Asymmetric Catalysis

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Highly Enantioselective Direct Michael Addition of Nitroalkanes to Nitroolefins Catalyzed by La(OTf)$_3$/*N*,*N*′-Dioxide Complexes**

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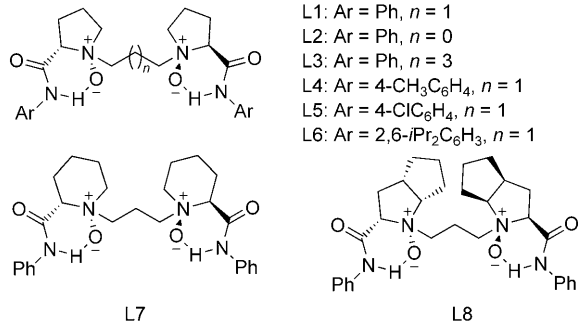
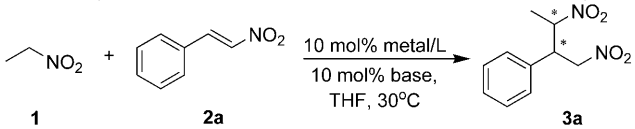
The conjugate addition of carbon nucleophiles to nitroalkenes[1,2] is an important synthetic process in organic synthesis mainly because of the large range of subsequent possible transformations of the nitro group.[3,4] The generation of optically active 1,3-dinitro compounds[5] is an attractive facet of this research area because they are precursors of enantioenriched 1,3-diamines,[6] which can serve as versatile building blocks for pharmaceutical compounds. However, enantioselective versions of these processes have only just started to emerge. In 2006, Du and co-workers reported the direct asymmetric Michael addition of nitroalkanes to nitroalkenes by using zinc(II)bis(oxazoline) and -bis(thiazoline) complexes as catalysts.[7] Wang et al. showed that a modified cinchona alkaloid was a useful asymmetric catalyst for the synthesis of 1,3-dinitroalkanes.[8] Subsequently, the Maruoka research group revealed that *N*-spiro chiral ammonium bifluorides could efficiently catalyze the asymmetric Michael addition with silyl nitronates.[9] Despite these important contributions, the development of new and efficient asymmetric catalytic systems is still an interesting challenge. *N*,*N*′-Dioxides have been successfully applied as excellent chiral scaffolds in many asymmetric reactions.[10,11] Moreover, the electropositive properties and high coordination ability of lanthanide ions[12] has resulted in them attracting significant attention in organic synthesis.[13] Herein, we describe the direct asymmetric Michael addition of unmodified nitroalkanes to nitroalkenes by using lanthanum(III) triflate in combination with an *N*,*N*′-dioxide ligand.

Initially, *N*,*N*′-dioxide L1 (Scheme 1) was complexed in situ with various metal salts to catalyze the Michael addition in the presence of *i*Pr$_2$NEt.[14] The metal source had a decisive effect on the enantioslectivity of the reaction. As shown in Table 1, the Cu^{I}, In^{III}, and Sc^{III} complexes of *N*,*N*′-dioxides[11] successfully employed in other asymmetric reactions only gave extremely poor results in the Michael reaction (Table 1, entries 1–3). Furthermore, although the Cu^{II} and Ni^{II} complexes showed excellent activating ability for the nitroolefins,[1] their *N*,*N*′-dioxide complexes catalyzed the



Scheme 1. Chiral ligands used in the study.

Table 1: Asymmetric Michael addition of nitroethane to β-nitrostyrene.



1 2a 3a

Entry[a]	Metal	L	Base	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][c]
1	$(CuOTf)_2$·Tol	L1	*i*Pr$_2$NEt	77	73:27	5
2	In(OTf)$_3$	L1	*i*Pr$_2$NEt	5	70:30	10
3	Sc(OTf)$_3$	L1	*i*Pr$_2$NEt	70	76:24	7
4	Cu(OTf)$_2$	L1	*i*Pr$_2$NEt	8	83:17	6
5	[Ni(acac)$_2$]	L1	*i*Pr$_2$NEt	87	45:55	3
6	La(OTf)$_3$	L1	*i*Pr$_2$NEt	55	78:22	77
7	Yb(OTf)$_3$	L1	*i*Pr$_2$NEt	6	49:51	4
8	La(OTf)$_3$	L2	*i*Pr$_2$NEt	28	68:32	29
9	La(OTf)$_3$	L3	*i*Pr$_2$NEt	16	66:34	9
10	La(OTf)$_3$	L4	*i*Pr$_2$NEt	37	82:18	50
11	La(OTf)$_3$	L5	*i*Pr$_2$NEt	15	72:28	39
12	La(OTf)$_3$	L6	*i*Pr$_2$NEt	17	58:42	44
13	La(OTf)$_3$	L7	*i*Pr$_2$NEt	26	73:27	44
14	La(OTf)$_3$	L8	*i*Pr$_2$NEt	27	63:37	19
15	La(OTf)$_3$	L1	Et$_3$N	44	83:17	68
16	La(OTf)$_3$	L1	K_2CO_3	18	76:24	38
17	La(OTf)$_3$	L1	DBU	54	78:22	84
18	La(OTf)$_3$	L1	imidazole	40	87:13	86
19[d]	La(OTf)$_3$	L1	imidazole	52	92:8	92
20[d,e]	La(OTf)$_3$	L1	imidazole	80	93:7	96

