

Chiral γ -Amino Amide Synthesis by Heterobimetallic Lanthanum/Lithium/Pybox-Catalyzed Direct Asymmetric Mannich-Type Reactions of α -Keto Anilides**

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Many excellent direct catalytic enantio- and diastereoselective Mannich(-type) reactions have been reported during the past decade,^[1] providing versatile synthetic methods for optically active β -amino acids and related compounds. In contrast, catalytic enantioselective methods leading to chiral γ -amino acids or their equivalents are limited,^[2–5] despite their importance as key structural motifs in natural products^[6] and in many pharmaceuticals, such as clinically used modulators of neurotransmission.^[7] Previously developed catalytic asymmetric methods for producing γ -amino acids mostly relied on asymmetric 1,4-additions, such as 1,4-additions of glycine Schiff bases for the synthesis of glutamic acid derivatives,^[2] 1,4-additions to nitroolefins,^[3] and 1,4-additions of cyanide for γ -aminobutyric acids synthesis.^[4] Alternatively, organocatalytic γ -amination of α,β -unsaturated aldehydes was accomplished with high enantioselectivity.^[5] To increase the structural diversity of chiral γ -amino acids available, synthesis by a different approach is desirable. A Mannich-type reaction of a homoenolate or its synthetic equivalent is a potentially useful strategy for producing γ -amino acids. Recently, Scheidt and co-workers reported chiral *N*-heterocyclic carbene-catalyzed additions of homoenolate equivalents to nitrones, affording γ -amino esters with two contiguous stereocenters at β - and γ -positions.^[8] Alternatively, Jørgensen and co-workers reported a direct Mannich-type reaction using α -keto ester donors as homoenolate synthetic equivalents.^[9] After stereoselective reduction of the α -keto unit in a Mannich adduct, a highly functionalized γ -aminoester with three contiguous stereocenters was obtained with excellent enantio- and diastereoselectivity.^[9] The method was limited, however, to reactions with a *N*-toluenesulfonyl α -imino ester. Therefore, a new comple-

mentary method to enable the use of imines with various substituents in the synthesis of γ -amino acid derivatives is in high demand. Herein, we describe direct catalytic asymmetric Mannich-type reactions of α -keto anilides **1** with various *N*-thiophenesulfonyl imines **2**. A heterobimetallic lanthanum aryloxide/lithium aryloxide/pybox complex (Figure 1,

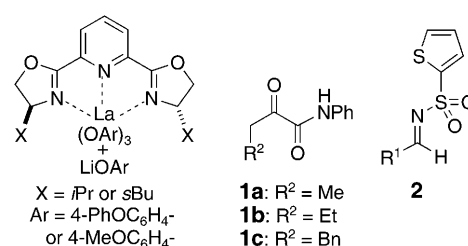


Figure 1. Components of heterobimetallic La(OAr)₃/LiOAr/(*S,S*)-pybox complexes and structures of α -keto anilides **1** and *N*-thiophenesulfonyl imine **2**.

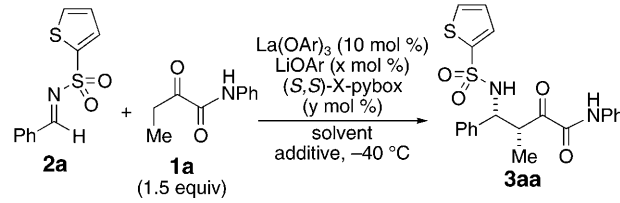
pybox = pyridine bisoxazoline) promoted Mannich-type reactions, giving γ -amino amides in up to > 99 % yield, 95 % *ee*, and > 97:3 *syn*-selectivity. Stereoselective reduction of the α -keto unit in the Mannich-adduct to give a β -alkyl- γ -amino- α -hydroxy amide with three contiguous stereocenters is also described.

