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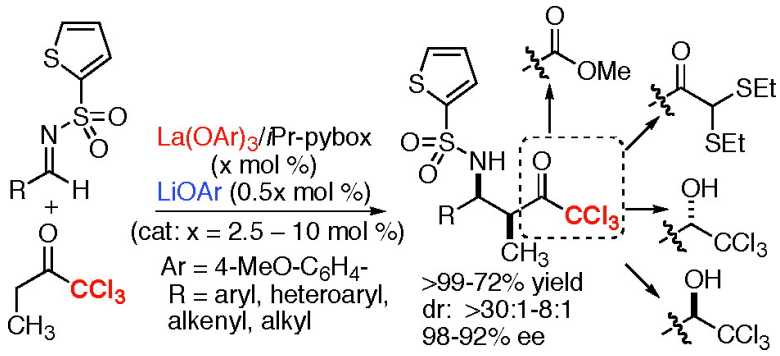
J. Am. Chem. Soc., **2007**, 129 (31), 9588-9589• DOI: 10.1021/ja073285p • Publication Date (Web): 14 July 2007



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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-substituent[4] 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-C$_6$H$_4$-) 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-C$_6$H$_4$-), 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-thiophenesulfonyl 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 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]

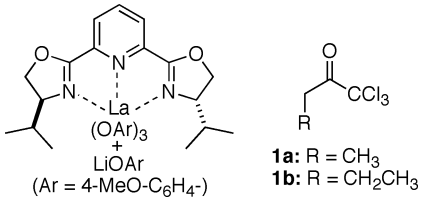
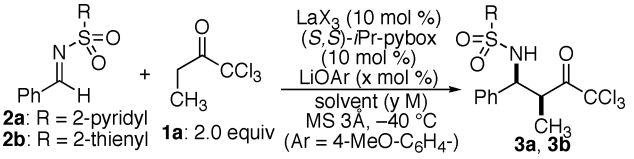


Figure 1. Trichloromethyl ketones **1** and postulated structures of La(OAr)$_3$−(*S*,*S*)-*i*Pr-pybox complex + LiOAr (Ar = 4-MeO-C$_6$H$_4$-).

Table 1. Optimization of Reaction Conditions



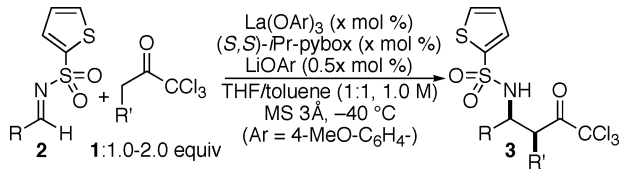
entry	imine	LaX_3	LiOAr (× mol %)	concn (y M)	time (h)	yield[a] (%)	dr[a] (syn/anti)	ee (%) (syn)
1[b]	**2a**	La(OTf)$_3$	15	0.5[c]	30	26	>30:1	78
2[b]	**2a**	La(OTf)$_3$	0	0.5[c]	48	0		
3	**2a**	La(OAr)$_3$	15	0.5[c]	21	99	>30:1	90
4	**2a**	La(OAr)$_3$	5	0.5[c]	30	61	>30:1	94
5	**2b**	La(OAr)$_3$	5	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 ^{1}H NMR analysis. [b] Reaction was run at 0 °C, no reaction proceeded at −40 °C. [c] THF/CH_2Cl_2 = 1:1 was used. [d] THF/toluene = 1:1 was used. [e] Isolated yield after purification.

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.

10.1021/ja073285p CCC: $37.00

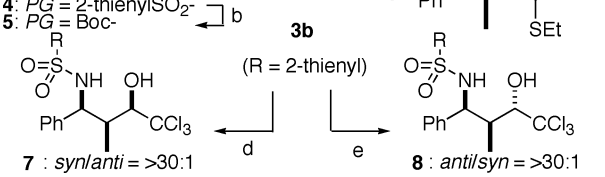
Table 2. Direct Catalytic Asymmetric Mannich-Type Reaction of Aryl, Heteroaryl, Alkenyl, and Alkyl Imines with Trichloromethyl Ketones[a]



entry	imine: R		La/pybox (× mol %)	1	time (h)	yield[b] (%)	dr[c] (syn/anti)	ee (%) (syn)
1	Ph	**2b**	10	**1a**	9	96	21:1	96
2[d]	Ph	**2b**	10	**1a**	24	96	18:1	95
3[e]	Ph	**2b**	10	**1a**	36	90	17:1	94
4	*p*-Cl-C_6H_4-	**2c**	10	**1a**	20	97	20:1	96
5	*p*-Me-C_6H_4-	**2d**	10	**1a**	20	>99	25:1	96
6	*p*-MeO-C_6H_4-	**2e**	10	**1a**	21	96	22:1	95
7	2-furyl	**2f**	10	**1a**	4	98	8:1	96
8	2-thienyl	**2g**	10	**1a**	19	98	20:1	95
9	(*E*)-PhCH=CH-	**2h**	10	**1a**	19	75	21:1	96
10	cyclohexyl	**2i**	10	**1a**	22	85	>30:1	96
11[f]	*i*Bu	**2j**	10	**1a**	25	72	30:1	98
12[f]	*i*Pr	**2k**	10	**1a**	23	74	>30:1	97
13[g]	Ph	**2b**	5	**1a**	14	96	30:1	95
14[g]	2-thienyl	**2g**	5	**1a**	29	93	17:1	92
15[g]	Ph	**2b**	2.5	**1a**	16	98	18:1	96
16	Ph	**2b**	10	**1b**	32	87	15:1	83
17	*p*-Cl-C_6H_4-	**2c**	10	**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 0.5*x* 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 ^{1}H 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) Boc_2O, DMAP, CH_3CN, rt, 98%; ii) Mg, MeOH, rt, 95%; (c) EtSH, BuLi, THF, 0 °C, 30 min, 79%; (d) DIBAL, CH_2Cl_2, −78 °C to −40 °C, 7.5 h, quant, **7**/**8** = >30:1; (e) DIBAL/$Ph_3P(O)$ (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/$Ph_3P(O)$ = 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 catalyst[13] as well as investigation of the reaction mechanism are ongoing.

Acknowledgment. This work was supported by Grand-in-Aid for Specially Promoted Research, Grant-in-Aid for Encouragements for Young Scientists (B), and the Sumitomo Foundation. H.M. thanks JSPS predoctoral fellowship. We thank Prof. J. C. Carretero and Dr. R. Gómez Arrayás for their helpful advice on imines synthesis.

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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(12) 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 transmetallation to generate La-enolate. Further mechanistic studies to clarify the role of LiOAr are ongoing.

(13) Preliminary investigation using trichloromethyl ketone **1c** with a larger substituent (R = CH_2Ph 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.

JA073285P