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syn-Selective Catalytic Asymmetric Nitro-Mannich Reactions Using a Heterobimetallic Cu−Sm−Schiff Base Complex

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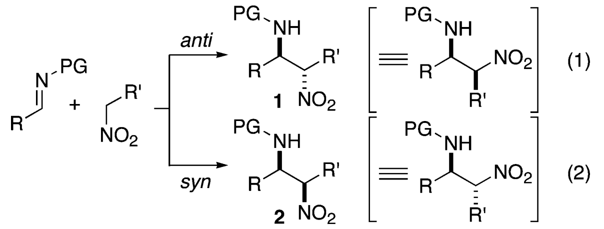
The nitro-Mannich (aza-Henry) reaction provides synthetically versatile β-nitroamines (eqs 1 and 2) that can be converted to 1,2-diamines, α-aminocarbonyl compounds, and others. Tremendous effort has been devoted to develop catalytic enantioselective variants over the past decade.[1] Since our reports using heterobimetallic metal−BINOLate complexes,[2] diastereo- and enantioselective reactions with various nitroalkanes have been realized using metal complexes[2b,3] and organocatalysts,[4] such as thioureas,[4a,b] a chiral proton catalyst,[4c] and cinchona alkaloids.[4d,5] Although those catalysts[2−4] gave *anti*-**1** in good yield and high stereoselectivity (eq 1),[6] there are no reports of a *syn*-selective catalytic asymmetric nitro-Mannich reaction (eq 2).[6] Herein, we report the utility of a heterobimetallic Cu−Sm−Schiff base **3** catalyst to realize a *syn*-selective nitro-Mannich reaction, giving *syn*-**2** in high *syn*-selectivity (>20:1 dr) and enantioselectivity (up to 98% ee). The present system complements the previously reported methods.[2b,3,4]



Scheme 1. Dinucleating Schiff Base Ligand **3** and Proposed Structure of Heterobimetallic Cu/Sm/**3** Complex with ArOH Additive

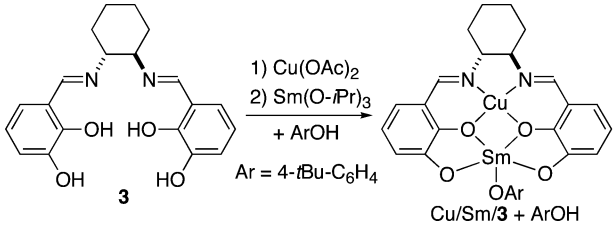
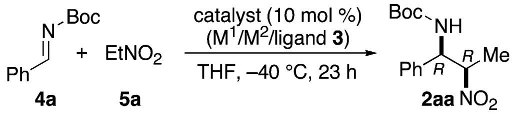


Table 1. Optimization of Reaction Conditions



entry	metal M^{1}[a]	sources M^{2}[b]	M^1/M^2/**3** ratio	additive	yield (%)	dr[c] (*syn/anti*)	% ee (*syn*)
1	Cu(II)	La	1:1:1	none	73	3:1	5
2	Cu(II)	Pr	1:1:1	none	82	1:1	9
3	Cu(II)	Sm	1:1:1	none	96	>20:1	80
4	Cu(II)	Eu	1:1:1	none	93	>20:1	64
5	Cu(II)	Dy	1:1:1	none	89	7:1	48
6	Zn(II)	Sm	1:1:1	none	0	−	−
7	Mg(II)	Sm	1:1:1	none	0	−	−
8	Ni(II)	Sm	1:1:1	none	0	−	−
9	Rh(II)	Sm	1:1:1	none	90	1:3	1[d]
10	Cu(II)	−	1:0:1	none	0	−	−
11	Cu(II)	−	1:0:1	*i*Pr$_2$NEt[e]	0	−	−
12	Cu(II)	−	1:0:1	*i*Pr$_2$NEt[f]	24	2:1	1[g]
13	−	Sm	0:1:1	none	14	2:1	29[g]
14	Cu(II)	Sm	1:0.5:1	none	14	16:1	3
15	Cu(II)	Sm	1:2:1	none	90	7:1	3
16	Cu(II)	Sm	1:1:1	phenol[h]	81	>20:1	85
17	Cu(II)	Sm	1:1:1	2,6-(*t*Bu)$_2$-phenol[h]	91	>20:1	76
18	Cu(II)	Sm	1:1:1	4-*t*Bu-phenol[h]	96	>20:1	94

[a] M^1(OAc)$_2$ was used. [b] M^2(O-*i*Pr)$_3$ was used. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis. [d] Enantiomeric excess of *anti*-isomer. [e] 20 mol % of *i*Pr$_2$NEt was used. [f] 100 mol % of *i*Pr$_2$NEt was used. [g] (*S*,*S*)-Enantiomer was major. [h] 10 mol % of ArOH was used.