Initially, we screened α -keto carboxylic acid derivatives as donors, imines, and several chiral catalysts developed in our group for other direct Mannich-type reactions,^[10] and found the lanthanum aryloxide/pybox complex^[11] to be a promising candidate. The optimization studies are summarized in Table 1.^[12] The La(OAr)₃/*i*Pr-pybox complex (Ar¹ = 4-MeOC₆H₄-), which was previously optimized for the reaction of trichloromethyl ketones, promoted the reaction of α -keto anilide **1a**^[13] with *N*-thiophenesulfonyl imine **2a**,^[14] giving product **3aa** in 97 % yield, but with poor stereoselectivity (Table 1, entry 1, 5 % *ee*). After chiral ligand screening, *s*Bu-pybox was selected for further studies in terms of enantioselectivity (Table 1, entry 2, 36 % *ee*). The addition of a catalytic amount of an achiral base, LiOAr¹, effectively improved the enantioselectivity (Table 1, entries 3–5). The amount of LiOAr¹ was important, and a La(OAr¹)₃/LiOAr¹ ratio of 1:1 was optimal, affording **3aa** in 68 % *ee* (Table 1, entry 4). Screening of the solvent (Table 1, entry 6, AcOEt), structures of aryloxides (Table 1, entry 7, Ar² = 4-PhOC₆H₄-), and molecular sieves (MS, Table 1, entry 8) further improved the results. The structure of the aryloxide affected the diastereoselectivity (Table 1, entry 6, 78:22 vs entry 7, 87:13) and

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Table 1: Optimization of reaction conditions.


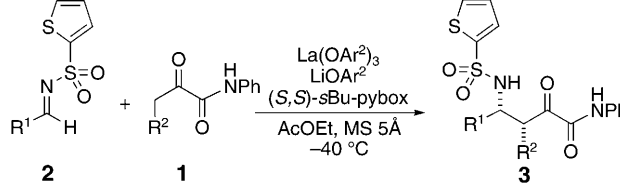
Entry	Ar ^[a]	X	y	x	Additive	t [h]	Yield [%]	syn:anti ^[b]	ee of syn [%]
1 ^[c]	Ar ¹	iPr	15	0	MS 3 Å	24	97	76:24	5
2 ^[c]	Ar ¹	sBu	15	0	MS 3 Å	24	99	81:19	36
3 ^[c]	Ar ¹	sBu	15	5	MS 3 Å	24	97	82:18	61
4 ^[c]	Ar ¹	sBu	15	10	MS 3 Å	24	97	83:17	68
5 ^[c]	Ar ¹	sBu	15	15	MS 3 Å	16	99	84:16	60
6 ^[d]	Ar ¹	sBu	15	10	MS 3 Å	17	95	78:22	75
7 ^[d]	Ar ²	sBu	15	10	MS 3 Å	17	97	87:13	84
8 ^[d]	Ar ²	sBu	15	10	MS 5 Å	17	95	94:6	88
9 ^[d]	Ar ²	sBu	10	10	MS 5 Å	15	98	95:5	90

[a] Ar¹ = 4-MeOC₆H₄-, Ar² = 4-PhOC₆H₄-. [b] Determined by ¹H NMR analysis. [c] THF was used as solvent. [d] AcOEt was used as solvent.

enantioselectivity (Table 1, entry 6, 75% ee vs entry 7, 84% ee). Interestingly, reducing the amount of chiral ligand from 15 mol % to 10 mol % improved the enantioselectivity (Table 1, entry 9, 90% ee).

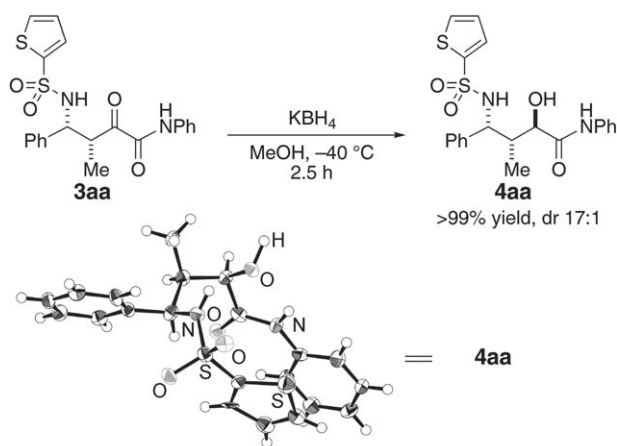
Having identified the optimum reaction conditions, 10 mol % of La(OAr²)₃/LiOAr²/sBu-pybox (1:1:1 mixture, Ar² = 4-PhOC₆H₄-), the scope of the reaction was investigated with a variety of substrates (Table 2).^[15] The present hetero-bimetallic system was applicable not only to α-keto anilide **1a**, but also to other α-keto anilides **1b** (R² = Et) and **1c** (R² = Bn). Products were obtained in high yield and enantioselectivity (Table 2, entry 2, >99% yield, 92% ee; entry 3, >99% yield, 94% ee), but with somewhat decreased syn-

