# Practical and Efficient Enantioselective Conjugate Radical Additions

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Achievement of high enantioselectivity in carbon−carbon bond formation using catalytic amounts of chiral Lewis acid at practical temperatures is still a formidable challenge.[1] Enantioselective carbon−carbon bond construction using free-radical intermediates has begun to emerge,[2,3] and the first example of chiral Lewis acid-mediated conjugate radical additions was recently reported.[4] The use of bisoxazoline (box) ligands[5] in conjunction with magnesium and zinc Lewis acids provided moderate enantiomeric excess (ee) in the conjugate additions. Key features of this methodology were the formation of enantiomeric products by changing the nature of the C4-substituent in the box ligands and the use of substoichiometric amounts of the Lewis acid. The enantioselectivity using catalytic amounts of the chiral Lewis acids, however, was very low (57% ee with 20 mol % of the catalyst and 50% chemical yield). We surmised that improvements in enantioselectivity should be possible by the use of (box) ligands that incorporated two structural features, (1) a different bite angle[6] and (2) a change in the dihedral angle of the box C4-substituent, i.e., ring constraint. *In this paper, we report outstanding levels of enantioselectivity using catalytic amounts of chiral Lewis acids in conjugate radical additions. Additionally, high levels of enantioselectivity at room temperature using substoichiometric amounts of chiral Lewis acid are also reported.*

The results from isopropyl radical addition to the cinnamoyl oxazolidinone **1** using magnesium iodide as a Lewis acid[7] (eq 1) are tabulated in Table 1.[8] Three types

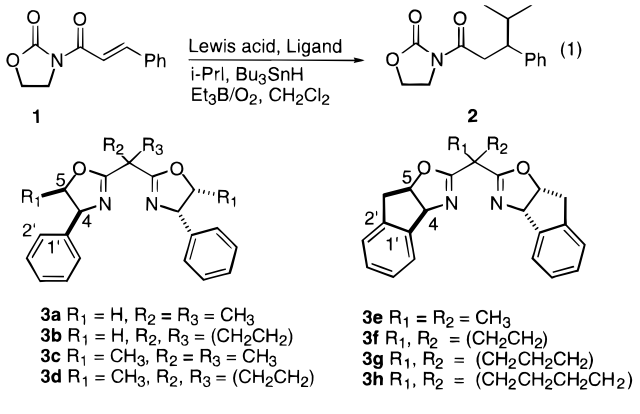


**Table 1. Enantioselective Radical Additions Using $MgI_2$ as Lewis Acid. Effect of Ligand Structure**[a]

| entry | ligand (stereochem) | yield[b] (%) | % ee (er)[c,d] | stereochemistry[e] |
|---|---|---|---|---|
| 1 | **3a** (*SS*) | 88 | 47 (2.8:1) | *S* |
| 2 | **3b** (*SS*) | 87 | 37 (2.1:1) | *S* |
| 3 | **3c** (4*S*,5*R*) | 79 | 31 (2.0:1) | *S* |
| 4 | **3d** (4*S*,5*R*) | 88 | 36 (2.1:1) | *S* |
| 5 | **3e** (4*S*,5*R*) | 88 | 89 (17:1) | *R* |
| 6 | **3f** (4*S*,5*R*) | 88 | 93 (28:1) | *R* |
| 7 | **3g** (4*S*,5*R*) | 90 | 82 (10:1) | *R* |
| 8 | **3h** (4*S*,5*R*) | 92 | 82 (10:1) | *R* |

[a] For experimental conditions see the Supporting Information. One equiv of the chiral Lewis acid was used in all the experiments. [b] Yields are for isolated and purified materials. [c] Ee's were determined by chiral HPLC analysis using a Chiralcel OD column. [d] Enantiomeric ratios above 10:1 are rounded off to the nearest integer. [e] The absolute stereochemistry of the product was established by hydrolysis to the known carboxylic acid and comparison of the sign of its rotation.

