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anti-Selective Asymmetric Henry Reaction Catalyzed by a Heterobimetallic Cu–Sm–Aminophenol Sulfonamide Complex

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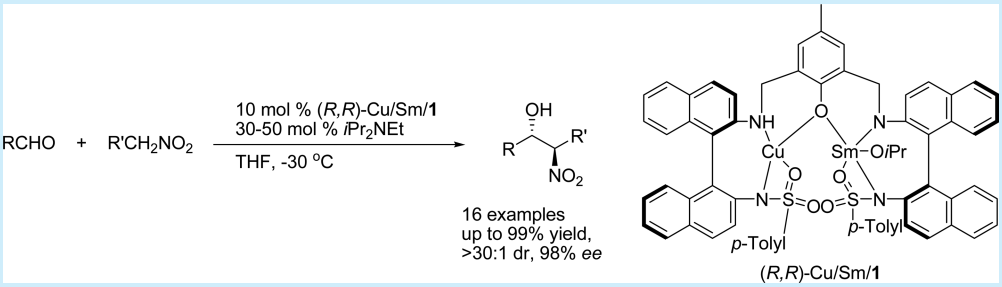
Supporting Information



ABSTRACT: A novel heterobimetallic Cu/Sm/aminophenol sulfonamide complex has been developed by a convenient one-pot method for the *anti*-selective asymmetric Henry reaction. The corresponding *anti*-*β*-nitro alcohols are obtained in up to 99% yield, >30:1 dr, and 98% ee. The results of control experiments and ESI-MS analysis of the complex indicate that the monomeric bimetallic Cu/Sm/**1** complex would be the active species.

Optically active *β*-nitro alcohols are key intermediates and building blocks for the synthesis of bioactive natural products and pharmaceutical agents.[1] The catalytic asymmetric Henry reaction is a useful, atom-economical, step-economical, carbon–carbon bond-forming reaction that affords enantiomerically enriched *β*-nitro alcohols.[2] Since the pioneering application of Shibasaki's heterometallic catalyst[3,4] in the Henry reaction, increasing efforts have been directed toward developing novel catalytic systems. A series of metal complexes, especially dinuclear metal complexes (such as Shibasaki's heterobimetallic Cu/Sm,[4g,h] Pd/La,[6c,d] and Nd/Na[6e,m−o] complexes, Trost's dinuclear Zn complex,[4l,o] Hong's self-assembled dinuclear Co complex,[5m] and Savoia's dinuclear Cu complex[5n] for Henry reaction or related aza-Henry reaction), as well as organocatalysts, were developed for the catalytic asymmetric Henry reaction.[5] However, diastereo- and enantioselective Henry reactions between aldehydes and nitroethane or other nitroalkanes are more challenging for low reactivity and poor selectivity.[6] Although great progress has been achieved, developing new catalysts for the diastereoselective and enantioselective Henry reaction of aldehydes with nitroethane is still necessary. Herein, we report a novel heterobimetallic Cu/Sm/**1** complex (Scheme 1) generated in one pot for the *anti*-selective Henry reaction.

We recently reported an asymmetric Henry reaction with nitromethane as a donor promoted by a dinuclear nickel complex.[5o] This catalytic system was not suitable for nitroethane or other nitroalkanes. Therefore, a series of aminophenol sulfonamide ligands derived from chiral diamine were screened for this conversion, and we found that **1** was a promising candidate. The initial results of metal screening are summarized in Table 1. The combination of $Cu(OAc)_2$ and $Sm(O\text{-}iPr)_3$ with **1** afforded the corresponding product **4aa** in 90% yield with 14:1 *anti*/*syn* and 93% ee (entry 1, Table 1). Neither $Cu(OAc)_2$ nor $Sm(O\text{-}iPr)_3$ alone gave good results (entries 2–5, Table 1).

The 1:1:1 ratio of $Cu(OAc)_2/Sm(O\text{-}iPr)_3$/**1** was also critical for good selectivity (entry 1 vs entries 6 and 7, Table 1). In the current catalytic system, $Cu(OAc)_2$ and $Sm(O\text{-}iPr)_3$, as well as the 1:1:1 ratio of Cu/Sm/**1**, were essential for good reactivity and selectivity.

