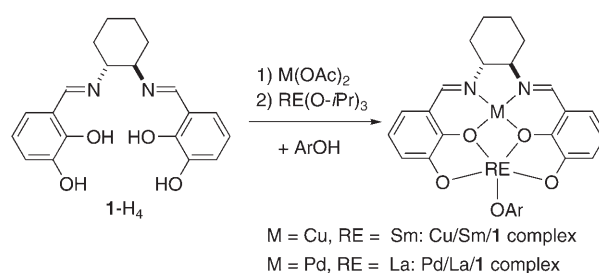


A Heterobimetallic Pd/La/Schiff Base Complex for *anti*-Selective Catalytic Asymmetric Nitroaldol Reactions and Applications to Short Syntheses of β -Adrenoceptor Agonists**

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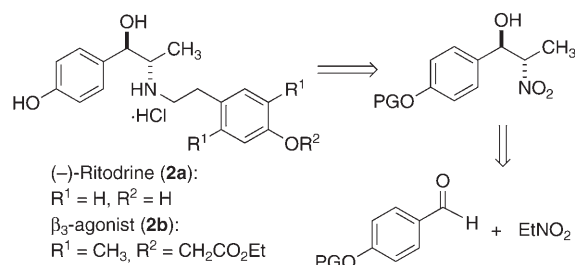
Chiral β -amino alcohols are useful building blocks found in various biologically active natural products, pharmaceuticals, chiral auxiliaries, and chiral ligands.^[1] Various methods for catalytic enantioselective synthesis of β -amino alcohols have been developed over the past decade,^[2] and the catalytic asymmetric nitroaldol (Henry) reaction is an efficient method for providing β -amino alcohols by reduction of the nitro moiety in nitroaldol adducts.^[3] Since our first report of the catalytic asymmetric nitroaldol reaction,^[4] various chiral catalysts, which are effective with nitromethane as a donor, have been developed.^[5] However, diastereo- and enantioselective nitroaldol reactions that use nitroethane and other nitroalkanes as donors are limited. To realize direct nitroaldol reactions, chiral Brønsted base catalysts could deprotonate the α proton of the nitroalkane to generate a metal nitronate, but epimerization of the products must be prevented to achieve high diastereoselectivity under kinetic control. *Syn*-selective asymmetric reactions have been established by our group and others;^[6] but *anti*-selective asymmetric reactions required pre-activation of nitroalkanes to silylnitronates^[7] to avoid basic conditions. Therefore, a new catalyst for *anti*-selective asymmetric nitroaldol reactions for direct use with nitroalkanes is needed in terms of atom economy.^[8] Quite recently, Ooi and co-workers^[9] reported an elegant chiral *P*-spiro triaminoiminophosphorane catalyst for the first direct nitroaldol reaction with excellent *anti* selectivity, enantioselectivity, and broad substrate generality.^[10–11] Considering the importance of *anti* amino alcohols as precursors for various important pharmaceuticals such as β -adrenoceptor agonists, additional studies of the *anti*-selective reactions are desirable. Herein, we report a new heterobimetallic Pd/La/1 complex (Scheme 1) for *anti*-selective nitroaldol reactions, and its



Scheme 1. Dinucleating (*R,R*)-Schiff base ligand **1-H₄** and the proposed structures of heterobimetallic Cu/Sm/(*R,R*)-**1** and Pd/La/(*R,R*)-**1** complexes with an ArOH additive.

application to short syntheses of β -adrenoceptor agonists **2a**-HCl (ritodrine-HCl) and **2b**-HCl.

2a-HCl is a selective β_2 -adrenoceptor agonist, clinically used for the prevention of pre-term birth (Scheme 2),^[12] and related compound **2b**-HCl is a selective β_3 -adrenoceptor



Scheme 2. Structures and retrosynthesis of (-)-ritodrine **2a**-HCl and β_3 -adrenoceptor agonist **2b**-HCl. PG = protecting group.

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agonist that provides a new therapeutic for urinary dysfunction.^[13] The common chiral *anti* β -amino alcohol unit (4'-hydroxynorephedrine) in both drugs is key for high biological activity, and we anticipated the *anti*-nitroaldol reaction to be one of the most straightforward methods for constructing two contiguous stereocenters in the common unit (Scheme 2). **2a** and **2b** could be synthesized by reduction of the nitro group of the *anti*-nitroaldol adduct with subsequent reductive alkylation of the amine moiety. Initially, we planned to utilize *anti*-selective nitroaldol reactions catalyzed by a Nd/Na/chiral amide complex recently developed by our group,^[11] but when used with aldehyde precursors suitable for **2a** and **2b** the reactions resulted in low enantioselectivities of the prod-

ucts.^[14] Therefore, we turned our attention to developing a new catalyst suitable for β -adrenoceptor agonists syntheses.

