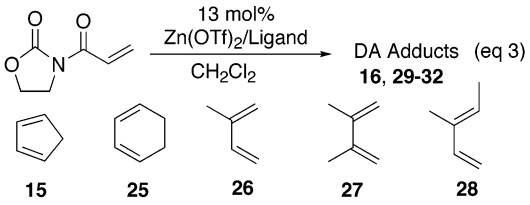
Table 2. Evaluation of Different Dienophiles in Diels−Alder Reactions Using Fluxional Ligands **11** and **12** and Zinc Triflate



entry	ligand	subs.	prod.	yield (%)[a]	endo/exo[b]	ee endo (exo)[c]
1[d]	**11**	**14**	**16**	85	3.4	89 (87)
2	**11**	**17**	**21**	82	17	90 (80)
3	**11**	**18**	**22**	86	6.0	96 (94)
4	**12**	**19**	**23**	94	1.5	94 (94)
5[d]	**12**	**20**	**24**	90	1.3	96 (−)

[a] Isolated yield. [b] Diastereomer ratio determined by ^{1}H NMR (500 MHz). [c] Determined by chiral HPLC. [d] Reaction at 0 °C.

Table 3. Evaluation of Different Dienes in Diels−Alder Reactions



entry	diene	prod.	ligand	temp., °C	yield (%)[a]	ee endo (exo)[b]
1[c]	**15**	**16**	**12**	0	83	96 (95)
2[d]	**25**	**29**	**11**	rt	86	98 (70)
3	**26**	**30**	**11**	rt	54	69
4	**26**	**30**	**12**	rt	81	89
5	**26**	**30**	**12**	0	69	95
6	**27**	**31**	**11**	rt	60	64
7	**27**	**31**	**12**	rt	67	79
8	**27**	**31**	**12**	0	67	90
9[e]	**28**	**32**	**12**	rt	67	76
10	**28**	**32**	**12**	0	27	82

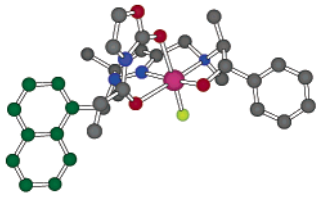
[a] Isolated yield. [b] Determined by chiral HPLC. [c] endo:exo = 3.8:1. [d] endo:exo = 40:1. [e] 6.9:2.6:1 mixtures of isomers; ee is for the major isomer.

the endo as well as the exo isomer. These results clearly suggest that the size of the fluxional group is a primary determinant of face selectivity. The outstanding level of selectivity with $Zn(OTf)_2$ is worthy of note, because it has only shown marginal effectiveness when used in combination with a variety of ligands in Diels−Alder reactions.[6] The absolute stereochemistry of **16** was determined to be *S* using ligands **10**−**12** and either Cu or $Zn(OTf)_2$ as the Lewis acid.[5] The near racemic reaction with **13** indicates that a hydroxyl group on the ligand is required for obtaining high selectivity (compare entries 6 and 8).

Having established that stereocontrol using ligands with fluxional groups is efficient, we investigated their utility in DA reactions of more complex substrates (eq 2, Table 2). As can be discerned from the table, a variety of dienophiles provide DA adducts with high enantioselectivity (entries 1−5). It is important to note that in these reactions, ligand **11**, a ligand containing a moderately bulky benzyl substituent, provides excellent levels of selectivity at room temperature.

The next series of experiments involved the evaluation of different dienes in cycloadditions with **14** using $Zn(OTf)_2$ as a Lewis acid and **11** or **12** as a ligand (eq 3, Table 3). As discussed earlier, reaction with cyclopentadiene is very efficient (reactions take <5 h for completion at 0 °C, entry 1). Similarly, reaction with cyclohexadiene was also highly efficient and selective (entry 2). The less reactive dienes took longer reaction time for completion. The power of the modular ligand design is apparent in reactions with the less reactive substrates. For example, in reactions with **26** at room temperature, the bulkier ligand **12** gave higher selectivity in contrast to reaction with **11** (compare entry 4 to entry 3). The ee for the reaction could be improved to >90% by cooling the reaction to 0 °C (compare entry 5 to entry 4). A similar trend of an increase in ee using ligand **12** was observed for reactions with dienes **27** (entries 6−8) and **28** (entries 9 and 10).

We have a tentative model for the observed selectivity with ligand **12** and Cu or Zn as the Lewis acid. The requirement of a hydroxyl group for obtaining high selectivity suggests an octahedral environment around the metal (see structure: the yellow atom represents a triflate for clarity). The observed product stereochemistry is consistent with the naphthyl group shielding the *re* face of the substrate. In conclusion, we have developed a novel class of modular ligands, containing fluxional groups, which provide highly organized structures to control face selectivity. Evaluation of these new ligands and congeners in other asymmetric transformations is underway.



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Supporting Information Available: Characterization data for compounds **6**−**32** and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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