To gain some insight into the complex, ESI-MS (electrospray ionization mass spectroscopy) studies were carried out.[7] The spectrum of the 1:1:1 Cu/Sm/**1** mixture with the additive iPr_2NEt displayed ions at *m*/*z* 1131.43 and 1279.42, which corresponded to Cu_2/**1** and Cu/Sm/**1**. As the corresponding complexes between $Cu(OAc)_2$ and **1** could not catalyze this reaction even in the presence of 30 mol % of iPr_2NEt (entries 2 and 3, Table 1), we speculated that the 1:1:1 Cu/Sm/**1** complex (Scheme 1) would be the active species.[8,9]

It is worth mentioning that the addition order of $Cu(OAc)_2$ and $Sm(O\text{-}iPr)_3$ could hardly affect the ee values of the *anti*-product (entries 1, 8, and 9, Table 1), whereas an inferior yield and dr were observed when reversing the addition order of $Cu(OAc)_2$ and $Sm(O\text{-}iPr)_3$ (entry 9 vs entries 1 and 8, Table 1). We speculated that the resulting active species by the stepwise method and the one-pot method were the same. So we chose the

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Scheme 1. Aminophenol Sulfonamide Ligand 1 and the Proposed Structure of the Heterobimetallic Cu/Sm/1 Complex

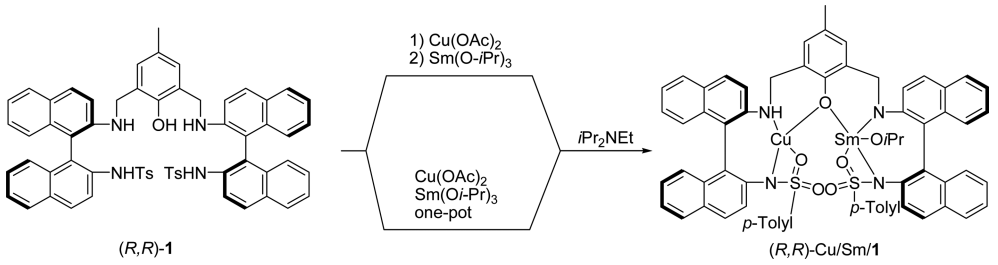
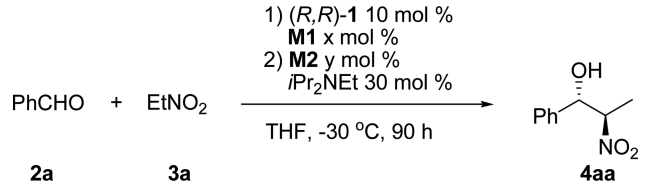


Table 1. Screening of Metal Salts[a,b]

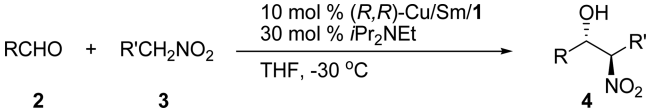


2a 3a 4aa

entry	M1	M2	yield (%)[c]	*anti*/*syn*[d]	ee (%)[e] (*anti*)
1	$Cu(OAc)_2$ (10 mol %)	$Sm(O\text{-}iPr)_3$ (10 mol %)	90	14:1	93
2	$Cu(OAc)_2$ (10 mol %)	none	nr[f]		
3	$Cu(OAc)_2$ (20 mol %)	none	nr[f]		
4	$Sm(O\text{-}iPr)_3$ (10 mol %)	none	23	2:1	0
5	$Sm(O\text{-}iPr)_3$ (20 mol %)	none	89	2:1	0
6	$Cu(OAc)_2$ (10 mol %)	$Sm(O\text{-}iPr)_3$ (20 mol %)	90	6:1	87
7	$Cu(OAc)_2$ (20 mol %)	$Sm(O\text{-}iPr)_3$ (10 mol %)	56	11:1	91
8[g]	$Cu(OAc)_2$ (10 mol %)	$Sm(O\text{-}iPr)_3$ (10 mol %)	90	14:1	93
9	$Sm(O\text{-}iPr)_3$ (10 mol %)	$Cu(OAc)_2$ (10 mol %)	80	11:1	94

[a]Reactions were carried out on a 0.2 mmol scale (benzaldehyde) with nitroethane (0.2 mL) in THF (0.9 mL) in the presence of **1** (10 mol %), **M1** (*x* mol %), and **M2** (*y* mol %) at −30 °C for 90 h. [b]Unless otherwise noted, the catalyst was prepared as follows: **1** and **M1** were stirred in THF at 35 °C for 1 h to generate the precatalyst; **M2** was added to the precatalyst in THF, and stirring was continued for another 1 h to generate the catalyst. For details, see Supporting Information. [c]Isolated yield. [d]Determined by chiral HPLC analysis (Chiralpak AD-H). [e]Determined by chiral HPLC analysis (Chiralpak AD-H) for the *anti*-product. [f]No reaction. [g]**1**, **M1**, and **M2** were added in one pot.

