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A catalytic asymmetric *anti*-selective nitroaldol reaction with a neodymium–sodium heterobimetallic complex

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Abstract—A catalytic asymmetric *anti*-selective nitroaldol reaction with a neodymium–sodium heterobimetallic catalyst is described. A readily accessible amide ligand works efficiently as a chiral platform for the Nd/Na heterobimetallic catalyst in the reaction of various aldehydes and nitroethane, affording *anti*-1,2-nitro alkanols in good diastereo- and enantioselectivity.

A number of enzymes contain metal cations at the active site, which make a crucial contribution to the extraordinary high catalytic activity and stereoselectivity of the enzyme. Without exception, the enzyme works cooperatively with the neighboring peptide chain and its associated functional groups in a sophisticated spatial arrangement, exhibiting a highly ordered transition state (TS) architecture.[1] In Nature, there are many combinations of diverse peptide chains and metals with distinct coordination modes. Lanthanides, characterized by a variable coordination number ($6 \leqslant CN \leqslant 12$) and geometry, seldom display simple coordination chemistry.[2] Their coordination mode is not predictable and depends largely on the ligand structure.[2] We hypothesized that the combination of a lanthanide and a simple amide ligand with suitable functionality would mimic the highly ordered TS exhibited by enzymes. Although numerous asymmetric catalysts containing lanthanides have been reported, asymmetric catalysis by lanthanide/amide combination has not been well explored.[3] Recently, we reported that a lanthanum/amide complex promoted the catalytic asymmetric amination of a highly coordinative substrate, which could not be addressed by other types of asymmetric catalysts.[4] In our continuing studies of lanthanide/amide chemistry, we aimed to expand the scope of lanthanide/amide complex in asymmetric catalysis.

The catalytic asymmetric nitroaldol (Henry) reaction[5,6] falls in a category of the most efficient carbon–carbon bond forming reactions, in which the optically active 1,2-nitro alkanols are produced through a proton transfer without waste. 1,2-Nitro alkanols have direct access to 1,2-amino alcohols, a common structural motif that frequently occurs in biologically active natural products, pharmaceuticals, and chiral ligands.[7] The obvious synthetic utility of the product has promoted considerable research progress in this field, leading to the development of chiral metal catalysts and organocatalysts to exert the asymmetric nitroaldol reaction.[8] Diastereoselectivity in asymmetric nitroaldol reactions, however, has been less studied and *syn*-selective reactions are sporadically reported.[9] On the other hand, an *anti*-selective asymmetric nitroaldol reaction remains to be developed. Seebach et al. introduced an achiral nitroaldol reaction via a silyl nitronate strategy, providing *anti*-1,2-nitro alkanols in a highly diastereoselective manner.[10,11] Maruoka and co-workers elegantly applied a chiral quaternary ammonium bifluoride catalyst to silyl nitronate chemistry to obtain *anti*-1,2-nitro alkanols with high diastereo- and enantioselectivity.[12] Another example of this strategy was reported by Jørgensen and co-workers using a Cu-Box catalyst with moderate enantioselectivity.[13] A catalytic asymmetric *anti*-selective nitroaldol reaction through proton transfer, an ideal form of the reaction in terms of atom-economy,[14] remains to be developed.[15] Quite recently, Ooi and co-workers revealed that chiral *P*-spiro triaminoiminophosphorane is an effective catalyst for the *anti*-selective catalytic asymmetric nitroaldol reaction.[16] In this context, the catalytic asymmetric *anti*-selective nitroaldol reaction

Keywords: Nitroaldol (Henry) reaction; Neodymium; Heterobimetallic catalyst; Asymmetric catalysis.
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is still an intriguing objective to be addressed. Herein, we report the catalytic asymmetric *anti*-selective nitroaldol reaction with a newly developed heterobimetallic catalyst composed of a neodymium/sodium/amide ligand.