[a] Unless noted otherwise, reactions were carried out with β-nitrostyrene (0.2 mmol) and nitroethane (0.4 mmol) at 30 °C under nitrogen in THF (1.0 mL) for 2.5 days. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] The ratio of La(OTf)$_3$/L1/imidazole was 1:1.2:1. [e] CH_2Cl_2 was used. Tf = trifluoromethanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

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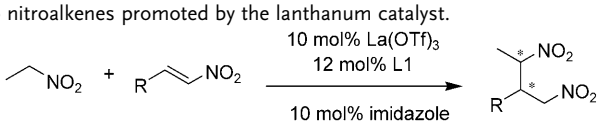
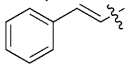
reaction with only low enantioselectivities (Table 1, entries 4 and 5). Fortunately, after a further screening of the potential Lewis acids,[15] the combination of $La(OTf)_3$ with ligand L1 was found to catalyze the Michael addition smoothly and provided the desired product with good enantioselectivity (77% *ee*; Table 1, entry 6). In contrast, the rare earth metal salt $Yb(OTf)_3$ gave low enantioselectivity and reactivity (Table 1, entry 7). The effect of the structure of the *N*,*N*′-dioxide ligands was next examined. The results showed that the linker length in the *N*,*N*′-dioxides had a significant impact on the enantioselectivity of the reaction. Compared with L1, a ligand with a C_2 linkage (L2) led to a significant decrease in the enantioselectivity (29% *ee*; Table 1, entry 8), and a C_5 linkage (L3) exhibited poor asymmetric induction (9% *ee*; Table 1, entry 9). Intensive studies on the amide moiety revealed that ligands bearing electron-donating (Table 1, entry 10) or electron-withdrawing groups (Table 1, entry 11) resulted in lower yields and lower enantioselectivities. Ligand L6, with bulky isopropyl groups, was less efficient and resulted in relatively low levels of enantioselectivity (Table 1, entry 12). Moreover, in regards to the chiral backbone of *N*,*N*′-dioxides, L1 (derived from L-proline) was superior to L7 (derived from L-pipecolic acid) and L8 (derived from L-ramiprol acid) in terms of both diastereo- and enantioselectivity (Table 1, entry 6 versus entries 13 and 14). Further screening of the reaction conditions identified that the base had a significant effect on the formation of adduct **3a** (Table 1, entries 15–20); the best results (80% yield, d.r. 93:7, and 96% *ee*) were obtained with L1/$La(OTf)_3$ (1.2:1) in CH_2Cl_2 and using imidazole as the base.

A series of representative nitroalkenes were investigated under the optimized reaction conditions (Table 2). A variety of nitroalkene substrates proved to be excellent Michael acceptors for this lanthanum(III)-catalyzed reaction, and provided the corresponding products in good to high yields, with good diastereoselectivities (up to d.r. 93:7) and excellent *ee* values (up to 97% *ee*). The aromatic nitroolefins (**2a**–**j**) underwent the Michael reactions to yield the optically active adducts (**3a**–**j**) in excellent yields and 88–97% *ee* regardless of the electronic and steric properties of the substituents. The position of the substituted group on the aromatic nitroolefins only slightly influenced the diastereoselectivity and enantioselectivity of the reaction: 4-methoxy-, 3-methoxy-, and 2-methoxyphenyl-substituted nitroalkenes reacted smoothly with nitroethane to afford the desired 1,3-dinitro compounds with similar diastereo- and enantioselectivities (Table 1, entries 3–5). The reaction of 2,4-dichlorophenyl nitroalkene **2i** provided the product **3i** in 95% *ee* and d.r. 83:17. Condensed-ring nitroalkene **2k** was also found to be an excellent substrate for the reaction, and afforded the desired product **3k** with d.r. 92:8 and 92% *ee* (Table 2, entry 12). Adduct **3l** was obtained in 80% yield and 86% *ee* by the Michael addition of the corresponding furyl-substituted nitroolefin **2l** (Table 2, entry 13). Furthermore, 1-nitro-4-phenylbutadiene (**2m**) was also shown to be an efficient activated alkene, affording the Michael addition product in 85% *ee* (Table 2, entry 14). It is noteworthy that this kind of substrate (**2m**) has never been reported in the Michael addition of a nitroalkane to a nitroalkene. Good enantioselectivity (83% *ee*) was also observed with an isopropyl-substituted nitroolefin, albeit with low yield (Table 2, entry 15).

