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Asymmetric Michael Addition of Nitroalkanes to Nitroalkenes Catalyzed by C_2-Symmetric Tridentate Bis(oxazoline) and Bis(thiazoline) Zinc Complexes

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In carbon−carbon bond formation reactions, the use of nitroalkanes as a source of stabilized carbanions[1] and the use of nitroalkenes as Michael acceptors[2] have attracted significant interest in recent years. Because of the activating effect of the nitro group, as well as its facile transformation to a legion of diverse functionality, nitro compounds have been useful in the synthesis of complex molecules.[3] The conjugate addition of nitroalkanes to nitroalkenes is particularly interesting because the reaction products (1,3-dinitro compounds) are precursors of a variety of other 1,3-difunctionalized compounds, heterocycles,[4] carbohydrate derivatives,[5] and potentially active energetic materials.[6] However, to our best knowledge, no studies on the catalytic asymmetric synthesis of optically active 1,3-dinitro compounds have appeared.[7]

Our laboratory has demonstrated a family of chiral C_2-symmetric tridentate bis(oxazoline) **1**[8] and bis(thiazoline) **2** ligands (Figure 1) for Lewis acid-catalyzed Henry reaction of nitromethane with α-keto esters.[9] In this reaction, a dinuclear zinc catalyst is proposed to activate α-keto esters and to orient nitromethane simultaneously.[9b] Intrigued by the dinuclear zinc catalysts,[9b,10] we investigated their activities in the Michael addition. Herein, we report the first asymmetric synthesis of 1,3-dinitro compounds through the catalytic Michael addition of nitroalkanes to nitroalkenes. High enantioselectivities (up to 95% ee) are achieved.

Our initial exploratory efforts involved screening of ligands **1** and **2** for the addition of β-nitrostyrene in neat nitroethane, using 20 mol % catalyst for 5 days. The major Michael adduct was assigned to be *syn* according to the literature.[7a] However, even in the best case (ligand **2c**), results were unsatisfactory (44% yield, 11.0:1 *syn*:*anti*, 69% ee). We hypothesized that addition of a less polar solvent might help to desolvate the carbanionic intermediate and thus alter its reactivity. Thus, we added nonpolar solvents to the system and added $Ti(O^iPr)_4$ to activate Et_2Zn. Fortunately, both the yield and enantioselectivity were improved significantly (Table 1). These results indicate that bis(oxazoline) and bis(thiazoline) ligands show similar enantiofacial selectivity. Ligand **1e** showed excellent diastereoselectivity with very low yield possibly due to bulky *tert*-butyl groups near the reactive center (entry 5). Ligands **1c** (entry 3) and **2c** (entry 6) bearing phenyl substituents provided significantly better enantioselectivity (up to 95% ee) than alkyl-substituted ligands. Ligand **1c** appeared to give higher performance than ligand **2c** in both substrate conversion (96% vs 74%) and product yield (82% vs 54%).

We therefore selected ligand **1c** to further optimize the reaction conditions. Preliminary investigations suggest that the reaction is optimally performed at or near room temperature (entries 3, 8, and 9). On one hand, high temperature might accelerate the side reaction of β-nitrostyrene, such as dimerization and polymerization, reducing the yield of the desired product (entry 8). On the other hand, lower temperature decelerated the Michael addition significantly even

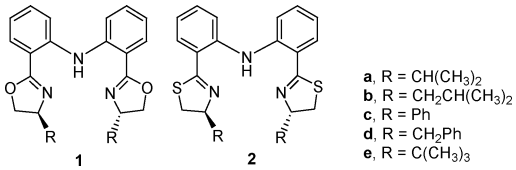
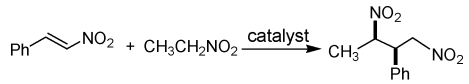


Figure 1. C_2-Symmetric tridentate bis(oxazoline)s and bis(thiazoline)s.