On the basis of TS model, an extended TS affords *anti* diastereomers whereas a cyclic TS affords the syn counterparts (Fig. 1).[17] The extended TS is favored in the reaction using silyl nitronates likely due to the preferential antiparallel orientation of nitronates and aldehydes.[10,18] In contrast, the reaction with metal catalysts tends to proceed through the cyclic TS via chelate formation, thereby predominantly affording syn diastereomers. We hypothesized that a heterobimetallic catalyst with an appropriate chiral platform would provide a suitable environment for the extended TS, where each metal works independently as a Lewis acid for the aldehyde and as a Brønsted base for the nitronate formation, overriding the undesirable chelate formation. Our initial focus was devoted to the combination of a lanthanide metal as a Lewis acid and alkaline metal as a Brønsted base part,[19] which are assembled with amide ligand **1a** derived from L-Val.[20] A bimetallic catalyst prepared from **1a**, $Ln(O^iPr)_3$ (Ln = lanthanides), and NaHMDS in a ratio of 2/1/1 was evaluated in the nitroaldol reaction of benzaldehyde (**2a**) and nitroethane in THF at −40 °C (Table 1). As we anticipated, the present catalytic system displayed *anti*-diastereoselectivity. Among the lanthanides examined, Nd gave the highest diastereoselectivity (*anti*/*syn* = 85:15), although the enantiomeric excess was not satisfactory (entry 3). Using another alkaline metal or performing the reaction without an alkaline metal resulted in inferior diastereoselectivity (entries 9–11), suggesting that the Ln/Na heterobimetallic catalyst would be preferred to form the extended TS. Increasing the amount of NaHMDS (Nd/Na = 1/2) significantly enhanced the catalytic activity, affording the product in 96% yield with comparable stereoselectivity (entry 12). The addition of 1 equiv of H_2O to the complex proved to be beneficial for further improvement of stereoselectivity, affording **3a** in 83% yield with *anti*/*syn* = 91:9 and 43% ee (*anti*) (entry 13).

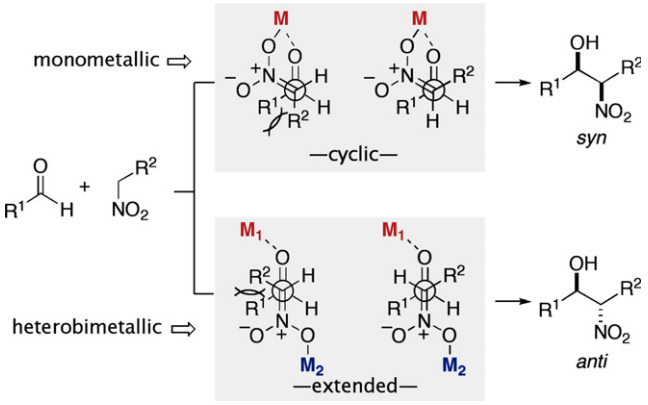
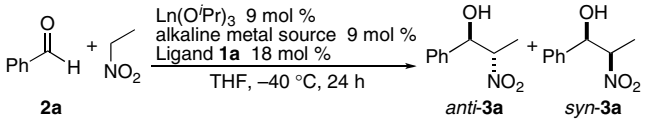


Figure 1. TS models of metal-catalyzed nitroaldol reaction.

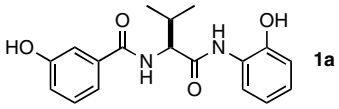
Next, our efforts were directed toward the modification of the amide ligand structure. The effect of an amino

Table 1. Catalytic asymmetric *anti*-selective nitroaldol reaction with Ln/Na/**1a** heterobimetallic complex[a]



2a *anti*-**3a** *syn*-**3a**

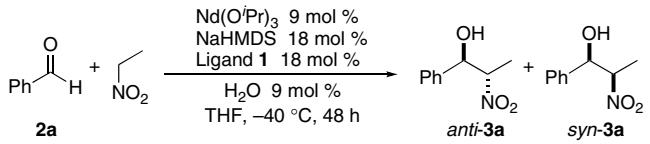
Entry	Ln	Alkaline metal source	H_2O (mol %)	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee (*anti*) (%)
1	La	NaHMDS	—	48	72/28	−4
2	Pr	NaHMDS	—	23	70/30	15
3	Nd	NaHMDS	—	36	85/15	35
4	Sm	NaHMDS	—	16	73/27	20
5	Eu	NaHMDS	—	15	74/26	22
6	Gd	NaHMDS	—	9	71/29	15
7	Dy	NaHMDS	—	15	69/31	4
8	Yb	NaHMDS	—	23	64/36	−29
9	Nd	^{n}BuLi	—	10	68/32	0
10	Nd	KHMDS	—	73	67/33	0
11	Nd	—	—	1	57/43	0
12[d]	Nd	NaHMDS	—	96	85/15	38
13[d]	Nd	NaHMDS	9	83	91/9	43



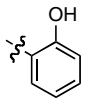
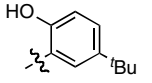
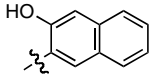
1a

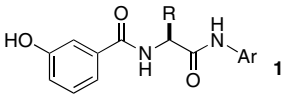
[a] Aldehyde 0.1 mmol, nitroethane 1.0 mmol.
[b] Determined by ^{1}H NMR analysis with $(Me_3Si)_2O$ as internal standard.
[c] Determined by ^{1}H NMR analysis.
[d] $Nd(O^iPr)_3$/NaHMDS/**1a** = 1/2/2, Nd = 9 mol %.

