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Enantioselective radical reactions: the use of metal triflimides as Lewis acids

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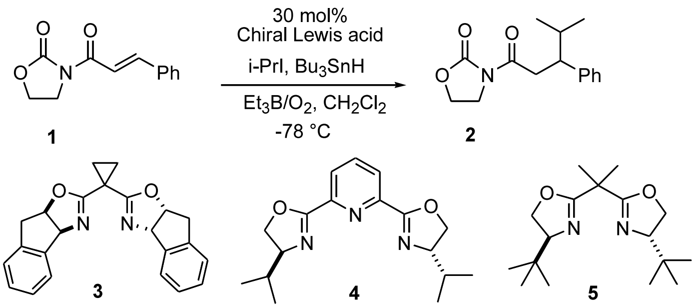
Abstract—Several metal triflimides in conjunction with chiral ligands have been evaluated in conjugate radical additions. Chiral Lewis acids derived from magnesium and iron triflimides and bisoxazolines gave high enantioselectivity.

Asymmetric synthesis using chiral Lewis acid catalysis continues to attract interest from organic chemists.[1] In this context, new methodologies for enantioselective carbon–carbon construction using free radical intermediates[2] have begun to emerge in the past five years.[3] These methods have relied on the use of chiral Lewis acids. The most often used Lewis acids have been magnesium, zinc and copper salts usually as their halides, triflates or perchlorates.[4] There are several drawbacks to the use of these compounds: (1) limited solubility in non-polar solvents, (2) explosiveness of perchlorates, and (3) moderate Lewis acidity for the halides and triflates.

The use of triflimides[5] as Lewis acid counterions is under-explored in chiral catalysis.[6] Triflimides offer several unique properties which are important for catalysis: stability,[7] high solubility in typical non-polar organic solvents, ease of preparation, minimal hygroscopic nature and high Lewis acidity.[8] Herein the evaluation of chiral Lewis acids derived from various metal triflimides and chiral ligands in enantioselective conjugate radical addition is the main focus.[9]

Our work began with the evaluation of different metal triflimides in combination with chiral ligands. The reaction we chose to investigate was the addition of the isopropyl radical to cinnamate **1** using triethylborane/oxygen as the radical initiator (Scheme 1).[10] The results from these experiments are tabulated in Table 1. We investigated three different classes of metal salts with +1, +2, and +3 charges. Three bisoxazolines that have shown excellent characteristics in a variety of transformations were chosen as the chiral ligands.[11] Reactions with the moderately Lewis acidic lithium and silver triflimides were sluggish and the chemical yields ranged from 20 to 45% (entries 1 and 2). The enantioselectivities were also disappointingly low (<10%) irrespective



Scheme 1.

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Table 1. Evaluation of metal triflimides in conjugate radical additions[a]

Entry	Lewis acid	Ligand **3**		Ligand **4**		Ligand **5**	
		Yield[b]	ee[c]	Yield[b]	ee[c]	Yield[b]	ee[c]
1	$LiNTf_2$	26	12	32	5	42	2
2	$AgNTf_2$	22	0	22	0	24	0
3	$Mg(NTf_2)_2$	99	98	90	22	50	10
4	$Zn(NTf_2)_2$	68	12	96	20	86	16
5	$Fe(NTf_2)_2$	95	98	62	8	94	80
6	$Sc(NTf_2)_3$	30	3	27	2	22	0
7	$Y(NTf_2)_3$	83	11	45	31	66	0
8	$Yb(NTf_2)_3$	60	0	26	25	52	0

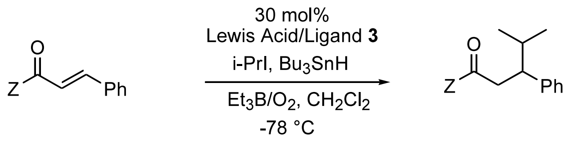
[a] 5 equiv. of *i*-PrI, 2 equiv. of Bu_3SnH, and 3 equiv. of Et_3B was used. The reactions took 2–6 h to reach completion.

[b] Isolated yield after column chromatography.

[c] Determined by chiral HPLC using chiralcel OD column.

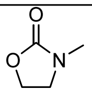
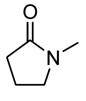
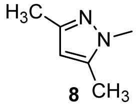
of the ligand employed (entries 1 and 2). Reactions with divalent metals, magnesium, zinc, and iron, were more successful. Conjugate radical addition using $Mg(NTf_2)_2$ and ligand **3** gave outstanding selectivity and chemical yield (entry 3). In contrast, neither ligand **4** nor **5** gave high selectivity with magnesium triflimide. Reactions with zinc triflimide were chemically efficient, but the enantioselectivities were disappointing (entry 4). Conjugate addition with iron(II)triflimide as the Lewis acid was also investigated. This Lewis acid turned out to be very effective, providing high yields for **2** (entry 5) except for reaction with ligand **4**. The enantioselectivity for the product was also outstanding (98% ee with **3**). This was the only Lewis acid other than magnesium that provided high enantioselectivity with bisoxazoline ligands. We also investigated three prelanthanide and lanthanide Lewis acids (entries 6–8). Of these, only yttrium triflimide gave good chemical yields (entry 7). Scandium triflimide gave racemic product with all the three ligands (entry 6) while yttrium and ytterbium triflimides gave only moderate ee for the product (entries 7 and 8).