Table 1. Asymmetric Catalytic Addition of Nitroethane to β-Nitrostyrene[a]



3a 4a

entry	ligand	*T* (°C)	conv (%)	yield[b] (%)	dr[c] (*syn*:*anti*)	ee%[d] (*syn*)
1	**1a**	rt	52	43	5.8:1	80
2	**1b**	rt	48	44	5.3:1	38
3	**1c**	rt	96	82	6.1:1	91[g]
4	**1d**	rt	46	44	3.8:1	71
5	**1e**	rt	26	21	only *syn*	78
6	**2c**	rt	74	54	11.7:1	95[g]
7	**2e**	rt	11	nd		
8	**1c**	65	80	32	0.7:1	83
9[e]	**1c**	0	50	50	6.2:1	82
10[f]	**1c**	rt	95	83	6.5:1	85

[a] Unless noted otherwise, reactions were carried out with 1 equiv of β-nitrostyrene (0.50 mmol), 4 equiv of nitroethane, 10 mol % ligand, 25 mol % Et_2Zn, and 80 mol % $Ti(O^iPr)_4$ in a mixture of 1.2 mL of toluene and 0.8 mL of hexane for 3 days. [b] Yield isolated after silica gel chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC through the thiourea derivative; see Supporting Information. [e] Reaction performed by using 20 equiv of nitroethane. [f] $Al(O^iPr)_3$ was used instead of $Ti(O^iPr)_4$. [g] After recrystallization from EtOH, the ee could reach >99%.

when the molar ratio of nitroethane to β-nitrostyrene was increased to 20:1. We also tried $Al(O^iPr)_3$ instead of $Ti(O^iPr)_4$ to accelerate the catalytic circulation (entry 10), and comparable result (95% conv, 83% yield, 6.5:1 *syn*:*anti*, 85% ee) was achieved.

Results obtained in the addition of nitroalkanes to a variety of nitroalkenes are summarized in Table 2. The temperature of the reaction using **1c** as the chiral ligand was kept at 30 °C. High enantioselectivities were achieved with a series of substituted phenyl nitroalkenes bearing electron-donating and electron-withdrawing substituents (entries 1−11, 86−95% ee). These substrates afforded acceptable *syn* diastereoselectivity (3.8−11.7:1 *syn*:*anti*). Naphth-2-yl nitroethene **3i** (entries 12 and 13, 3.8−7.4:1 *syn*:*anti*, 88% ee) and fur-2-yl nitroethene **3j** (entry 14, 6.7:1 *syn*:*anti*, 88% ee) afforded good enantioselectivity and provided products with synthetically useful levels of diastereoselectivity, too. Bis(thiazoline) **2c** gave better diastereoselectivity than bis(oxazoline) **1c** in our experiments (entries 2 vs 1, 4 vs 3, 9 vs 8, and 13 vs 12, respectively) but with slightly reduced yields. This asymmetric

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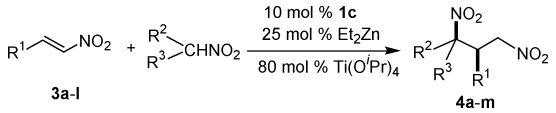
Table 2. Asymmetric Catalytic Addition of Nitroalkanes to Representative Nitroalkenes[a]



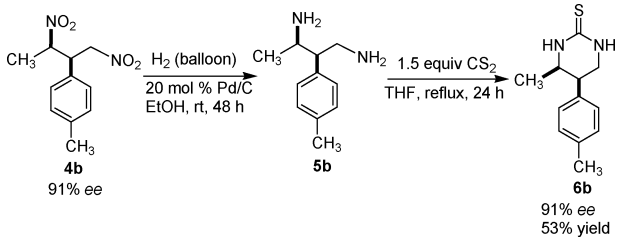
entry	R^1	R^2	R^3	conv (%)	yield[b] (%)	dr[c] (*syn*:*anti*)	product (*syn*)	ee%[d] (*syn*)
1	Ph	Me	H	91	87	5.8:1	**4a**	90
2[e]	Ph	Me	H	74	54	11.7:1	**4a**	95
3	4-MeC_6H_4	Me	H	99	83	6.1:1	**4b**	91
4[e]	4-MeC_6H_4	Me	H	91	75	6.9:1	**4b**	89
5	4-$MeOC_6H_4$	Me	H	92	83	6.5:1	**4c**	89
6	2-$MeOC_6H_4$	Me	H	96	90	5.8:1	**4d**	91
7	3,4-$(MeO)_2C_6H_3$	Me	H	74	67	9.6:1	**4e**	86
8	4-FC_6H_4	Me	H	94	80	3.9:1	**4f**	91
9[e]	4-FC_6H_4	Me	H	93	79	9.3:1	**4f**	92
10	2-FC_6H_4	Me	H	89	87	6.2:1	**4g**	90
11	2-ClC_6H_4	Me	H	87	83	3.8:1	**4h**	91
12	naphth-2-yl	Me	H	92	83	3.8:1	**4i**	88
13[e]	naphth-2-yl	Me	H	85	66	7.4:1	**4i**	88
14	fur-2-yl	Me	H	93	67	6.7:1	**4j**	88
15	4-ClC_6H_4	Me	H	91	68	5.2:1	**4k**	nd[f]
16	$PhCH_2CH_2$	Me	H	95	80	3.4:1	**4l**	72
17	Ph	Et	H	98	88	4.1:1	**4m**	88
18	Ph	Me	Me	10	0			

