Asymmetric Catalysis

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Direct *anti*-Selective Catalytic Asymmetric Mannich-Type Reactions of α-Ketoanilides for the Synthesis of γ-Amino Amides and Azetidine-2-amides**

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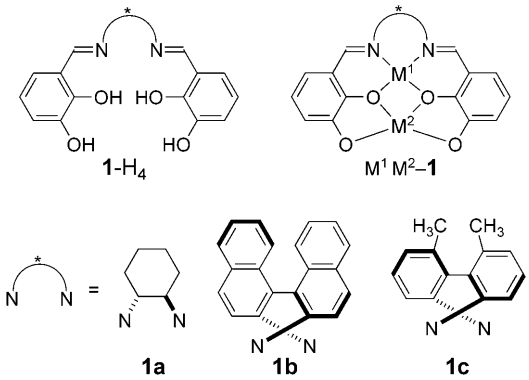
Catalytic asymmetric Mannich(-type) reactions of aldehydes, ketones, esters, and other donors for the synthesis of β-amino carbonyl compounds have been investigated intensively over the past decade.[1,2] In contrast, Mannich-type reactions of homoenolates or their synthetic equivalents for the production of γ-amino acids have not been studied as extensively.[3–6] Recently, Scheidt and co-workers[3a] and Bode and co-workers[3b] reported the enantioselective addition of homoenolate equivalents to nitrones and a ketimine under the catalysis of N-heterocyclic carbenes to afford γ-amino esters with contiguous stereocenters at the β and γ positions. Jørgensen and co-workers reported a *syn*-selective asymmetric direct Mannich-type reaction with α-ketoester donors as homoenolate synthetic equivalents. After the stereoselective reduction of the α-keto unit in the Mannich adduct, a highly functionalized γ-amino ester with three contiguous stereocenters was obtained with excellent enantio- and diastereoselectivity.[4] The method was limited, however, to reactions with an *N*-tosyl α-iminoester. Recently, we also reported *syn*-selective Mannich-type reactions of α-ketoanilide donors with aryl, heteroaryl, and alkyl *N*-thiophenesulfonyl imines in the presence of a heterobimetallic lanthanum aryl oxide/lithium aryl oxide/pyridine-2,6-bisoxazoline (pybox) catalyst.[5] Owing to the stereodiversity of γ-amino acids, a complementary *anti*-selective reaction is in high demand. Herein, we describe an *anti*-selective direct catalytic asymmetric Mannich-type reaction of α-ketoanilide donors and its application to the stereoselective synthesis of γ-amino amides and azetidine-2-amides. A homodinuclear nickel complex prepared from a new biphenyldiamine-based dinucleating Schiff base **1c** (Scheme 1) promoted the reaction of α-ketoanilides **2** with *o*-nitrobenzenesulfonyl (*o*-Ns) imines **3** to afford the products in up to 99% yield with an *anti*/*syn* ratio of more than 50:1 and 95% *ee*.



Scheme 1. Structures of the dinucleating Schiff bases **1a**-H_4, **1b**-H_4, and **1c**-H_4 and dinuclear complexes M^1M^2–**1**.

