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Lanthanide Lewis Acid-Mediated Enantioselective Conjugate Radical Additions

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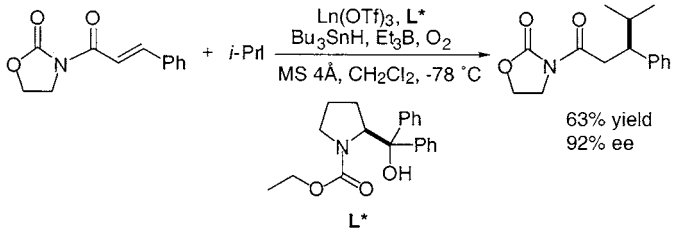
ABSTRACT



Lanthanide triflates along with proline-derived ligands have been found to be efficient catalysts for enantioselective conjugate addition of nucleophilic radicals to enoates. *N*-Acyl oxazolidinones, when used as achiral additives, gave meaningful enhancements in the ees for the product.

Asymmetric synthesis is at the forefront of modern organic chemistry, especially using chiral Lewis acids in enantioselective transformations.[1] There are a large number of ionic and neutral methods that have been reported for the formation of carbon−carbon bonds stereoselectively.[2] In contrast, only a handful of methods have been reported for enantioselective C−C formation using radical intermediates.[3] Using well-established precedents from the ionic literature, the chiral Lewis acid-mediated radical reactions have mostly relied on only a few Lewis acid/ligand combinations.[4] In this regard, our group has developed conjugate additions[5] of nucleophilic radicals using chiral Lewis acids derived from magnesium (zinc) salts and bisoxazoline ligands.[6]

We have previously demonstrated that lanthanide triflates are excellent Lewis acids in diastereoselective conjugate radical additions.[7] Lanthanide triflates are superior Lewis acids in terms of both their strength and their stability toward

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air and moisture.[8] They also allow for the tuning of reactivity/selectivity due to their small variations in ionic radii. Lanthanides can adopt coordination numbers varying from 6 to 12.[9] Several examples of asymmetric reactions are known with chiral lanthanide Lewis acids, including a recent example in conjugate addition of thiols.[10] We have been interested in utilizing lanthanide triflates in enantioselective transformations and document here our initial success with proline-based ligands (Figure 1).

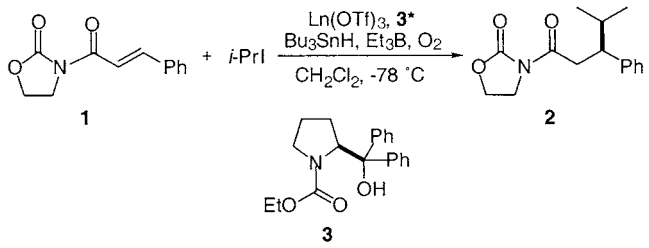
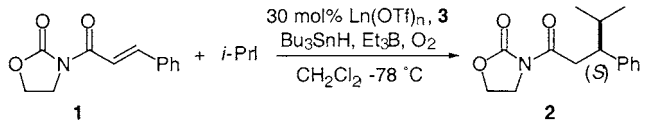


Figure 1.

Our initial studies were directed toward finding a suitable chiral ligand for lanthanides in enantioselective conjugate addition. For this purpose, we chose to study the addition of nucleophilic radicals to α,β-unsaturated enoate **1**. Popular chiral ligands for lanthanides were initially evaluated. For example, a combination of $Yb(OTf)_3$ and (*R*)-BINOL, TADDOL, or tartaric acid resulted in very low conversions and enantioselection.[11] Recently, it has been shown that $Hf(OTf)_4$ and a proline-derived ligand similar to **3** was found to provide moderate selectivity in conjugate thiol additions.[10d] Using ligand **3**, we performed a brief survey of lanthanide triflates (Scheme 1, Table 1). Samarium triflate proved to

Scheme 1



be the most efficient Lewis acid with a stoichiometric amount of chiral Lewis acid furnishing 70% ee of the product (data not shown). Substoichiometric amounts of the chiral Lewis acid gave better enantioselectivity, with 30 mol % being