Table 2. *anti*-Selective Henry Reactions with Various Aldehydes and Nitroalkanes[a]



2 3 4

entry	R	2	R′	3	product	time (h)	yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	Ph	**2a**	CH_3	**3a**	**4aa**	90	90	14:1	93
2	$2\text{-}NO_2C_6H_4$	**2b**	CH_3	**3a**	**4ba**	121	99	>30:1	96
3	$4\text{-}F_3CC_6H_4$	**2c**	CH_3	**3a**	**4ca**	87	99	11:1	92
4	$4\text{-}FC_6H_4$	**2d**	CH_3	**3a**	**4da**	140	99	14:1	92
5	$2\text{-}MeC_6H_4$	**2e**	CH_3	**3a**	**4ea**	115	68	16:1	89
6	$3\text{-}MeC_6H_4$	**2f**	CH_3	**3a**	**4fa**	115	98	24:1	96
7	$4\text{-}MeC_6H_4$	**2g**	CH_3	**3a**	**4ga**	115	77	12:1	94
8	2-furyl	**2h**	CH_3	**3a**	**4ha**	162	96	20:1	94
9	5-Br-2-furyl	**2i**	CH_3	**3a**	**4ia**	116	99	24:1	94
10	PhCH=CH	**2j**	CH_3	**3a**	**4ja**	112	97	>30:1	98
11[e]	$4\text{-}MeOC_6H_4$	**2k**	CH_3	**3a**	**4ka**	162	68	11:1	92
12[e]	1-naphthyl	**2l**	CH_3	**3a**	**4la**	162	93	24:1	88
13[e]	2-naphthyl	**2m**	CH_3	**3a**	**4ma**	162	99	14:1	92
14[e]	2-thienyl	**2n**	CH_3	**3a**	**4na**	162	78	16:1	95
15[f]	*n*-hexyl	**2o**	CH_3	**3a**	**4oa**	168	54	3:1	85
16[e]	Ph	**2a**	CH_3CH_2	**3b**	**4ab**	168	56	20:1	86

[a]Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale of aldehyde with nitroalkane (0.2 mL) in THF (0.9 mL) in the presence of 10 mol % of Cu/Sm/**1** generated in one pot and 30 mol % of iPr_2NEt at −30 °C. [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy analysis. [d]Determined by chiral HPLC analysis for the *anti*-product. [e]40 mol % of iPr_2NEt was used. [f]50 mol % of iPr_2NEt was used.

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one-pot method to prepare the heterometallic catalyst, which would greatly facilitate the operation.

Next, the substrate scope of the reaction was evaluated, and the results are summarized in Table 2. Aryl aldehydes with either an electron-donating substituent or an electron-withdrawing substituent, as well as heteroaryl aldehydes, afforded the products in high yield, *anti*-selectivity, and ee (entries 2−9, Table 2). The α,β-unsaturated aldehyde **2j** gave product **4ja** with excellent yield, dr, and ee (entry 10, Table 2). For the less reactive aldehydes **2k**−**o**, more $i\mathrm{Pr}_2\mathrm{NEt}$ was required for good conversion (entries 11−15, Table 2). The aliphatic aldehyde **2o** afforded product **2oa** in high ee, albeit with moderate yield and *anti*-selectivity (entry 15, Table 2). Besides, 1-nitropropane was also employed as the nucleophile to react with benzaldehyde. The corresponding product **4ab** was obtained with 20:1 *anti*/*syn* and 86% ee (entry 16, Table 2).

In summary, a highly efficient *anti*-selective catalytic asymmetric Henry reaction has been developed by using a novel heterometallic Cu/Sm/**1** complex generated in one pot. Various *anti*-β-nitro alcohols were obtained in moderate to excellent yields with high to excellent enantioselectivities and moderate to excellent diastereoselectivities. Further investigations are underway in our laboratory for the detailed mechanism[10] and the application of the desired catalyst to other reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00432.

Synthetic procedure for the ligand and complex, catalytic procedure, and NMR, MS, and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(7) For more detailed results of ESI-MS analysis, see Supporting Information.

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(9) For the discussion of the speculated structure of the complex, see Supporting Information.

(10) The proposed working model is described in Supporting Information.

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