To develop the *anti*-selective reaction, we initially screened several chiral catalysts for the reaction of the α-ketoanilide **2a** with the *N*-thiophenesulfonyl imine **3a**. These compounds were found to be the best substrates for a previously reported *syn*-selective Mannich-type reaction.[5,7] Among the Lewis acid/Brønsted base bifunctional catalysts[8] developed by our research group for other direct Mannich-type reactions,[9] dinuclear Schiff base complexes[10,11] gave promising results in terms of *anti* selectivity (Table 1). Originally developed for a nitro-Mannich-type reaction,[10a] a heterobimetallic Cu/Sm(OAr) (Ar = 4-*t*BuC_6H_4) complex with the Schiff base **1a** gave the product **4aa** in 93% yield with good *anti* selectivity (*anti*/*syn* = 9.5:1) at −40 °C, but with poor enantioselectivity (1% *ee*; Table 1, entry 1). The homodinuclear complex Ni_2–**1b** that was developed for a Mannich-type reaction of nitroacetates and other active methylene compounds[10c] promoted the reaction at 0 °C to give **4aa** in 88% yield (*anti*/*syn* > 20:1) and with 82% *ee* (Table 1, entry 2). Other homodinuclear complexes of Schiff base **1b** were not suitable for this reaction (Table 1, entries 3–5). The protecting group on the imine affected the *anti* selectivity as well as the enantioselectivity (Table 1, entries 6–11).[12] The *o*-Ns-protected imine[13] **3g** gave the best result: The Ni_2–**1b** complex promoted the reaction of **3g** with α-ketoanilide **2a** to afford the product **4ag** (*anti*/*syn* > 20:1) in 93% yield with 88% *ee* (Table 1, entry 11). Ligand tuning revealed that the new biphenyldiamine-based Schiff base **1c**[14] gave better enantioselectivity (91% *ee*; Table 1, entry 12), possibly as a result of a slight change in the dihedral angle of the biaryl moiety. When the solvent was changed from THF to THF/

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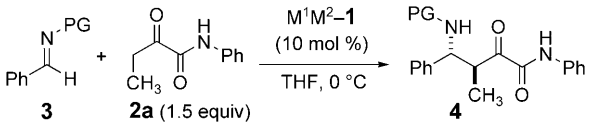
Table 1: Optimization of the *anti*-selective direct catalytic asymmetric Mannich-type reaction with α-ketoanilide **2a**.[a]



Entry	M^1	M^2	Ligand	PG	*t* [h]	Yield[b] [%]	d.r.[b] (*anti*/*syn*)	*ee* (*anti*) [%]
1[c,d]	Cu	Sm(OAr)	**1a**	2-thienyl-SO_2 (**3a**)	62	93	9.5:1	1
2	Ni	Ni	**1b**	2-thienyl-SO_2 (**3a**)	30	88	>20:1	82
3	Co(OAc)	Co(OAc)	**1b**	2-thienyl-SO_2 (**3a**)	44	61	1.3:1	16
4	Cu	Cu	**1b**	2-thienyl-SO_2 (**3a**)	38	0	–	–
5	Zn	Zn	**1b**	2-thienyl-SO_2 (**3a**)	38	0	–	–
6	Ni	Ni	**1b**	Boc (**3b**)	38	messy	–	–
7	Ni	Ni	**1b**	$Ph_2P(O)$ (**3c**)	64	trace	–	–
8	Ni	Ni	**1b**	*p*-Ts (**3d**)	41	62	4.5:1	69
9	Ni	Ni	**1b**	2-pyridyl-SO_2 (**3e**)	53	4	9:1	85
10	Ni	Ni	**1b**	*p*-Ns (**3f**)	36	88	>20:1	79
11	Ni	Ni	**1b**	*o*-Ns (**3g**)	18	93	>20:1	88
12	Ni	Ni	**1c**	*o*-Ns (**3g**)	21	98	>20:1	91
13[e]	Ni	Ni	**1c**	*o*-Ns (**3g**)	25	98	>20:1	93

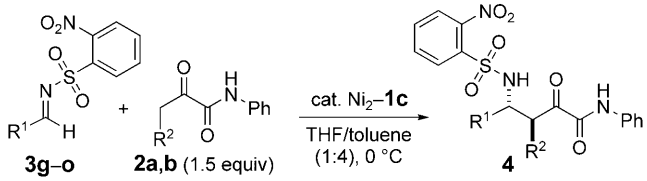
[a] The reaction was performed at 0°C in THF under argon unless otherwise noted. [b] The yield and diastereomeric ratio were determined by ^{1}H NMR spectroscopic analysis. [c] The reaction was carried out at −40°C. [d] Ar = 4-*t*BuC_6H_4. [e] THF/toluene (1:4) was used as the solvent. Boc = *tert*-butoxycarbonyl, Ts = *p*-toluenesulfonyl.

toluene (1:4), **4ag** (*anti*/*syn* > 20:1) was obtained in 98% yield with 93% *ee* (Table 1, entry 13).