As a part of our continuing project on asymmetric bifunctional catalysis, we developed various heterobimetallic complexes using BINOL derivatives as ligands.[7] None of the metal−BINOLate complexes screened, however, were suitable to realize a *syn*-selective nitro-Mannich reaction. Therefore, we screened other chiral scaffolds that can incorporate two different metals and found that the dinucleating Schiff base ligand **3** (Scheme 1) was a promising candidate.[8] The initial optimization studies with *N*-Boc imine **4a** and nitroethane **5a** are summarized in Table 1.[9,10] The combination of Cu(OAc)$_2$ and La(O-*i*Pr)$_3$ with ligand **3** afforded product **2aa** slightly in favor of the *syn*-isomer (entry 1, *syn/anti* = 3:1), despite poor enantioselectivity (5% ee). Rare earth metals affected both *syn*-selectivity and enantioselectivity (entries 1−5), and Sm(O-*i*Pr)$_3$ gave the best selectivity (entry 3, *syn/anti* = >20:1, 80% ee). Cu(II) was also essential to realize high selectivity and good reactivity (entry 3 vs entries 6−9). Neither Cu(OAc)$_2$ nor Sm(O-*i*Pr)$_3$ alone gave good results (entries 10 and 13). Cu(II)−Lewis acid in the presence of amine base resulted in poor reactivity (entry 11, 20 mol % of amine, 0% yield) and selectivity (entry 12, 1 equiv of amine, 24% yield, 1% ee, *syn/anti* = 2/1), implying the importance of Sm(O-*i*Pr)$_3$. The ratio of Cu/Sm/ligand **3** was also critical for good selectivity (entry 3 vs entries 14 and 15). To further improve the enantioselectivity, achiral additives were screened, and phenol showed positive effects (entry 16, 85% ee). Further screening of phenolic additives revealed that 4-*t*Bu-phenol gave the best results (entries 16−18).[9] Under the optimized conditions, **2aa** was obtained in 96% yield, *syn/anti* = >20:1, and 94% ee (entry 18).

The heterobimetallic Cu/Sm/**3** complex with a 4-*t*Bu-phenol additive was applicable to various *N*-Boc imines (Table 2).[10] Aryl imines with either an electron-donating substituent or an electron-withdrawing substituent, as well as heteroaryl imine **4g**, afforded the products in high *syn*-selectivity and ee (entries 3−7).[11] Readily isomerizable alkyl Boc imine **4h**[12] was also applicable, giving the product in good ee (entry 7). High *syn*-selectivity was also achieved with nitropropane **5b** (entries 9−11). Catalyst loading was successfully reduced to 5 and 2.5 mol % without any loss of stereoselectivity. With 2.5 mol % of catalyst, nitro-Mannich adduct **2aa** was obtained in 99% yield, *syn*:*anti* = >20:1, and 97% ee

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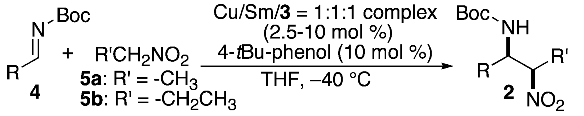
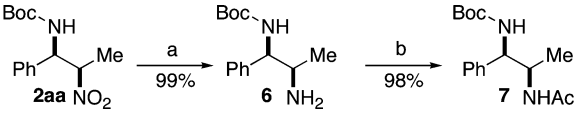
Table 2. *syn*-Selective Catalytic Asymmetric Nitro-Mannich Reactions with Various *N*-Boc Imines **4**[a]