selectivity. Aryl imines **2b–g** afforded products in >99–74% yield, 91–80% ee, and syn/anti >97:3–87:13 (Table 2, entries 4–9). A substituent on the aromatic ring at the *ortho*-position gave higher diastereoselectivity (Table 2, entry 9, >97:3). Heteroaryl imines **2h–j** also afforded products in good yield and enantioselectivity (Table 2, entries 10–13, 95–89% ee). Conversely, when a readily enolizable alkyl imine was used, there remained room for improvement in enantioselectivity (Table 2, entry 14, *n*Bu-imine **2k** gave product **3ka** in 70% ee).^[16] The α-keto moiety in Mannich adduct **3aa** was stereoselectively reduced with KBH₄, giving β-alkyl-γ-amino-α-hydroxy amide **4aa** with three contiguous stereocenters in >99% yield and 17:1 diastereoselectivity (Scheme 1).^[17,18]

Table 2: Direct catalytic asymmetric Mannich-type reaction of aryl, heteroaryl, and alkyl imines **2** with α-keto anilides **1**.^[a]


Entry	R ¹	2	R ²	1	Product	t [h]	Yield ^[b] [%]	syn:anti ^[c]	ee of syn [%]
1	Ph-	2a	Me	1a	3aa	15	98	95:5	90
2	Ph-	2a	Et	1b	3ab	48	> 99	88:12	92
3	Ph-	2a	Bn	1c	3ac	15	> 99	84:16	94
4	2-naphthyl	2b	Bn	1c	3bc	20	98	90:10	91
5	4-F-C ₆ H ₄ -	2c	Me	1a	3ca	14	94	90:10	88
6 ^[d]	4-Cl-C ₆ H ₄ -	2d	Me	1a	3da	16	95	87:13	90
7 ^[e]	4-MeO-C ₆ H ₄ -	2e	Me	1a	3ea	48	74	91:9	80
8 ^[e]	4-Me-C ₆ H ₄ -	2f	Me	1a	3fa	40	95	92:8	85
9 ^[e]	2-Me-C ₆ H ₄ -	2g	Me	1a	3ga	15	> 99	> 97:3	83
10 ^[e]	3-thienyl-	2h	Me	1a	3ha	20	96	90:10	89
11 ^[f]	3-thienyl-	2h	Bn	1c	3hc	19	95	77:23	95
12 ^[e]	2-thienyl-	2i	Me	1a	3ia	38	97	85:15	90
13	2-furyl-	2j	Bn	1c	3jc	20	99	88:12	90
14	<i>n</i> Bu-	2k	Me	1a	3ka	20	66	89:11	70

[a] Reaction was run using 1.5 equiv of **1**, 10 mol % of La(OAr²)₃/LiOAr²/sBu-pybox = 1:1:1 mixture in AcOEt (0.2 M) at -40 °C, unless otherwise noted. Ar² = 4-PhOC₆H₄-. [b] Yield isolated after column chromatography. [c] Determined by ¹H NMR analysis. [d] Reaction was run in AcOEt (0.1 M). [e] Reaction was run in THF. [f] 1.3 equiv of **1c** were used.



Scheme 1. Top: Stereoselective reduction of α -keto moiety in Mannich adduct. Bottom: ORTEP structure of **4aa** (thermal ellipsoids set at 50% probability).

The absolute and relative configuration of **4aa** was determined by X-ray crystallographic analysis.^[15]

In these reactions, the use of a heterobimetallic mixture of lanthanum aryloxide and lithium aryloxide was essential to obtain high stereoselectivity. To gain insight into the heterobimetallic system, we performed several control experiments using α -keto anilide **1a** and imine **2a** (Table 3). Unsatisfactory results were obtained with both the $\text{La}(\text{OAr}^2)_3/\text{sBu-pybox}$ complex in the absence of LiOAr^2 and the $\text{LiOAr}^2/\text{sBu-pybox}$ complex in the absence of $\text{La}(\text{OAr}^2)_3$ (Table 3, entry 2, 94% yield, *syn/anti* = 81:19, 43% *ee*; entry 3, 98% yield, *syn/anti* = 92:8, 12% *ee*). The use of either NaOAr^2 or KOAr^2 instead of LiOAr^2 also resulted in poor stereoselectivity (Table 3, entries 4 and 5), indicating that both La and Li metals were required for high diastereo- and enantioselectivity.^[19] On the basis of the results shown in Table 3, we speculated that a heterobimetallic lanthanum aryloxide/lithium aryloxide/pybox ate-complex would work as an active species in the present system.^[20] Some of the results in Table 1 supported this assumption. The amount of lithium aryloxide (Table 1, entries 3–5) as well as *sBu-pybox* (Table 1, entries 8–9) affected enantioselectivity, and lanthanum/lith-

