

Lanthanum Aryloxide/Pybox-Catalyzed Direct Asymmetric Mannich-Type Reactions Using a Trichloromethyl Ketone as a Propionate Equivalent Donor

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Enantioselective Mannich reactions are useful for providing β -amino carbonyl compounds. Direct catalytic asymmetric Mannich-type reactions using unmodified aldehydes and ketones as donors have been intensively investigated over the past decade.^{1,2} On the other hand, the use of carboxylic acid derivatives as donors, a straightforward method to synthesize β -amino acid derivatives, requires further development. In contrast to recent reports on direct catalytic asymmetric aldol reactions using propionate equivalent donors,³ the corresponding Mannich-type reactions are limited to donors with an α -OH-substituent⁴ and active methylene units.⁵ There are only two known racemic reactions using α -alkyl-substituted ester equivalent donors.^{6,7} We previously reported the usefulness of trichloromethyl ketones **1** (Figure 1) as a propionate equivalent donor in a racemic reaction. Trichloromethyl ketone units in Mannich adducts were transformed not only into esters, but also into various building blocks such as dithianes, trichloromethyl carbinols, and azetidine carboxylates.^{6,8} Herein, we report a direct catalytic enantio- and diastereoselective variant using **1**. A new lanthanum aryloxide-*i*Pr-pybox + lithium aryloxide combined catalyst (Figure 1) was the most effective, giving *syn*-Mannich adducts in high yield, dr, and enantioselectivity (up to 98% ee). Transformations of the Mannich adduct are also described.

To develop an enantioselective variant, we screened libraries of our Lewis acid-Brønsted base bifunctional metal-BINOLate complexes;⁹ however, all of them resulted in poor enantioselectivity (<10% ee). Therefore, we screened various Lewis acid-chiral ligand-Brønsted base combinations to activate both **1** and imine. La(OTf)₃-pybox + LiOAr (Ar = 4-MeO-C₆H₄-) gave promising results: 10 mol % of La(OTf)₃-*i*Pr-pybox and 15 mol % of LiOAr promoted the reaction of 2-pyridinesulfonyl imine **2a**¹⁰ with **1a** at 0 °C, giving Mannich adduct **3a** in 78% ee and *syn*/*anti* of >30:1, albeit in poor yield (26%; Table 1, entry 1). No reaction proceeded at -40 °C in entry 1. With La(OTf)₃-pybox alone, no reaction proceeded at 0 °C (entry 2). A lanthanum metal counteranion had crucial effects on reactivity, and aryloxide was the best. With La(OAr)₃ (Ar = 4-MeO-C₆H₄-), the reaction proceeded at -40 °C, and **3a** was obtained in 99% yield and 90% ee (entry 3). Mixing La/Li in a 1:0.5 ratio improved ee but decreased the reactivity (entry 4, 61%, 94% ee). Screening of imines revealed that 2-thiophene-sulfonyl imine **2b**¹⁰ had the best reactivity, and **3b** was obtained in 97% yield, while maintaining a good dr and ee (entry 5). Further optimization of the concentration and solvent improved the reaction rate, and **3b** was obtained in 96% after 9 h (entry 7, *syn*/*anti* = 21:1, 96% ee). The reaction proceeded with La(OAr)₃-*i*Pr-pybox alone without LiOAr, albeit with a lower reaction rate (entry 8, 21 h). In entries 7 and 8, similar diastereoselectivity and enantioselectivity were observed. In contrast, the reaction completed within 2 h using LiOAr and *i*Pr-pybox, but with low selectivity (entry 9, *syn*/*anti* = 5:1, 5% ee). Results in entries 7–9 suggested that a La(OAr)₃-*i*Pr-pybox complex is important for high selectivity. No reaction proceeded with the La(OTf)₃-*i*Pr-pybox complex in the absence of LiOAr (entry 10), suggesting that the La-OAr moiety

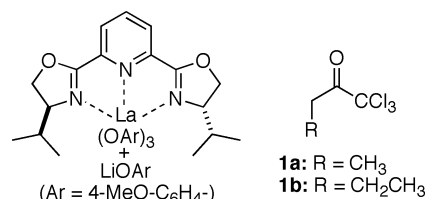


Figure 1. Trichloromethyl ketones **1** and postulated structures of La(OAr)₃–(*S,S*)-*i*Pr-pybox complex + LiOAr (Ar = 4-MeO-C₆H₄-).