We recently reported the utility of dinucleating Schiff base **1-H₄** (Scheme 1) in nitro-Mannich reactions of *N*-Boc imines (Boc = *tert*-butylcarboxy) with nitroethane and nitropropane.^[15] Schiff base **1-H₄** selectively incorporated Cu into the inner N₂O₂ cavity and an oxophilic rare earth metal, having a large ionic radius, into the outer O₄ cavity. The cooperative functions of the two metals^[16,17] in the hetero-bimetallic Cu/Sm/**1** complex (Scheme 1; M = Cu, RE = Sm) were key to achieving high diastereo- and enantioselectivity in the nitro-Mannich reactions. An achiral 4-*tert*-butylphenol additive improved the enantioselectivity by performing as an achiral ligand. We hypothesized that suitable selection of a dinucleating Schiff base, a transition metal (M)/rare earth metal (RE) combination, and a phenolic additive would afford an optimal chiral environment for the *anti*-selective nitroaldol reaction. Thus, we initiated optimization reactions by using Schiff base **1-H₄**, a phenolic additive, aldehyde **3a**, and nitroethane **4a** (Table 1). The Cu/Sm/**1** and 4-*tert*-butylphenol system, which was optimal for the nitro-Mannich reactions, gave poor reactivity and selectivity (Table 1, entry 1). Screening of other rare earth metals (Table 1, entries 1–4) indicated that La(O-*i*Pr)₃ had the best reactivity (Table 1, entry 4), and additional optimization with regard to the inner metal (Table 1, entries 4–7) revealed that the best combination was Pd(OAc)₂ and La(O-*i*Pr)₃. These conditions gave **5aa** in 82 % yield, *anti*/*syn* = 5.3:1, and 58 % *ee* (Table 1, entry 7). Other metals such as Ni(OAc)₂ and Zn(OAc)₂ gave less satisfactory results (Table 1, entries 5–6). The phenolic additive also affected both the diastereo- and enantioselectivity (Table 1, entries 7–9), and 4-bromophenol was found to be optimal (Table 1, entry 9). Finally, minor modifications of the solvent and the reaction time gave the optimum results in THF/xylenes, producing **5aa** in 92 % yield, *anti*/*syn* = 19:1, and 84 % *ee* (Table 1, entry 10).

The substrate scope and limitations are shown in Table 2. Aromatic aldehydes with electron-donating substituents at the *para*-, *meta*-, or *ortho*-position gave products with high *anti* selectivity and good enantioselectivity (Table 2, entries 2–7). For the less reactive aldehyde **3e**, the reaction at –30 °C was required for good conversion (Table 2, entry 6 versus entry 7), and aldehyde **3f** having an electron-withdrawing substituent resulted in a slightly lower stereoselectivity (Table 2, entry 8). Heteroaromatic aldehyde **3g** gave product **5ga** with good d.r. and *ee* values (Table 2, entry 9). The present system is also applicable to both α,β -unsaturated and aliphatic aldehydes, which delivered products in

Table 1: Optimization of the reaction conditions.

(*R,R*)-catalyst **1-H₄** (10 mol %)
(M/RE/(*R,R*)-**1** = 1:1:1)
ArOH (10 mol %)
solvent, –40 °C, 48 h

Entry	M ^[a]	RE ^[b]	ArOH	Solvent	Yield [%]	d.r. <i>anti</i> / <i>syn</i> ^[c]	<i>ee</i> [%] ^[f]
1	Cu	Sm	4- <i>t</i> -BuC ₆ H ₄ OH	THF	33	2.3:1	1 ^[d]
2	Cu	Gd	4- <i>t</i> -BuC ₆ H ₄ OH	THF	26	2.3:1	4 ^[d]
3	Cu	Dy	4- <i>t</i> -BuC ₆ H ₄ OH	THF	25	2.8:1	3
4	Cu	La	4- <i>t</i> -BuC ₆ H ₄ OH	THF	73	2:1	28
5	Ni	La	4- <i>t</i> -BuC ₆ H ₄ OH	THF	61	2:1	12
6	Zn	La	4- <i>t</i> -BuC ₆ H ₄ OH	THF	30	1:2	2
7	Pd	La	4- <i>t</i> -BuC ₆ H ₄ OH	THF	82	5.3:1	58
8	Pd	La	4-MeO-C ₆ H ₄ OH	THF	65	3.3:1	49
9	Pd	La	4-BrC ₆ H ₄ OH	THF	77	12:1	77
10 ^[e]	Pd	La	4-BrC ₆ H ₄ OH	THF/xylenes	92	19:1	84