Table 2: Catalytic asymmetric Michael addition reactions of nitroethane to nitroalkenes promoted by the lanthanum catalyst.



Entry[a]	R	Product	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][c]
1	Ph	**3a**	80	93:7	96 (*R*)[d]
2	4-MeC_6H_4	**3b**	88	88:12	96 (*R*)[d]
3	4-$MeOC_6H_4$	**3c**	89	86:14	93 (*R*)[d]
4	3-$MeOC_6H_4$	**3d**	90	84:16	97
5	2-$MeOC_6H_4$	**3e**	73	73:27	88
6[e]	2-$MeOC_6H_4$	**3e**	78	71:29	90
7	4-BrC_6H_4	**3f**	88	89:11	96
8	3-ClC_6H_4	**3g**	87	86:14	97
9	2-ClC_6H_4	**3h**	77	85:15	96
10	2,4-$Cl_2C_6H_3$	**3i**	79	83:17	95
11	2-$NO_2C_6H_4$	**3j**	70	76:24	96
12	2-naphthyl	**3k**	71	92:8	92 (*R*)[d]
13	2-furyl	**3l**	80	81:19	86 (*R*)[d]
14		**3m**	79	81:19	85
15[f]	*i*Pr	**3n**	22	78:22	83

[a] Unless noted otherwise, reactions were carried out with nitroalkane (0.4 mmol), β-nitrostyrene (0.2 mmol), L1 (12 mol%), $La(OTf)_3$ (10 mol%), and imidazole (10 mol%) in CH_2Cl_2 (1 mL) at 30°C for 2.5 days. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] The absolute configurations were determined by comparison with literature data.[7] [e] $CHCl_3$ (1 mL) was used. [f] Performed with nitroethane (0.4 mL), isopropyl-substituted nitroalkene (0.5 mmol), L1 (12 mol%), $La(OTf)_3$ (10 mol%), imidazole (10 mol%) in $CHCl_3$ (0.5 mL) at 30°C for 2.5 days.

Furthermore, treatment of nitropropane (**4**) with 10 mol% of the lanthanum complex of L1 and 10 mol% imidazole at 30°C resulted in a highly diastereo- and enantioselective Michael addition to generate 1,3-dinitroalkane **5** in d.r. 92:8 and 95% *ee* (Scheme 2). Significantly, these 1,3-dinitro compounds with two contiguous stereocenters can be readily transformed by reduction into the corresponding 1,3-diamines,[7,9] which are versatile components not only as chiral ligands in asymmetric catalysis but also as biologically important compounds such as cisplatin derivatives.[6]

In summary, we have developed a highly efficient catalytic enantioselective conjugate addition of nitroalkanes to nitroalkenes by using a novel chiral $La(OTf)_3$/*N*,*N*′-dioxide complex. This process provides various 1,3-dinitro compounds bearing two stereocenters in high diastereo- (up to d.r. 93:7)

Scheme 2. Asymmetric Michael addition of 1-nitropropane to β-nitrostyrene.

and enantioselectivity (up to 97% *ee*) under mild conditions. These Michael adducts are versatile chiral intermediates by virtue of the range of subsequent transformations possible with the nitro group. Further investigation on the mechanism of this catalytic system is in progress.

Experimental Section

Typical experimental procedure: A mixture of L1 (12 mol%) and $La(OTf)_3$ (10 mol%) was stirred in CH_2Cl_2 at 30°C under N_2 for 30 min to form the catalyst. The nitroalkane (0.4 mmol), imidazole (0.02 mmol), and the β-nitrostyrene (0.2 mmol) were then added sequentially, and the reaction was stirred at 30°C for 2.5 days. The *syn* and *anti* mixtures of products were isolated by column chromatography on silica gel (ethyl acetate/petroleum ether 1:4–1:9). After HPLC analysis, the pure *syn* diastereoisomers were obtained by another column chromatographic separation on silica gel (ethyl acetate/petroleum ether 1:4–1:9) and then the pure *syn* products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, as well as by the optical rotation and melting points.

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[15] Rare earth metal salts were found to coordinate effectively with the *N,N′*-dioxides and showed excellent ability to activate electrophiles.