Table 1. Optimization of Reaction Conditions

entry	imine	LaX ₃	LiOAr (\times mol %)	conc ^a (y M)	time (h)	yield ^a (%)	dr ^a (<i>syn</i> / <i>anti</i>)	ee (%) (<i>syn</i>)
1 ^b	2a	La(OTf) ₃	15	0.5 ^c	30	26	>30:1	78
2 ^b	2a	La(OTf) ₃	0	0.5 ^c	48	0		
3	2a	La(OAr) ₃	15	0.5 ^c	21	99	>30:1	90
4	2a	La(OAr) ₃	5	0.5 ^c	30	61	>30:1	94
5	2b	La(OAr) ₃	5	0.5 ^c	30	97	20:1	95
6	2b	La(OAr) ₃	5	1.0 ^c	19	99	20:1	95
7	2b	La(OAr) ₃	5	1.0 ^d	9	96 ^e	21:1	96
8	2b	La(OAr) ₃	0	1.0 ^d	21	99	18:1	95
9	2b	none	5	1.0 ^d	2	98	5:1	5
10	2b	La(OTf) ₃	0	1.0 ^d	24	0		

^a Determined by ¹H NMR analysis. ^b Reaction was run at 0 °C, no reaction proceeded at -40 °C. ^c THF/CH₂Cl₂ = 1:1 was used. ^d THF/toluene = 1:1 was used. ^e Isolated yield after purification.

in the La(OAr)₃-*i*Pr-pybox complex functions as a Brønsted base to form La-enolate in entry 8.¹¹ High ee in entry 7 as well as the difference in the reaction rate between entries 7 and 9 implied that the racemic pathway with LiOAr alone was negligible in entry 7. Because similar selectivity was obtained in entries 7 and 8, we assumed that the reaction proceeded via similar La-enolate species in both entries. We speculate that LiOAr in entry 7 would accelerate the reaction by enhancing the La-enolate-forming step.¹²

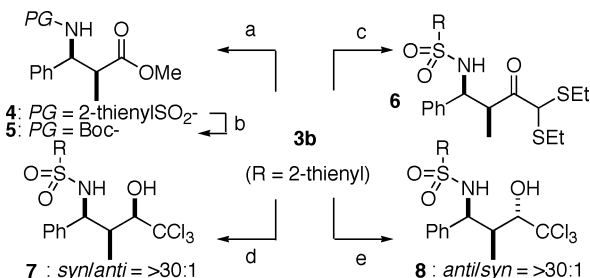
The substrate scope is summarized in Table 2. Various non-enolizable aryl, heteroaryl, and alkenyl imines afforded products in good yield and selectivity (entries 1–9). Product **3b** was obtained in good yield even with reduced amounts of **1a** (entry 2–3). It is noteworthy that isomerizable alkyl imines were also applicable (entries 10–12). In the case of alkyl imines **2j** and **2k**, the use of La(OAr)₃ alone was better to avoid undesired isomerization of the imines to enamines. Catalyst loading was successfully reduced to 5–2.5 mol % under concentrated conditions (entries 13–15, 2.0 M). Preliminary investigations using trichloromethyl ketone **1b** as a butanoate equivalent donor gave products in 83–87% ee (entries 16–17). Further optimizations studies are ongoing.

Table 2. Direct Catalytic Asymmetric Mannich-Type Reaction of Aryl, Heteroaryl, Alkenyl, and Alkyl Imines with Trichloromethyl Ketones^a