Table 1. Effect of Lewis Acid on Enantioselectivity[a−c]

entry	Lewis acid	yield (%)	ee (%)
1	$La(OTf)_3$	88	64
2	$Nd(OTf)_3$	84	76
3	$Sm(OTf)_3$	84	79
4	$Eu(OTf)_3$	62	58
5	$Y(OTf)_3$	83	62
6	$Yb(OTf)_3$	87	39
7	$Hf(OTf)_4$	34	0

[a] Entries arranged from large to small lanthanides. [b] For reaction details, see Supporting Information. Values of ees were determined using chiral HPLC. [c] Configuration of **2** was established by comparison of the HPLC retention times with that in ref 6a.

optimal.[12] A significant dependence of the enantioselectivity on the ionic radii of the lanthanide ion was observed (entries 1−6 show lanthanides in decreasing ionic radii). We found an initial increase in ee from La to Sm (entries 1−3) followed by a decrease in ee as the ionic radius was further decreased (entries 3−7). Various groups have previously reported such dependence of enantioselectivity on ionic radii of lanthanide metal ions.[13] The exact nature of such a dependence is related to the type of the reaction under study, and our results indeed parallel the effect observed in diastereoselective reactions previously documented in our laboratory.[7] The absolute configuration of the product was found to be *S* by comparison with the retention time in chiral HPLC analysis of a known sample.[14] The face selectivity in our experiments is the same as that observed by Kobayashi et al. for the addition of thiols to crotonyl oxazolidinone using $Hf(OTf)_4$ and an analogous ligand.[10d]

We altered the ligand structure to probe its effect on the enantioselectivity according to the reaction conditions in Scheme 1. Ligands **3**−**14** were synthesized from (*S*)-proline by previously known procedures.[15] Enantioselectivities from conjugate additions using these ligands **3**−**14** are shown in Figure 2. The effect of different alkyl groups on the

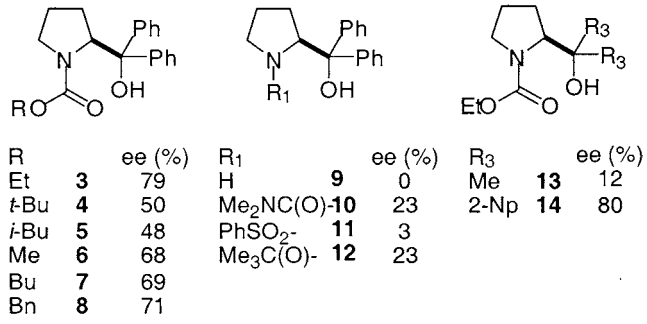


Figure 2.

carbamate moiety (**3**−**8**) was initially explored. Decreasing the bulk of the alkyl group decreases the selectivity, but increasing the bulk on the carbon either α or β to the oxygen

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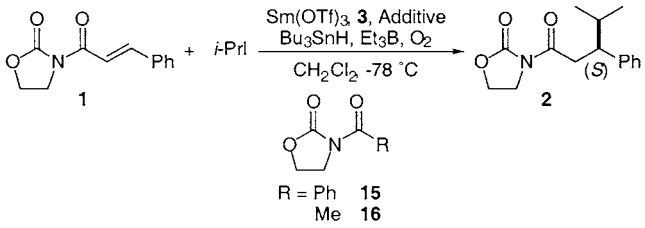
(11) The chemical efficiency for these chiral Lewis acid-mediated conjugate additions was low (<50% isolated yields) and the ees were <15%.

atom also leads to decreased selectivity. The chemical efficiencies using the carbamoyl ligands (**3**−**8**) were good (>80%) with little variation from ligand to ligand. The dependency of ee on variation in the alkyl group is not clear. The ligand **9** with the free NH group decreased the reactivity of the catalyst significantly. Modifying the type of substituent on the nitrogen can modulate the steric bulk and electronic nature of the ligand. Changing the carbamoyl group on nitrogen to a urea (**10**), sulfonamide (**11**), or amide (**12**) resulted in decreased reactivity and selectivity.[16] Large groups on the tertiary alcohol gave high selectivity (**3** and **14**), whereas the small methyl group (**13**) decreased selectivity.