of (box) ligands were chosen for structural modification to examine the effect of bite angle and ring constraint on enantioselectivity. Variation in bite angle[6a] was carried out by modifying the bridge carbon and introducing a spiro ring (**3a** to **3b**; **3c** to **3d**; **3e** to **3f**). A progression from a flexible C4-phenyl substituent (as in **3a** and **3b**) to a moderately restricted one (as in **3c** and **3d**) to a fully constrained analog (**3e** and **3f**) provided ligands to examine the effect of dihedral angle ($C_5-C_4-C_{1'}-C_{2'}$; for numbering see structure in eq 1) changes on enantioselectivity.[9] An increase in the bite angle of the phenylglycine-derived ligand (**3a** vs **3b**) led to a decrease in enantioselectivity (compare entries 1 and 2, Table 1). A similar structural change in the 1-amino-1-phenyl-2-propanol-derived ligands (**3c** vs **3d**) showed a small increase in selectivity (compare entries 3 and 4, Table 1). The absolute stereochemistry of the product using **3a**−**3d** was identical.[10] Thus, variation of the bite angle and/or the dihedral angle of the C4 substituent in the flexible models did not lead to high enantioselectivity. In contrast, complete restriction of the C4-Ph substituent by formation of a ring, as in ligands derived from amino

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(8) The starting materials and the ligands were prepared using literature procedures. See the Supporting Information.

(9) Geometry optimization (PC Model) for ligands **3b**, **3d**, and **3f** was carried out. The $C_5-C_4-C_{1'}-C_{2'}$ dihedral angles for these ligands are 70°, 81°, and 10°, respectively.

(10) The absolute stereochemistry of the product was established by hydrolysis to the known acid.

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**Table 2. Enantioselective Radical Additions Using $MgI_2$ and Ligand 3f. Effect of Stoichiometry and Temperature[a]**

| entry | Lewis acid[b] (mol %) | T (°C) | yield[c] (%) | ee[d] (%) | er[e] |
|---|---|---|---|---|---|
| 1 | 100 | −78 | 88 | 93 | 28:1 |
| 2 | 50 | −78 | 90 | 96 | 49:1 |
| 3 | 40 | −78 | 94 | 97 | 66:1 |
| 4 | 30 | −78 | 91 | 97 | 66:1 |
| 5 | 20 | −78 | 95 | 96 | 49:1 |
| 6 | 10 | −78 | 88 | 95 | 39:1 |
| 7 | 5 | −78 | 92 | 90 | 19:1 |
| 8 | 1 | −78 | 29 | 63 | 4:1 |
| 9 | 30 | −42 | 84 | 96 | 49:1 |
| 10 | 30 | −20 | 93 | 95 | 39:1 |
| 11 | 30 | 0 | 91 | 94 | 32:1 |
| 12 | 30 | 25 | 87 | 93 | 28:1 |
| 13 | 20 | −20 | 88 | 93 | 28:1 |
| 14 | 10 | −20 | 83 | 86 | 13:1 |

[a] For reactions conditions see the Supporting Information. [b] A 1:1 ratio of Lewis acid to ligand was used in all experiments. [c] Yields are for purified and isolated materials. [d] Ee's were determined by chiral HPLC analysis using a Chiralcel OD column. [e] Enantiomeric ratios are rounded off to the nearest integer.

indanol (ligands developed by Davies et al. at Merck),[6a] gave **2** with excellent enantioselectivity (compare entries 3 and 5, Table 1). Further enhancement in selectivity could be obtained by increasing the bite angle of the ring-constrained ligand (**3e** vs **3f**, compare entries 5 and 6, Table 1). Within the spriocyclic series (**3f**−**3h**), an increase in spiro ring size, i.e., a decrease of the bite angle,[6a] led to a decrease in enantioselectivity (compare entries 6−8, Table 1). Surprisingly, the absolute stereochemistry of the product using the constrained ligands **3e** to **3h** was opposite to that from their flexible analogs (**3a**−**3d** gave the *S* product whereas **3e**−**3h** gave the *R* product).