ium/pybox = 1:1:1 mixture gave the best results. Mechanistic studies are ongoing to unequivocally determine the structure of the heterobimetallic complex as well as to clarify the role of the two metals.^[21]

In summary, we developed direct catalytic asymmetric Mannich-type reactions using α -keto anilides **1** as synthetic equivalents of homoenolates. A heterobimetallic lanthanum aryloxide/lithium aryloxide/pybox complex catalyzed a direct Mannich-type reaction of various aryl, heteroaryl, and alkyl *N*-thiophenesulfonyl imines to give products in >99–66% yield, 95–70% *ee*, and >97:3–77:23 *syn*-selectivity. Stereoselective reduction of the α -keto moiety in the Mannich adduct afforded the β -alkyl- γ -amino- α -hydroxy amide with three contiguous stereocenters. Further investigations to clarify the structure of the heterobimetallic catalyst and the precise roles of the two metals, as well as improvement of enantioselectivity with aliphatic imines, are ongoing.

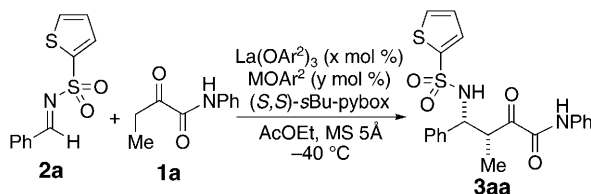
Experimental Section

General Procedure for Mannich-type Reaction: A test tube charged with molecular sieves (MS 5 Å, 60 mg, 200 mmol^{−1}) was flame-dried under reduced pressure (around 1.0 kPa). After cooling to room temperature, the tube was charged with argon. (*S,S*)-*sBu-pybox* (9.9 mg, 0.03 mmol, 10 mol %) and $\text{La}(\text{OAr}^2)_3$ (0.10 M in THF, 300 μL , 0.03 mmol, 10 mol %) were added. The resulting orange suspension was stirred at room temperature for 30 min and LiOAr^2 (0.10 M in THF, 300 μL , 0.03 mmol, 10 mol %) was added. After stirring for an additional 30 min at room temperature, the solvent was removed under reduced pressure. The residues were dried under reduced pressure for 2 h and taken up in dry EtOAc (1.0 mL). The mixture was cooled to -40°C , α -keto anilide (**1**, 0.45 mmol, 1.5 equiv) and imine (**2**, 0.30 mmol) were added successively as solids and the wall of the test tube was washed with EtOAc (0.5 mL). The resulting yellow suspension was stirred at -40°C for the time indicated in Table 2. The reaction mixture was quenched by adding silica gel and filtered through a short silica gel pad. After evaporation of the solvent, the crude mixture was purified by flash silica gel column chromatography to give the pure Mannich adduct **3**.

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Table 3: Control experiments.^[a]



Entry	x	MOAr^2	y	t [h]	Yield [%]	<i>syn:anti</i> ^[b]	<i>ee</i> of <i>syn</i> [%]
1	10	LiOAr^2	10	15	98	95:5	90
2	10	none	—	24	94	81:19	43
3	0	LiOAr^2	10	24	98	92:8	12
4	10	NaOAr^2	10	24	80	76:24	34
5	10	KOAr^2	10	24	65	73:27	33

[a] Reaction was run using 1.5 equiv of **1**, 10 mol % of *sBu-pybox* (0.2 M solution in AcOEt) at -40°C . $\text{Ar}^2 = 4\text{-PhOC}_6\text{H}_4$. [b] Determined by ^1H NMR analysis.

Keywords: amino acids · asymmetric catalysis · asymmetric synthesis · heterometallic complexes · Mannich reaction

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