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Fluxional Additives: A Second Generation Control in Enantioselective Catalysis

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The optimization of catalyst components is a prevalent theme in asymmetric catalysis.[1] One predominant approach is to modify the chiral ligand. Often ligand modification requires an increasingly complex synthesis and/or a new chiral source. The use of additives in asymmetric catalysis is also a powerful approach and has been documented in many examples.[2] However, very few additives display systematic effects that are applicable to various chiral Lewis acids. We now report achiral additives that dramatically amplify enantioselectivity in conjunction with a variety of chiral Lewis acids.

We recently disclosed the concept of chiral relay by incorporating fluxional blocking groups in the substrates (**1**, Scheme 1).[3] Chiral Lewis acids biased the configuration at the fluxional N1 center such that the pyrazolidinone functioned as a chiral auxiliary and amplified enantioselectivity.

Additives **2** were designed by replacing the enoyl portion of substrates **1** with an inert Lewis basic functionality. Their modular synthesis allows facile incorporation of different R_1, R_2, R_3, and X substituents. Variation at R_1 and X could alter both the sterics and the Lewis basicity of the additive, whereas varying R_2 and R_3 could provide steric tuning. Our hypothesis was that the chiral information from the ligand could be transferred to the fluxional additive. If the permanent chirality in the ligand and the induced chirality in the additive work in concert, the symbiotic interplay might result in significant improvements in the asymmetric power of the catalyst system. We also reasoned that incorporating an additive into a chiral Lewis acid complex could provide leverage in optimizing enantioselective reactions through a screening of additives rather than through modification of the substrates or chiral ligands.

We decided to evaluate this concept in the enantioselective Diels−Alder reaction of *N*-acryloyl oxazolidinone **3**. A plethora of information is available regarding selectivities observed in this reaction when catalyzed by various chiral Lewis acids.[4] This reference information would allow us to evaluate the efficacy of the additives. Bis(oxazoline) ligands have been successfully used in many enantioselective processes.[5] If fluxional additives could amplify enantioselectivity using bis(oxazoline) ligands, their use could find broad application. Hence, we initially examined magnesium salts in combination with the bisoxazoline ligand **5**.[6]

In the event of using the fluxional additive **7** (10 mol %) in the Diels−Alder reaction (Table 1) with 10 mol % $Mg(ClO_4)_2$ and (*S*)-phenyl bisoxazoline **5**, we observed a large increase in ee compared to the reaction without the additive (entries 1 and 3).[7] To ascertain that this effect was originating from the fluxional substituent, we performed the reaction with *N*-benzoyl oxazolidinone **6** as the additive (entry 2): the ee remained the same as without any additive. Reactions were best conducted using 4 Å molecular sieves, without which the ee enhancements were lower in magnitude. The molecular sieves probably maximize the availability of coordination sites, as is required if the Lewis acid is to coordinate the bidentate ligand, substrate, and additive simultaneously. Amplification of enantioselectivity was also observed whether the magnesium counterion

Scheme 1

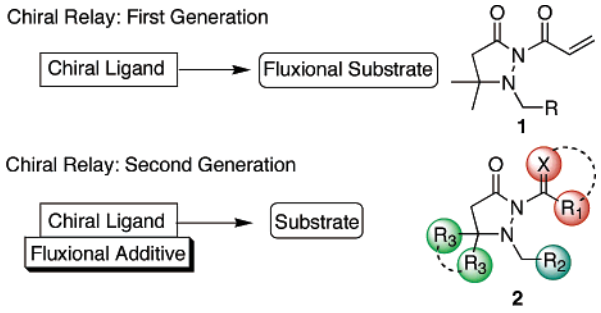
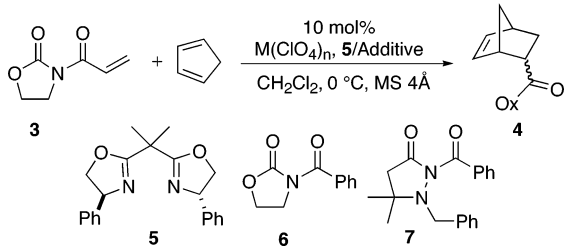