Having established the cyclopropyl ligand **3f** as the candidate with optimal shielding characteristics, we examined the catalytic nature of the chiral Lewis acid and effect of practical temperatures on enantioselectivity. The results from these experiments are listed in Table 2. Several entries in Table 2 are noteworthy. The use of a substoichiometric amount of the chiral Lewis acid (50−10 mol %) gave higher enantioselectivity for the conjugate addition as compared to reaction with stoichiometric amounts (compare entries 2−6 with 1, Table 2). Decreasing the amount of the chiral Lewis acid to 5 mol % led to a small lowering of enantioselectivity (90% ee, 19:1 er, entry 7, Table 2). The chemical yields were still excellent (entries 1−7, Table 2). Further lowering of the catalyst loading to 1 mol % led to a large decrease in enantioselectivity as well as the chemical yield (entry 8, Table 2). The effect of temperature on enantioselectivity using 30 and 20 mol % of catalyst loading was also examined, and it was found that outstanding levels of enantioselectivity can be obtained at room temperature or slightly below (entries 9−14, Table 2). *These results are significant because they now provide a basis for conducting enantioselective conjugate additions at practical temperatures using substoichiometric amounts of the chiral Lewis acid.*

We provide a rationalization for the high levels of enantioselectivity as well as the observed absolute stereochemistry for isopropyl radical addition to **1**. Of the two key variants tested, bite angle changes had a small effect on enantioselectivity. In contrast, the dihedral angle changes had a greater impact on the level of enantioselectivity as well as the absolute stereochemistry of the product. Two octahedral models are consistent with the observed absolute stereochemistry of the product (see Figure 1).[11] In reactions with ligands in which the C−Ph bond is flexible (**3a**−**3d**), the substrate−$MgI_2$−

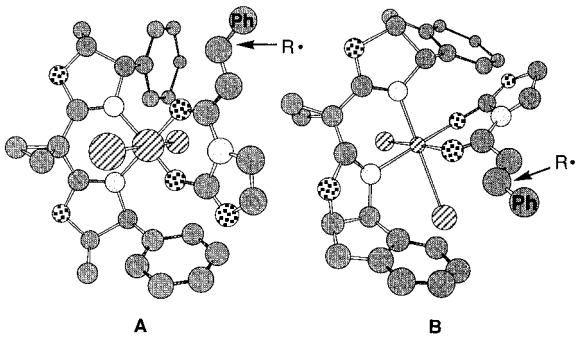


**Figure 1.**

ligand complex adopts an octahedral geometry with the iodides in a *trans* arrangement (structure A, Figure 1).[12,13] The observed low level of enantioselectivity with **3a**−**3d** also indicates that the flexible C4-Ph substituent does not provide for optimal face shielding. Attack of the radical on the least hindered *si*-face of the substrate accounts for the absolute stereochemistry of the product ((4*S*,5*R*)-**3d** gave *S* product). In the case of the aminoindanol-derived ligands, the ligand−$MgI_2$−substrate complex adopts an octahedral geometry where the two iodides have a *cis* orientation and the more Lewis-basic carbonyl oxygen is *trans* to the iodide (structure B, Figure 1).[14] The ring constraint and the larger bite angle in **3f** provides for optimal face shielding in the radical addition and thus accounts for the high levels of enantioselectivity. Attack of the radical on the least hindered *re*-face of the substrate accounts for the observed absolute stereochemistry of the product ((4*S*,5*R*)-**3f** gave *R* product). Our results provide a better insight into the ligand design features that should have broad implications to a variety of Lewis acid-mediated processes. Experiments to further refine the model and extension to tandem addition reactions are underway.[15]

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**Supporting Information Available:** Experimental procedures and characterization data for all compounds (10 pages).

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(11) In structures **A** and **B**, the counterions are still within bonding distance from the metal. An extreme situation would be one in which the ions are completely dissociated, imparting a square planar geometry around the metal for **A** and a tetrahedral arrangement for **B**.

(12) This organization is favored over the alternate *cis*-octahedral (tetrahedral) arrangement because it has the least amount of substrate: ligand and ligand:counterion steric interactions.

(13) The substrate is in an *s-cis* conformation. This is based on our previous work (ref 4) and literature precedents: Gothelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 4435. Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436.

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(15) Prof. Ned Porter, Duke University, has informed us that *tert*-butyl radical addition to oxazolidinone crotonate proceeds with >98% ee using stoichiometric $MgI_2$ and ligand **3f**.