The generality and limitations of the reaction were investigated under the optimized reaction conditions (Table 2). The complex Ni_2–**1c** not only catalyzed reactions of the α-ketoanilide **2a**, but also the transformation of **2b** (R^2 = Et): Product **4bg** was obtained in high yield with high *anti* selectivity and high enantioselectivity (94% yield, *anti*/*syn* = 45:1, 92% *ee*; Table 2, entry 2). The nonisomerizable aryl imines **3i**–**m**, with either an electron-withdrawing or an electron-donating substituent on the aromatic ring, gave Mannich adducts in 76–99% yield with at least 29:1 and in some cases greater than 50:1 *anti* selectivity and with 91–95% *ee* (Table 2, entries 4–8). The heteroaryl imine **3n** also gave the desired product **4an** in good yield and with high enantioselectivity (90% yield, 93% *ee*; Table 2, entry 9), albeit with slightly decreased *anti* selectivity (*anti*/*syn* = 15:1). The readily isomerizable alkyl imine **3o** with a 2-thiophenesulfonyl protecting group could also be used: Product **4ao** was formed in 87% yield with an *anti*/*syn* ratio of 10:1 and 91% *ee* (Table 2, entry 10).[15] Good *anti* selectivity and enantioselectivity were maintained when the catalyst loading was decreased to 2.5 mol% (Table 2, entry 11).

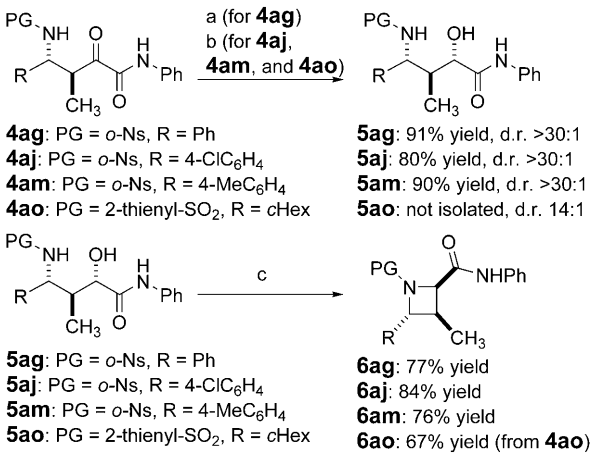
We investigated transformations of the products to demonstrate the synthetic utility of these compounds (Scheme 2). The keto group α to the amide in the Mannich adduct **4ag** was reduced stereoselectively with $LiBHEt_3$ to give the α-hydroxy β-alkyl γ-amino amide **5ag** with three contiguous stereocenters with the relative configuration *anti*–*anti* in 91% yield and with greater than 30:1 diastereoselectivity (Scheme 2). The absolute and relative configuration of **5ag** was determined by X-ray crystallographic analysis (Figure 1).[16] As Ns amides are known to be suitable nucleophiles for Mitsunobu reactions,[13a] we anticipated that compound **5ag** would be a good precursor for a fully substituted azetidine-2-amide: a useful nonnatural amino acid derivative.[17,18] The intramolecular Mitsunobu cyclization proceeded smoothly, and the optically active azetidine-2-amide **6ag** with the *syn*–*anti* configuration was obtained in 77% yield. The Mannich adducts **4aj** and **4am** were converted successfully into the azetidine-2-amides **6aj** and **6am** by a procedure that differed from that used for **4ag** only in the reagent for reduction. Adduct **4ao** with the 2-thiophenesulfonyl protecting group also underwent stereoselective

Table 2: Direct catalytic *anti*-selective asymmetric Mannich-type reaction of *o*-Ns imines **3g**–**o** with α-ketoanilides **2**.