Table 1. Generality of Fluxional Additives in Diels−Alder Reactions



entry[a]	$M(ClO_4)_n$	additive	endo/exo[b]	ee (endo, %)[c]
1	$Mg(ClO_4)_2$		5	56 (*R*)
2	$Mg(ClO_4)_2$	**6**	5	56 (*R*)
3	$Mg(ClO_4)_2$	**7**	7	84 (*R*)
4	$Ni(ClO_4)_2$		5	66 (*R*)
5	$Ni(ClO_4)_2$	**6**	6	66 (R)
6	$Ni(ClO_4)_2$	**7**	13	92 (*R*)
7	$Fe(ClO_4)_2$		6	60 (*R*)
8	$Fe(ClO_4)_2$	**7**	6	85 (*R*)
9	$Co(ClO_4)_2$		5	69 (*R*)
10	$Co(ClO_4)_2$	**7**	10	95 (*R*)
11	$Zn(ClO_4)_2$		7	3
12	$Zn(ClO_4)_2$	**7**	10	71 (*R*)
13	$Fe(ClO_4)_3$		7	1
14	$Fe(ClO_4)_3$	**7**	12	1
15	$Cu(ClO_4)_2$		3	12 (*S*)
16	$Cu(ClO_4)_2$	**7**	9	16 (*S*)

[a] For reaction conditions, see Supporting Information. Isolated yields were >85%. [b] Measured from ^1H NMR or HPLC. [c] Obtained from chiral HPLC analysis.

was perchlorate, triflimide, iodide, or bromide.[8] Eventually, perchlorate was chosen since it is most common in commercially available Lewis acids.

We surmised that such an increase in enantioselectivity should be accessible, in general, with other Lewis acids that have a preference for expanding their coordination numbers from four to six.[9] Indeed, entries 4−16 in Table 1 confirm our hypothesis. As expected, Ni(II), Fe(II), Co(II), and Zn(II) showed substantial increases in ee values with the additive **7**, whereas Fe(III) and Cu-

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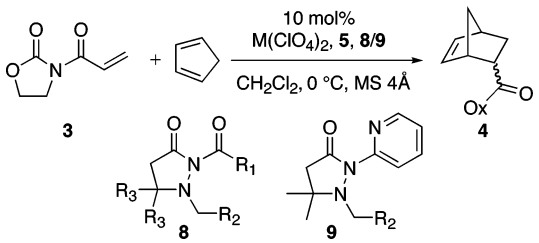
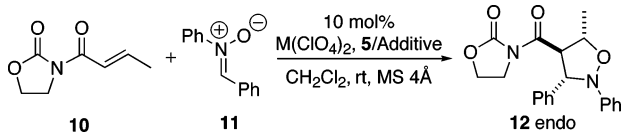
Table 2. Evaluation of Substituents on Fluxional Additives



entry[a]	M	8/9	R_1	R_2	R_3	endo/exo	ee (%)
1	Mg	**8a**	Ph	Me	Me	7	75 (*R*)
2	Mg	**8b**	Ph	Ph	Me	7	84 (*R*)
3	Mg	**8c**	Ph	1-Np	Me	9	86 (*R*)
4	Mg	**8d**	Ph	2-Np	Me	9	89 (*R*)
5	Mg	**8e**	Me	Ph	Me	8	81 (*R*)
6	Mg	**8f**	*t*-Bu	Ph	Me	7	78 (*R*)
7	Mg	**8g**	2-Np	Ph	Me	7	76 (*R*)
8	Mg	**8h**	Ph	Ph	Et	4	87 (*R*)
9	Mg	**8i**	Ph	Ph	*c*-pentyl	7	82 (*R*)
10	Mg	**9a**		Ph		12	88 (*R*)
11	Fe	**8b**	Ph	Ph	Me	6	85 (*R*)
12	Fe	**9a**		Ph		11	91 (*R*)
13	Co	**8b**	Ph	Ph	Me	10	95 (*R*)
14	Co	**9a**		Ph		11	98 (*R*)
15	Co	**9b**		2-Np		18	97 (*R*)

[a] See footnotes for Table 1.