[a] M(OAc)₂ was used. [b] RE(O-*i*Pr)₃ was used. [c] Determined by ¹H NMR analysis. [d] *ent*-**5aa** was the major product. [e] Reaction time was 69 h. [f] Values determined for the *anti* product.

92–77 % *ee*, albeit with modest *anti* selectivity (Table 2, entries 10–12). The reaction with nitropropane (**4b**) as a donor proceeded smoothly to give product **5ab** in *anti*/*syn* = 19:1 and 85 % *ee* (Table 2, entry 13). By using a 5 mol % catalyst loading, good *anti* selectivity and enantioselectivity were maintained, but a long reaction time was required (Table 2, entry 14).

4-benzyloxybenzaldehyde **3k** was selected for the synthesis of **2a** and **2b**. A catalytic asymmetric nitroaldol

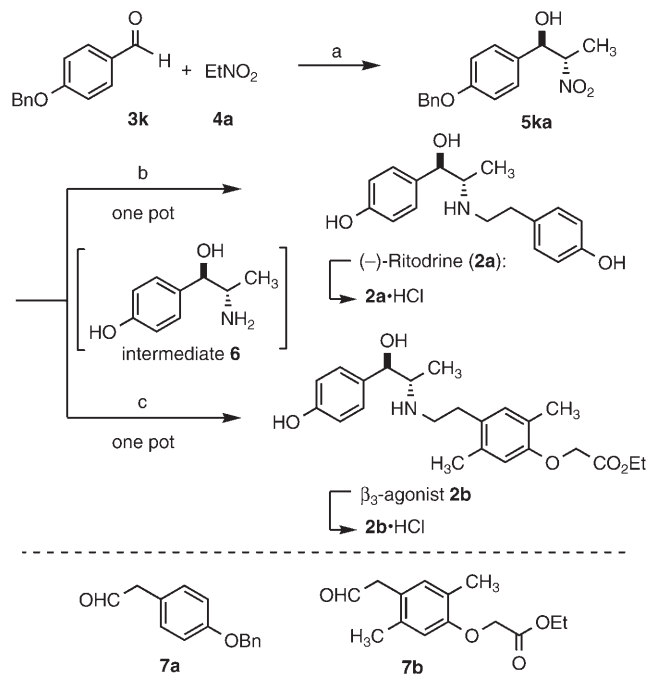
Table 2: *anti*-Selective nitroaldol reactions with various aldehydes and nitroalkanes.^[a]

(*R,R*)-catalyst (**1**) (10 mol %)
(Pd/La/(*R,R*)-**1** = 1:1:1)
4-bromophenol (10 mol %)
THF/xylenes, –40 °C

Entry	R	3	R'	4	Product	<i>t</i> [h]	Yield ^[b] [%]	d.r. <i>anti</i> / <i>syn</i> ^[c]	<i>ee</i> [%] ^[f]
1	C ₆ H ₅	3a	CH ₃	4a	5aa	69	92	19:1	84
2	4-CH ₃ C ₆ H ₄	3b	CH ₃	4a	5ba	72	80	19:1	87
3 ^[d]	4-CH ₃ C ₆ H ₄	3b	CH ₃	4a	5ba	72	97	15:1	83
4	3-CH ₃ C ₆ H ₄	3c	CH ₃	4a	5ca	72	81	13:1	83
5	2-CH ₃ C ₆ H ₄	3d	CH ₃	4a	5da	72	83	21:1	81
6	4-CH ₃ OC ₆ H ₄	3e	CH ₃	4a	5ea	72	47	22:1	88
7 ^[d]	4-CH ₃ OC ₆ H ₄	3e	CH ₃	4a	5ea	72	78	15:1	83
8	4-ClC ₆ H ₄	3f	CH ₃	4a	5fa	72	87	8:1	72
9	2-furyl	3g	CH ₃	4a	5ga	72	80	12:1	80
10	<i>E</i> -cinnamyl	3h	CH ₃	4a	5ha	85	70	5:1	80
11	Ph(CH ₂) ₂	3i	CH ₃	4a	5ia	85	75	3:1	77
12 ^[d]	Cy	3j	CH ₃	4a	5ja	72	65	4:1	92
13	C ₆ H ₅	3a	CH ₃ CH ₂	4b	5ab	85	67	19:1	85
14 ^[e]	C ₆ H ₅	3a	CH ₃	4a	5aa	120	82	16:1	85