entry	imine (R)	nitroalkane	product	time (h)	yield[b] (%)	dr[c] (*syn*/*anti*)	% ee (*syn*)
1	C_6H_5- (**4a**)	**5a**	**2aa**	23	96	>20:1	94
2[d]	2-naphthyl- (**4b**)	**5a**	**2ba**	48	87	>20:1	93
3	4-Me-C_6H_4- (**4c**)	**5a**	**2ca**	48	90	>20:1	98
4	3-Me-C_6H_4- (**4d**)	**5a**	**2da**	48	77	>20:1	96
5	4-MeO-C_6H_4- (**4e**)	**5a**	**2ea**	48	87	>20:1	94
6	4-Cl-C_6H_4- (**4f**)	**5a**	**2fa**	48	81	>20:1	90
7[d]	2-furyl (**4g**)	**5a**	**2ga**	48	71	>20:1	91
8[d]	$C_6H_5CH_2CH_2$- (**4h**)	**5a**	**2ha**	48	62	>20:1	83
9[d]	C_6H_5- (**4a**)	**5b**	**2ab**	44	84	>20:1	88
10	4-Me-C_6H_4- (**4c**)	**5b**	**2cb**	48	68	>20:1	95
11	4-MeO-C_6H_4- (**4e**)	**5b**	**2eb**	48	64	>20:1	91
12[e]	C_6H_5- (**4a**)	**5a**	**2aa**	44	92	>20:1	96
13[f]	C_6H_5- (**4a**)	**5a**	**2aa**	72	99	>20:1	97

[a] Reaction was performed in THF (0.2 M on imines **4**) at −40 °C using 10 mol % of Cu/Sm/**3** complex and 10 mol % of 4-*t*Bu-phenol unless otherwise noted. [b] Isolated yield. [c] Diastereomeric ratio was determined by ^{1}H NMR analysis. Minor *anti*-isomer was not detected on ^{1}H NMR (>20:1 dr). [d] Reaction was run at −50 °C. [e] 5 mol % of Cu/Sm/**3** complex was used. [f] 2.5 mol % of Cu/Sm/**3** complex and 5 mol % of 4-*t*Bu-phenol were used.

Scheme 2 . Conversion to *syn*-1,2-Diamine[a]



[a] Reagents and conditions: (a) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, 0 °C, 15 min, 99%; (b) Ac_2O, Et_3N, CH_2Cl_2, rt, 30 min, 98%.

(entry 13). To demonstrate the utility of β-nitroamine products, **2aa** was successfully converted into *syn*-1,2-diamine **6** in 99% yield without epimerization using $NaBH_4$ and $NiCl_2$ (Scheme 2).

In the present reaction, both $Cu(OAc)_2$ and Sm(O-*i*Pr)$_3$ were essential for good reactivity and selectivity. The 1:1 ratio of Cu(II) and Sm was also crucial (Table 1),[9] and the addition of 4-*t*Bu-phenol had beneficial effects on enantioselectivity. Sterically hindered 2,6-(*t*Bu)$_2$-phenol was not effective as an additive (Table 1, entry 17), suggesting that 4-*t*Bu-phenol would work not as a simple proton source but as an achiral ligand. In ESI-MS analysis,[13] peaks corresponding to a Cu/Sm/**3** complex trimer and oligomers were observed in the absence of 4-*t*Bu-phenol. With 4-*t*Bu-phenol, a new peak corresponding to a monomeric Cu/Sm/**3** = 1:1:1 complex was observed. On the basis of the ESI-MS analysis, as well as previous reports of related heterobimetallic Cu/rare earth metal/Schiff base complexes,[14] we assumed that a monomeric Cu/Sm/**3**/4-*t*Bu-phenol = 1:1:1:1 complex (Scheme 1) would be the active species. At the moment, we believe that the bimetallic Cu−Sm system, aligned suitably in dinucleating ligand **3**, would play a key role for high stereoselectivity. Further mechanistic studies to clarify the precise role of each metal, reaction mechanism, and origin of *syn*-selectivity are ongoing.[15]

In summary, we achieved *syn*-selective catalytic asymmetric nitro-Mannich reactions using a heterobimetallic Cu/Sm/Schiff base ligand **3**. The present method is complementary to the previously reported methods, and products were obtained in high *syn*-selectivity (>20:1), yield (99−62%), and enantioselectivity (98−83% ee). Both Cu and Sm metals were essential to realize high *syn*-selectivity. Further mechanistic studies as well as applications of the present heterobimetallic catalyst to other asymmetric reactions are in progress.

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Supporting Information Available: Experimental procedures, spectra data of the new compounds, determination of relative and absolute configurations, and ESI-MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For determination of relative and absolute configurations of products in Tables 1 and 2, see Supporting Information.
(11) When using aryl imine with an *ortho*-substituent (R = 2-Me-C_6H_4), the reaction did not proceed cleanly under the present reaction conditions. Product was obtained in low yield (25% yield).
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(15) Postulated reaction mechanism and transition state model for the *syn*-isomer are described in Supporting Information.

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