Table 3. Effect of Fluxional Additives in Nitrone Cycloaddition



entry[a]	M	additive	endo/exo	ee (endo, %)
1	Mg		5	71
2	Mg	**8d**	10	90
3	Co		3	53
4	Co	**8d**	10	88

[a] See footnotes for Table 1.

(II) showed either small or no increase in ee values.[10] Although the increments in ee values were not predictable, the general fidelity of the concept was noticeable.[11]

The importance of additive structure/substituents was screened with $Mg(ClO_4)_2$ (Table 2).[12] The ee values were found to be dependent on R_1, R_2, and R_3. Varying the fluxional R_2 revealed a clear correlation between increasing size of R_2 and an increase in enantioselectivity (entries 1−4). Increasing the size of R_1 from Me to *t*-Bu in the alkyl series (entries 5 and 6) and from phenyl to 2-naphthyl in the aromatic series (entries 2 and 7) decreases ee values. The importance of the C5 substituents is displayed by the increase in ee values from R_3 = Me to R_3 = Et (entries 2 and 8). However, constraining the R_3 as a cyclopentyl (entry 9) leads to lower ee.

Replacement of the acyl group in **8** with a pyridyl group (**9**) was explored. The pyridyl additives **9** provided comparable or superior ee values compared to the corresponding acyl additives **8** (see entries 2, 10, and 11−14). Increasing the size of R_2 did not increase the ee values (entries 14 and 15).

We have explored the effect of fluxional additives in nitrone cycloadditions (Table 3).[13] Comparable amplification of enantioselectivity was observed with both Mg and Co(II) perchlorates. Thus, the beneficial nature of the fluxional additive is not limited to the Diels−Alder reaction.

The pyrazolidinone additives clearly have a stronger Lewis basicity compared to the oxazolidinone substrates as evidenced from ^{13}C NMR experiments.[12] Even at 10 mol % loading, the additives are able to bind to the chiral Lewis acid preferentially over the substrates/products. The origin of ee enhancements from these additives is not completely clear at present. We believe that the phenyl substituent of the BOX ligand still provides the face shielding.[14] The additive aids in the formation of a well-defined octahedral complex in which the ligand phenyl group is compressed nearer the substrate resulting in enhanced face shielding.[15]

In summary, fluxional additives contain multiple sites for modification and are applicable with many Lewis acids. Hence, they can be optimized for other enantioselective reactions. A significant advantage with these additives is that they are achiral and can be used with either antipode of a chiral ligand. Experiments to better understand the effects of the additives are currently being pursued in our laboratory.

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

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(7) Similar ee values were obtained irrespective of the order in which the Lewis acid, ligand, additive, and substrate were mixed to obtain the reactive complex.

(8) Comparison of counterions with additive **8d**: $Mg(ClO_4)_2$ (56 → 89); $Mg(NTf_2)_2$ (72 → 84); $MgBr_2$ (20 → 81); MgI_2 (43 → 91).

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(10) Control experiments with **6** showed similar ee values as the experiments without additive for all Lewis acids.

(11) It is important to note that the high selectivities with the additives are for reactions at 0 °C, unlike the situation with many chiral Lewis acids.

(12) See Supporting Information.

(13) For a recent review see (a) Kanemasa, S. *Synlett* **2002**, 1371. (b) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687.

(14) Preliminary analysis of possible octahedral complexes using molecular models (HGS Stereochemistry Set) shows that the phenyl group of the BOX ligand provides face shielding.

(15) The antipodal ligand, (*R*)-**5**, provides the enantiomeric product (*S*)-**4** with 84% ee.

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