[a] The reaction was run with 10 mol % of Pd/La/**1** complex and 4-bromophenol at –40 °C unless otherwise noted. Cy = cyclohexyl. [b] Yield of product isolated after column chromatography. [c] Determined by ¹H NMR analysis of the crude reaction mixture. [d] Reaction was run at –30 °C. [e] Reaction was performed with 5 mol % of Pd/La/**1** complex and 4-bromophenol. [f] Determined for *anti*-**5**.

reaction run with the Pd/La/(*S,S*)-**1** complex and 4-bromophenol afforded *anti*-adduct **5ka** in 85% yield, *anti/syn* = 14:1, and 83% *ee* on a 1.0-mmol scale.^[18] Salt-free ritodrine (**2a**) was obtained in a one-flask operation from **5ka** (Scheme 3). Treatment of **5ka** in ethyl acetate with Pd/C under H₂ (1 atm) at room temperature for 12 h gave



Scheme 3. Syntheses of β_2 -adrenoceptor agonist (–)-ritodrine **2a**·HCl and β_3 -adrenoceptor agonist **2b**·HCl; Reagents and conditions: a) Pd/La/(*S,S*)-**1** (10 mol %), 4-bromophenol (10 mol %), THF/xylenes, –30 °C, 85 h, 85%, *anti/syn* = 14:1, 83% *ee*; b) 1. Pd/C, H₂, EtOAc, RT, 12 h; 2. **7a**, 60 °C, 24 h; then HCl in CH₃OH, 93%; c) 1. Pd/C, H₂, EtOAc, RT, 12 h; 2. **7b**, 60 °C, 24 h; then HCl in CH₃OH, 73%.

intermediate **6** without epimerization. Completion of the conversion of **5ka** into **6** was verified by TLC analysis, and then aldehyde **7a**^[19] was added to the reaction mixture. The reaction mixture was heated at 60 °C under H₂ (1 atm) for 24 hours to facilitate the reductive alkylation to afford salt-free ritodrine (**2a**). After treating **2a** with HCl in methanol **2a**·HCl was obtained in 93% yield. Both the use of ethyl acetate as the solvent, instead of methanol, and the addition of aldehyde **7a** after the formation of intermediate **6** were important in achieving the one-pot process to transform **5ka** into **2a**. Under similar conditions **2b**·HCl was obtained from **5ka** and aldehyde **7b**^[13c] in 73% yield by the one-pot process to convert **5ka** into **2b**.

In summary, we developed an *anti*-selective catalytic asymmetric nitroaldol reaction utilizing a newly tuned Pd/La/**1** complex with 4-bromophenol as an additive. *anti*-Nitroaldol adducts were obtained in up to 97% yield, *anti/syn* = 22:1–3:1, and 92–72% *ee*. We also demonstrated the utility of the reaction in the short syntheses of clinically important β -adrenoceptor agonists **2a**·HCl and **2b**·HCl. Investigations into improving the stereoselectivity and reactivity of the

reaction, and mechanistic studies to elucidate the precise roles of the two metals^[20,21] are ongoing.

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- [21] One of the possible reaction mechanisms is as follows; the La–OAr moiety could function as a Brønsted base to deprotonate α proton of the nitroalkane. The La–nitronate would then react with the aldehyde, which is coordinated to the Pd metal center, from TS-A rather than TS-B (see scheme below) to avoid steric repulsion between the R' group and the Pd/La catalyst, preferentially giving *anti*-adducts. However, other reaction mechanisms cannot be ruled out at this stage. Detailed mechanistic studies will be reported in due course as a full article. For a recent example utilizing the Brønsted basic property of La–OAr moiety in asymmetric catalysis, see: H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 9588, and references therein.