[a] For reaction conditions, see Table 1 or Supporting Information. [b] Yield isolated after silica gel chromatography. [c] Determined by ^{1}H NMR. [d] Determined by HPLC directly or through thiourea derivatives; see Supporting Information. [e] Ligand **2c** was used instead of **1c**, and the reaction was conducted at room temperature. [f] Enantiomers of **4k** and its thiourea derivative cannot be separated by HPLC.

Michael addition was successfully extended to 2-phenylethyl-substituted nitroalkene **3l**, and 72% ee was obtained (entry 16); however, aliphatic alkyl-substituted nitroalkenes produced mixtures of diastereoisomers that could not be analyzed by ^{1}H NMR spectroscopy. Other normal nitroalkanes can also be used as Michael donors in this addition. The addition of nitromethane to β-nitrostyrene afforded achiral product in 85% yield. The addition of 1-nitropropane to β-nitrostyrene afforded the corresponding *syn* product with 88% ee (entry 17). No addition product was formed using 2-nitropropane as Michael donor (entry 18), which we ascribed to the steric bulk of the 2°-carbon. This steric effect also explains why the nitroalkane product does not compete with the starting nitroalkane for the Michael acceptor. The X-ray diffraction analysis of single crystals obtained from compounds **4f** and **4k** indicates that they both have *syn* relative configuration and (2*R*,3*R*) absolute configuration (see Supporting Information). Thus, we propose by analogy that all the major products had the same stereochemistry. In addition, most *syn* products are solid, which can be easily recrystallized from ethanol and/or methanol to improve their optical purity.

These synthesized 1,3-dinitroalkanes can be further transformed to useful compounds. For example, **4b** (91% ee) was catalytically hydrogenated to the corresponding 1,3-diamine **5b** in almost quantitative yield after evaporation of filtrates. Without further purification, the diamine was refluxed with carbon disulfide in THF to afford chiral cyclic thiourea **6b** in 53% yield without loss of enantioselectivity (Scheme 1). Since bioactivities of 1,3-diamine derivatives have been investigated,[11] enantiopure 1,3-diamines should be valuable synthetic intermediates. In addition, chiral thioureas have attracted attention in recent years due to their anti-HIV activities.[12]

Scheme 1. Derivation of 1,3-Dinitroalkane



Regarding the reaction mechanism, we propose that the tridentate ligand and Et_2Zn form a dinuclear Zn(II) complex.[9b] One zinc atom could activate the nitroalkene through the coordination of the nitro group to the Lewis acid center. Another zinc atom coordinates to the nitro group of nitronate. The Michael addition proceeds by the nucleophilic attack of nitronate on the nitroalkene from the *Re* face (see Supporting Information) to afford the observed stereochemistry. The presence of $Ti(O^iPr)_4$ seems to be crucial for the reaction, and it may activate the Et_2Zn through the formation of an ate complex.

In summary, bis(oxazoline) ligand **1c** and bis(thiazoline) ligand **2c** were found to promote the Zn(II)-catalyzed stereoselective addition of nitroalkanes to a range of nitroalkenes. This new procedure represents an important advance in the chemistry of the nitro group, allowing the catalytic asymmetric synthesis of 1,3-dinitroalkanes with high diastereoselectivity and enantioselectivity. These 1,3-dinitroalkanes can be conveniently transformed to the corresponding enantioenriched 1,3-diamines and cyclic thioureas.

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Supporting Information Available: Experimental procedures, copies of spectra, and the crystal data of **4f** and **4d** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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