Entry	R^1	R^2	4	Catalyst [mol%]	*t* [h]	Yield[a] [%]	d.r.[b] (*anti*/*syn*)	*ee* (*anti*)[c] [%]
1	Ph (**3g**)	Me (**2a**)	**4ag**	10	24	96	28:1	93
2	Ph (**3g**)	Et (**2b**)	**4bg**	10	40	94	45:1	92
3	2-naphthyl (**3h**)	Me (**2a**)	**4ah**	10	48	85	>50:1	94
4	4-FC_6H_4 (**3i**)	Me (**2a**)	**4ai**	10	24	99	29:1	92
5	4-ClC_6H_4 (**3j**)	Me (**2a**)	**4aj**	10	24	99	48:1	95
6	4-BrC_6H_4 (**3k**)	Me (**2a**)	**4ak**	10	24	99	>50:1	91
7[d]	4-$MeOC_6H_4$ (**3l**)	Me (**2a**)	**4al**	10	48	86	>50:1	93
8	4-MeC_6H_4 (**3m**)	Me (**2a**)	**4am**	10	48	76	>50:1	91
9	3-thienyl (**3n**)	Me (**2a**)	**4an**	10	24	90	15:1	93
10[e]	cyclohexyl (**3o**)	Me (**2a**)	**4ao**	10	48	87	10:1	91
11	4-ClC_6H_4 (**3j**)	Me (**2a**)	**4aj**	2.5	48	99	50:1	94

[a] Yield of the isolated product after column chromatography. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [c] The *ee* value was determined by HPLC analysis on a chiral phase. [d] The reaction was performed in THF/toluene (4:1). [e] The 2-thiophenesulfonyl imine was used, as the synthesis of the aliphatic *o*-Ns imine was not successful.



Scheme 2. Transformation of *anti* Mannich adducts into α-hydroxy γ-amino amides and azetidine-2-amides: a) $LiBHEt_3$, THF, −78 °C, 30 min; b) K-selectride, THF, −78 °C, 2 h; c) diisopropyl azodicarboxylate, PPh_3, THF, 0 °C→RT, 3 h.

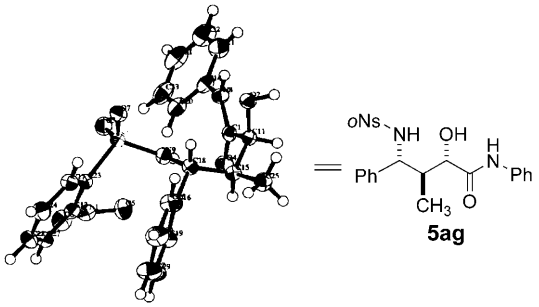


Figure 1. ORTEP plot of the α-hydroxy β-alkyl γ-amino amide **5ag**.

reduction and intramolecular cyclization to give the azetidine-2-amide **6ao** in 67% yield (over the two steps from **4ao**). The present method is synthetically useful; the method reported previously by our research group for *syn–anti* azetidine-2-carboxylic acids gave compounds only in racemic form or in modest optical purity.[18a]

In summary, we have developed an *anti*-selective direct catalytic asymmetric Mannich-type reaction of α-ketoanilide donors as synthetic equivalents of homoenolates. A homodinuclear Ni complex prepared from the new biphenyldiamine-based dinucleating Schiff base **1c** promoted the reaction of α-ketoanilides **2** with *o*-Ns imines **3** to give the products in up to 99% yield, with an *anti*/*syn* ratio often greater than 50:1, and with up to 95% *ee*. Stereoselective reduction of the Mannich adduct afforded α-hydroxy β-alkyl γ-amino amides **5** with three contiguous stereocenters with an *anti–anti* relative configuration. An intramolecular Mitsunobu cyclization then gave optically active azetidine-2-amides **6** with a *syn–anti* configuration. Further investigations to clarify the origin of the *anti* selectivity in the Mannich-type reaction are ongoing.[19]

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[19] At the moment, the reason for the high *anti* selectivity is not clear. We speculate that the cooperative function of two Ni centers may be important, as observed in our previous studies on different reactions with bimetallic Schiff base complexes.[10] Mechanistic studies to clarify the role in the present reaction of the two nickel atoms in the catalyst are ongoing.

