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Highly *anti*-Selective Catalytic Aldol Reactions of Amides with Aldehydes

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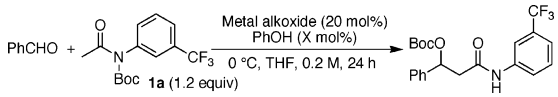
Aldol reactions are among the most powerful and efficient methods for carbon−carbon bond formation, and continuous efforts have been devoted to the development of catalytic asymmetric aldol reactions.[1] While almost all of these catalytic asymmetric reactions require the preconversion of ketone or ester moieties into more reactive species, such as silyl enol ethers or ketene silyl acetals, using more than stoichiometric amounts of bases and silicon sources, a great deal of effort has been put into the development of direct-type aldol reactions using metal catalysts or organocatalysts.[2] In such cases, however, the donor substrates are limited to specific ketones or aldehydes, which have relatively low pK_a values. Furthermore, conversion of the resulting β-hydroxy ketones into more useful β-hydroxy carbonyl compounds such as β-hydroxy esters, carboxylic acids, amides, and aldehydes requires an oxidation step, for example, a Baeyer−Villiger reaction, using more than stoichiometric amounts of oxidizing agents. Therefore, direct-type aldol reactions using ester equivalents have recently been attracting much attention. However, the use of ester equivalents is still very difficult, because the pK_a values of the α-protons of ester equivalents are much higher than those of ketones and aldehydes, and only isolated examples have been reported.[3−5] Herein, we disclose direct-type catalytic aldol reactions of amides with aldehydes. The procedure only requires a slight excess of (*N*-Boc)acylanisidides (1.2 equiv), which are effective in generating metal enolates *in situ*, in contrast to other procedures. Moreover, the first highly *anti*-selective direct-type catalytic aldol reactions of (*N*-Boc)propioanisidide with aldehydes are also described.

In the initial investigation, we selected (*N*-Boc)acetanilide derivatives as donor substrates. We expected that these substrates would be suitable, because *in situ* enolate formation might be facilitated *via* a bidentate chelation based on appropriate metals. We first examined alkaline earth and rare earth metals as catalysts in the reaction of benzaldehyde with (*N*-Boc)acetanilide derivative **1a**, as shown in Table 1. In the case of rare earth metals, the reaction did not proceed at all. On the other hand, when alkaline earth metals were used, we were pleased to find that the desired direct-type catalytic aldol reaction was found to proceed through an intramolecular Boc-transfer process. In particular, barium alkoxide[6] gave the highest yield among the alkaline earth metals tested.[7]

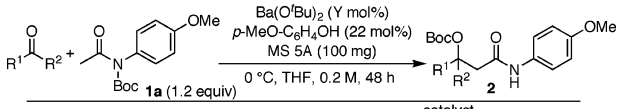
After screening several ligands, substrates, and additives, it was found that a combination of a barium complex prepared from Ba(O-*t*-Bu)$_2$, *p*-methoxyphenol, and (*N*-Boc)acetanisidide (**1a**) was effective for this catalytic reaction. Under the optimized reaction conditions, a wide range of aromatic, heterocyclic, α,β-unsaturated, and aliphatic aldehydes were applicable, including even a ketone (Table 2, entry 15). It is notable that the catalyst loading could be reduced to 5 mol % and that bulky pivalaldehyde (entry 12) reacted smoothly to afford the desired adducts in high yields. Secondary and primary aliphatic aldehydes having acidic α-protons also reacted to afford the desired aldol adducts in moderate yields. Remarkably, a slight excess amount of (*N*-Boc)acetanisidide (**1a**, 1.2 equiv) was enough to obtain the desired aldol adducts effectively in all cases.[8]

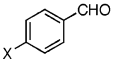
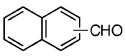
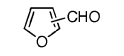
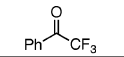
Table 1. Effect of Metal Sources



entry	metal alkoxide	PhOH (*x* mol %)	yield (%)
1	Y(O*i*-Pr)$_3$	66	N. R.
2	La(O*i*-Pr)$_3$	66	N. R.
3	Mg(O*n*-Pr)$_2$	44	10
4	Ca(O*i*-Pr)$_2$	44	28
5	Sr(O*i*-Pr)$_2$	44	33
6	Ba(O*t*-Bu)$_2$	44	50

Table 2. Catalytic Aldol Reactions of an Amide with Various Aldehydes and a Ketone



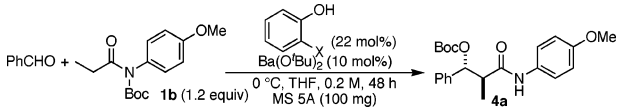
entry	RCHO		product	catalyst (Y mol%)	yield (%)
1[a,c]		X = OMe	**2a**	10	quant
2		X = CH$_3$	**2b**	10	95
3		X = H	**2c**	10	98
4[a,b]		X = H	**2c**	5	83
5		X = Cl	**2d**	10	83
6		1-Naphthyl	**2e**	10	98
7		2-Naphthyl	**2f**	10	92
8		2-Furaldehyde	**2g**	10	86
9		3-Furaldehyde	**2h**	10	90
10	3-Thienal		**2i**	10	90
11	(*E*)-PhCH=CHCHO		**2j**	10	83
12[c]	^{t}BuCHO		**2k**	10	83
13[b,d]	^{c}HexCHO		**2l**	10	45
14[b,d]	$CH_3C(CH_3)_2CH_2CHO$		**2m**	10	45
15			**2n**	10	85

[a] 72 h. [b] Room temperature. [c] −20 °C. [d] DME was used as a solvent.