Lanthanides, due to their larger size and vacant f-orbitals, can attain higher coordination numbers than the Lewis acids in either main group or transition metals. Such higher coordination numbers can be achieved either by varying the stoichiometry of the Lewis acid to ligand or by introducing achiral additives (Scheme 2, Table 2). Increasing the amount

Scheme 2



of the ligand to 2 or 3 equiv compared to the Lewis acid decreased the enantioselectivity (compare entry 1 with entries 2 and 3). In this reaction, the product due to its similarity with the substrate can coordinate to the reactive complex.[17] To test this possible influence of the product, 2 equiv (compared to the Lewis acid) of the (±)-product **2** was added, and the ee of the product derived from the reaction decreased to 49% (entry 4). To prevent the product from hampering the efficacy of the chiral catalyst, achiral additives were considered. Achiral additives are known to affect the selectivity in asymmetric catalysis.[18] This is due to their coordination to the chiral Lewis acid and hence alteration of the catalyst superstructure and also to their filling of empty coordination sites. We initially evaluated ethylene glycol as

Table 2. Effect of Additives

entry	additive (equiv)	yield (%)[a]	ee (%)[b]
1	none	84	79
2	**3** (1 equiv)[c]	72	64
3	**3** (2 equiv)[c]	86	58
4	(±)-**2** (2 equiv)	84	49[d]
5	$HOCH_2CH_2OH$ (2 equiv)	73	64
6	**15** (1 equiv)	84	82
7	**15** (2 equiv)	67	89
8	**15** (3 equiv)	63	89
9	**16** (2 equiv)	95	84
10	MS 4 Å (17 mg)	67	73
11	MS 4 Å (150 mg)	45	83
12	**15** (2 equiv) + MS 4 Å (150 mg)	63	92

[a] Isolated yields. The amount of Lewis acid used was 30 mol %. [b] HPLC analysis was used to determine ees. [c] Amount in parentheses refers to the extra ligand added. [d] See Supporting Information for calculation of the ee.

an additive since it had a beneficial effect in diastereoselective radical reactions mediated by lanthanide Lewis acids.[19] In contrast, ethylene glycol as an additive in enantioselective transformations was not favorable (compare entry 1 with 5). Next, we evaluated two *N*-acyl oxazolidinones (**15**−**16**) as additives.[20] Of these, *N*-benzoyl oxazolidinone **16** was the most effective (compare entry 1 with entries 7 and 9). Also, a dependence of selectivity on the amount of additive was observed: 2 equiv of the additive with respect to the chiral Lewis acid was found to be optimal (compare entries 6−8). We believe that after the 2 equiv is added, there is no vacant coordination site in the reactive complex for the additive to bind to the Lewis acid.

Molecular sieves play a major role in catalysis. Although the exact nature of their effect is not well understood, it is widely believed that they either remove the adventitious water in the catalyst or aid in blocking coordination sites.[21] Also, the amount of molecular sieves is an important parameter for observing beneficial effects.[10d] In our case, addition of small amounts of MS 4 Å led to a decrease in enantioselectivity (compare entry 1 with entry 10). However, larger amounts (150 mg) of MS 4 Å produced a small enhancement in selectivity (compare entry 1 with entry 11). Finally, we were able to obtain 92% enantioselectivity by combining 2 equiv of the additive **16** and MS 4 Å with 30 mol % of the chiral Lewis acid (entry 12).

Assuming that two triflate ions are bound to the metal and that the substrate, ligand, and additive bind in a bidentate

(12) 68% ee (10 mol %); 74% ee (20 mol %); 79% ee (30 mol %); 64% ee (40 mol %).

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(14) See Supporting Information in ref 6a for details on stereochemical analysis.

(15) Bhaskar Kanth, J. V.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127−5132.

(16) Reactions with these ligands were considerably slower. Yields averaged around 70%.

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fashion, the reactive complex must be 10-coordinate.[17a] However, the exact structure of the complex is yet to be determined.

In summary, we have described the development of lanthanides with proline-derived ligands in chiral Lewis acid catalysis. This remains a very attractive substitute for the chiral Lewis acids obtained from magnesium and zinc. Since lanthanides are water-tolerant Lewis acids, they provide opportunity for development of reaction in aqueous media. The use of proline-derived ligands also obviates the use of bisoxazoline ligands, which are more difficult to prepare and do not allow for as simple variations to be incorporated during ligand synthesis. Our study also provides further examples of achiral additives in enhancing the stereoselectivity obtained in a reaction. We are currently evaluating these ligand systems in other asymmetric processes, and the results will be disclosed in due course.

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

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