We have also evaluated conjugate radical addition with three different templates[12] using magnesium triflimide and ligand **3** (Scheme 2, Table 2). In an effort to compare the triflimides directly with perchlorates, results from reactions with magnesium perchlorate and ligand **3** are also included. As discussed earlier, reaction with $Mg(NTf_2)_2$ in combination with ligand **3** gave high selectivity (98% ee) in isopropyl radical addition using the oxazolidinone template (entry 1). Similar levels of selectivity was also observed with $Mg(ClO_4)_2$ as a Lewis



Scheme 2.

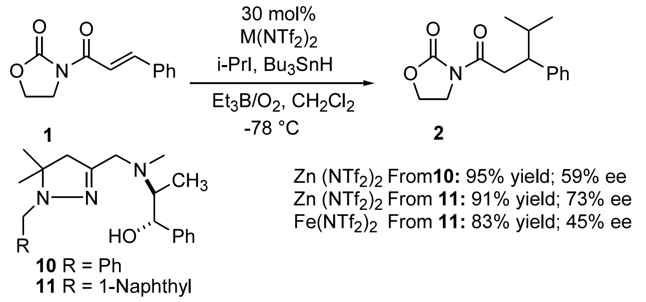
Table 2. Evaluation of different templates for conjugate radical addition[a]

Entry	Lewis Acid	Starting Material Z=	Product	Yield,%[b]	ee, %[c]
1	$Mg(NTf_2)_2$	 **1**	**2**	99	98
2	$Mg(ClO_4)_2$			91	94
3	$Mg(NTf_2)_2$	 **6**	**7**	95	98
4	$Mg(ClO_4)_2$			87	98
5	$Mg(NTf_2)_2$	 **8**	**9**	80	14
6	$Mg(ClO_4)_2$			62	02

[a] 5 equiv. of *i*-PrI, 2 equiv. of Bu_3SnH, and 3 equiv. of Et_3B was used. The reactions on average took 2–6 h to reach completion.

[b] Isolated yield after column chromatography.

[c] Determined by chiral HPLC (see Refs. 4a or b or f for conditions) using chiralcel OD column.



Scheme 3.

acid (entry 2). Radical addition to pyrrolidinone-derived enoate **8** was equally effective with both magnesium triflimide or perchlorate as Lewis acids (entries 3 and 4). In contrast to the highly selective reactions with substrates **1** and **6**, reactions with pyrazole-derived enoate **8** were not very selective with either Lewis acid (entries 5 and 6).

We have recently designed a novel class of modular ligands in which a fluxional group provides face selectivity.[13] Two ligands with a benzyl and a naphthylmethyl group in combination with zinc triflimide were evaluated in isopropyl radical addition to **1** (Scheme 3). The results from these experiments were very rewarding providing good to excellent selectivity for **2** depending on the size of the fluxional group. This was the only other class of ligands that gave good selectivity with triflimides.

In conclusion we have shown that metal triflimides are excellent Lewis acids in conjugate radical additions. The triflimide salts are equally effective as the perchlorates in terms of chemical efficiency as well as enantioselectivity and this fact combined with their stability, solubility in non-polar solvents, and ease of preparation make them ideal reagents for chiral catalysis. The use of these salts in other enantioselective transformations is underway in our laboratory.

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   Iron(II) bis-triflimide. To a solution of bistrifluoromethanesulfonimide (1.72 g, 6.12 mmol) in 10.0 mL deionized water, iron powder (0.86 g, 15.4 mmol) was added, and the resulting mixture was refluxed for 3 days. The reaction mixture was cooled, filtered, water was removed in vacuum to furnish a solid. The solid was dried under vacuum at 150°C for 20 h to give 1.27 g (67%) of iron(II) bis-triflimide. Anal. calcd for $C_4F_{12}FeN_2O_8S_4$: C, 7.80; N, 4.55. Found: C, 7.37; N, 4.71.

   Zinc(II) bis-triflimide. Zinc powder (0.23 g, 3.52 mmol) was added to a solution of bistrifluoromethanesulfonimide (1.51 g, 5.39 mmol) in 9.0 mL of deionized water, and the resulting mixture was stirred at room temperature for 4 h. The mixture was filtered to remove excess zinc. The water was removed in vacuum and the crude was dried under vacuum at 150°C for 7 h to give 0.84 g (50%) of zinc(II) bis-triflimide.
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