entry	imine: R	La/pybox (\times mol %)	1	time (h)	yield ^b (%)	dr ^c (syn/anti)	ee (%) (syn)
1	Ph	2b	1a	9	96	21:1	96
2 ^d	Ph	2b	1a	24	96	18:1	95
3 ^e	Ph	2b	1a	36	90	17:1	94
4	<i>p</i> -Cl-C ₆ H ₄ -	2c	1a	20	97	20:1	96
5	<i>p</i> -Me-C ₆ H ₄ -	2d	1a	20	>99	25:1	96
6	<i>p</i> -MeO-C ₆ H ₄ -	2e	1a	21	96	22:1	95
7	2-furyl	2f	1a	4	98	8:1	96
8	2-thienyl	2g	1a	19	98	20:1	95
9	(<i>E</i>)-PhCH=CH-	2h	1a	19	75	21:1	96
10	cyclohexyl	2i	1a	22	85	>30:1	96
11 ^f	<i>i</i> Bu	2j	1a	25	72	30:1	98
12 ^f	<i>i</i> Pr	2k	1a	23	74	>30:1	97
13 ^g	Ph	2b	1a	14	96	30:1	95
14 ^g	2-thienyl	2g	1a	29	93	17:1	92
15 ^g	Ph	2b	2.5	16	98	18:1	96
16	Ph	2b	1b	32	87	15:1	83
17	<i>p</i> -Cl-C ₆ H ₄ -	2c	1b	29	76	8:1	87

^a Reaction was run using 2.0 equiv of **1**, x mol % of La(OAr)₃/*i*Pr-pybox ($x = 2.5-10$), and 0.5x mol % of LiOAr in THF/toluene = 1:1 (1.0 M) at -40°C , unless otherwise noted. ^b Isolated yield after column chromatography. ^c Determined by ¹H NMR analysis. ^d Reaction run using 1.2 equiv of **1**. ^e Reaction run using 1.0 equiv of **1**. ^f Reaction was run in the absence of LiOAr. ^g Reaction was run in THF/toluene = 1:1 (2.0 M).

Scheme 1. Transformation of the Mannich Adduct^a



^a Reagents and conditions: (a) NaOMe, MeOH, 0°C , 20 min, quant; (b) i) Boc₂O, DMAP, CH₃CN, rt, 98%; ii) Mg, MeOH, rt, 95%; (c) EtSH, BuLi, THF, 0°C , 30 min, 79%; (d) DIBAL, CH₂Cl₂, -78°C to -40°C , 7.5 h, quant, **7/8** = >30:1; (e) DIBAL/Ph₃P(O) (1:2), THF, -78°C to -40°C , 2 h, 99%, **8/7** = >30:1.

The utility of the trichloromethyl ketone template was demonstrated by transformations in Scheme 1, in which **3b** was converted into ester and dithiane in good yield. The 2-thiophenesulfonyl group was removed after protection with Boc, followed by treatment with Mg.¹⁰ Either *syn*- or *anti*-trichloromethyl carbinol, a unique building block,^{6,8} was selectively obtained using either DIBAL (*syn*-**7**) or DIBAL/Ph₃P(O) = 1:2 mixture (*anti*-**8**).

In summary, we developed a direct catalytic asymmetric Mannich-type reaction of a trichloromethyl ketone **1a** as a propionate equivalent donor. The new La(OAr)₃-*i*Pr-pybox + LiOAr system gave products in >99–72% yield, >30:1–8:1 dr, and 98–92% ee (from **1a**). The La-OAr moiety in the La(OAr)₃-*i*Pr-pybox had a key role in promoting the reaction. La(OAr)₃-*i*Pr-pybox had different reactivity from La(OTf)₃-*i*Pr-pybox. Further applications of the catalyst¹³ as well as investigation of the reaction mechanism are ongoing.

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Supporting Information Available: Experimental procedures and characterization data, determination of relative and absolute configuration of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Preliminary kinetic studies on the concentration of trichloromethyl ketone **1** suggested that the enolate formation is the rate-determining step in the absence of LiOAr. There are two possibilities for the role of LiOAr: (a) Complexation with La(OAr)₃/pybox to form more basic ate complex or (b) LiOAr deprotonates **1** to form Li-enolate, followed by rapid transmetalation to generate La-enolate. Further mechanistic studies to clarify the role of LiOAr are ongoing.
- Preliminary investigation using trichloromethyl ketone **1c** with a larger substituent (R = CH₂Ph in Figure 1) gave Mannich adduct from imine **1b** in 94% yield, syn/anti = 7.4:1, and 78% ee after 20 h. Further optimization studies using **1b** and **1c** are ongoing.

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