Table 2. Catalytic asymmetric *anti*-selective nitroaldol reaction with Nd/Na/**1a** heterobimetallic complex[a]



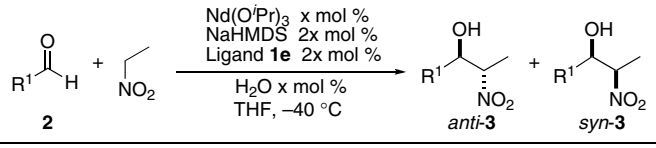
2a

Entry	Ligand	[R	Ar]	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee (*anti*) (%)
1	**1a**	^{i}Pr		43	91/9	43
2	**1b**	*c*Hex		79	85/15	43
3	**1c**	(*S*)-2-butyl		80	67/33	24
4	**1d**	Bn		83	85/15	32
5	**1e**	^{i}Bu		85	92/8	59
6[d,e]	**1f**	^{i}Pr		43	75/25	17
7[d]	**1g**	^{i}Pr		72	89/11	46
8	**1h**	^{i}Bu		82	89/11	51

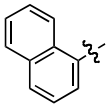
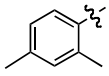
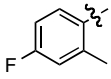
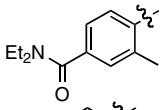
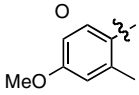
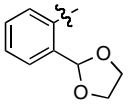

1

[a] Aldehyde 0.1 mmol, nitroethane 1.0 mmol.
[b] Determined by ^{1}H NMR analysis with $(Me_3Si)_2O$ as internal standard.
[c] Determined by ^{1}H NMR analysis.
[d] 18 mol % of H_2O was used.
[e] 9 mol % of NaHMDS was used.

Table 3. Catalytic asymmetric *anti*-selective nitroaldol reaction with Nd/Na/**1e** heterobimetallic complex[a]



2

Entry	R^1		*x*=	Product	Time (h)	Yield[b] (%)	dr[d] (*anti*/*syn*)	ee (*anti*) (%)
1	Ph	**2a**	9	**3a**	48	85	92/8	59
2	Ph	**2a**	3	**3a**	48	93[c]	90/10	57
3		**2b**	3	**3b**	48	91	96/4	80
4		**2b**	3	**3b**	48	93	98/2	84
5		**2c**	3	**3c**	48	90	98/2	84
6		**2d**	3	**3d**	48	67	97/3	79
7		**2e**	3	**3e**	17	74	96/4	76
8		**2f**	9	**3f**	48	63	98/2	81
9		**2g**	3	**3g**	48	99[c]	88/12	65

[a] Aldehyde 0.3 mmol, nitroethane 3.0 mmol.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis with $(Me_3Si)_2O$ as internal standard.
[d] Determined by ^{1}H NMR analysis.

acid residue and an aminophenol part on the stereochemical outcome was examined (Table 2). Bulkier substituents on the amino acid residue gave product **3a** in lower stereoselectivity (entries 2–4), presumably because the formation of polymetallic assembly was encumbered and higher fraction of the reaction would proceed through the chelated cyclic TS. Ligand **1e** derived from L-Leu performed best, affording **3a** in 85% yield with *anti*/*syn* = 92:8 and 59% ee (*anti*) (entry 5). Manipulations of the aminophenol part had less impact on stereoselectivity, implying that the amino acid residue is important for constructing a suitable chiral platform for the present bimetallic system (entries 6–8).

The optimized reaction conditions were evaluated with a variety of aldehydes (Table 3). The reaction reached completion with 3 mol % of catalyst loading without any detrimental effects (entries 1 and 2). *o*-Alkyl substituents on the aromatic ring of aldehyde enhanced both diastereo- and enantioselectivity, exhibiting nearly exclusive formation of *anti*-diastereomers with 76–84% ee (entries 3–8). The reaction of aldehyde with electron-withdrawing diethylaminocarbonyl group proceeded smoothly (entry 7), whereas the sluggish reactions were observed in the reaction of aldehyde with *p*-fluoro or *p*-methoxy substituent (entries 6 and 8).

In summary, we developed a catalytic asymmetric *anti*-selective nitroaldol reaction using a newly developed Nd/Na/amide heterobimetallic catalyst to afford *anti*-1,2-nitro alkanols, providing a facile entry to *anti*-1,2-amino alcohols with significant synthetic versatility. The catalyst worked particularly well in the reaction of aromatic aldehydes with an *o*-alkyl substituent and exhibits high diastereo- (*anti*/*syn* = 96:4–98:2) and enantioselectivity (76–84% ee (*anti*)) with 3 mol % catalyst loading. Investigations into the structure of the heterobimetallic catalyst and further improvement of enantioselectivity as well as substrate generality are currently underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.055.

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20. Ligand **1** was prepared from the corresponding amino acids, see Supplementary data.