Next, direct-type aldol reactions of (*N*-Boc)propioanisidide (**1b**) were investigated. In the presence of 10 mol % of Ba(O-*t*-Bu)$_2$ and 22 mol % of *p*-methoxyphenol, **1b** reacted with benzaldehyde in THF at 0 °C to afford the desired aldol product in 87% yield with good *anti*-diastereoselectivity (*syn*/*anti* = 13/87). After screening several ligands, *ortho*-substituted phenols were found to be effective to give the desired product in high yield with high *anti*-selectivity (Table 3). While a bigger *ortho*-substituted ligand **3** gave the desired aldol adduct in high yield and with excellent *anti*-selectivity (entry 7). The *ortho*-disubstituted ligand gave higher *anti*-selectivity, though in moderate yield (entry 8). Under the optimized reaction conditions, a wide range of aromatic, heterocyclic, and α,β-unsaturated aldehydes reacted with **1b** to afford the corresponding *anti*-aldol adducts in high yields with high diastereoselectivities (Table 4). (*N*-Boc)-3-methylbutanoanisidide (**1c**) also worked well (entry 2). It should be noted that this is the first example of highly *anti*-selective direct-type catalytic aldol reactions of amides with aldehydes. The product was readily converted to the corresponding β-hydroxy carboxylic acid (eq 1). Furthermore, low-loading catalyst

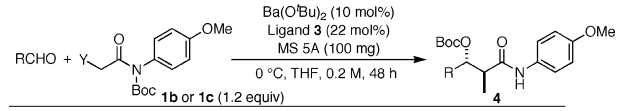
10.1021/ja061221t CCC: $33.50

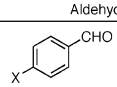
Table 3. Effect of *ortho*-Substituents of Phenol Ligands

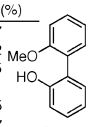


entry	X	yield (%)	dr (syn/anti)
1	H	81	17/83
2	H (*p*-$MeOC_6H_4OH$)	87	13/87
3	Me	98	8/92
4	*i*-Pr	68	5/95
5	*i*-Bu	61	4/96
6	Ph	99	6/94
7	*o*-$MeOC_6H_4$ (**3**)	87	5/95
8	2,6-dimethylphenol	64	2/98

Table 4. Highly *anti*-Selective Catalytic Aldol Reactions of an Amide with Various Aldehydes

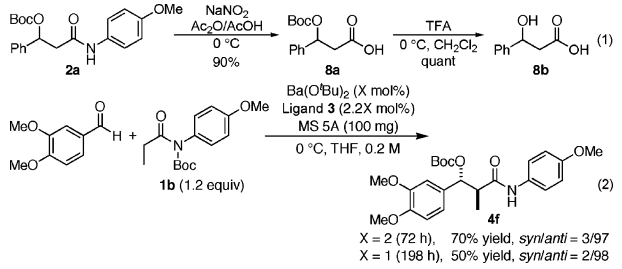


Entry	Aldehyde	Y	Product	dr (*syn*/*anti*)	Yield (%)
1	 X = H	Me (**1b**)	**4a**	5/95	87
2[a,b]	X = H	^{i}Pr (**1c**)	**4b**	4/96	82
3	X = Me	Me	**4c**	2/98	85
4	X = OMe	Me	**4d**	3/97	91
5	*o*-MeC_6H_4CHO	Me	**4e**	2/98	75
6	3,4-$(MeO)_2C_6H_3CHO$	Me	**4f**	2/98	97
7	1-Naphthaldehyde	Me	**4g**	4/96	74
8	2-Naphthaldehyde	Me	**4h**	7/93	71
9	3-Thienal	Me	**4i**	10/90	72
10[c]	(*E*)-PhCH=CHCHO	Me	**4j**	17/83	86
11	(*E*)-CH_3CH=CCH_3CHO	Me	**4k**	2/98	72
12[a]	^{c}HexCHO	Me	**4l**	2/98	41



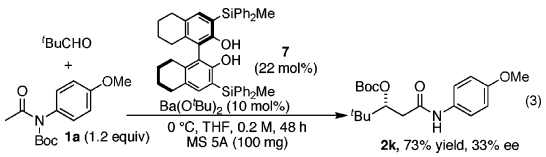
[a] Room temperature in DME. [b] Relative configuration was assigned by analogy. [c] 2,6-Dimethylphenol was used instead of ligand **3**.

(1∼2 mol %) could work well to afford the desired adducts in moderate yields with high *anti*-selectivities (eq 2).



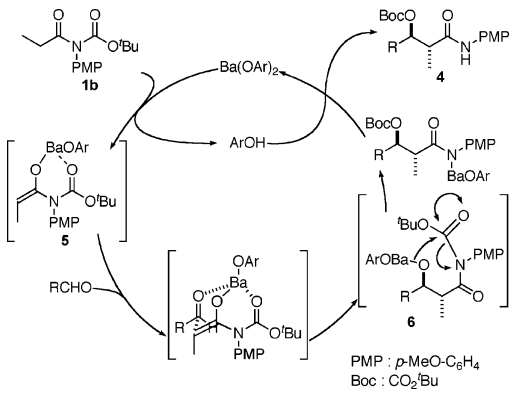
The proposed catalytic cycle is outlined in Scheme 1. At first, barium alkoxide removes the α-proton of acylamide (**1b**) to give a barium enolate (**5**)[9] *in situ*. This barium enolate formed then reacts with an aldehyde to afford the initial aldol adduct (**6**). Subsequent intramolecular Boc-transfer[10] then occurs spontaneously with concomitant release of steric strain, followed by a protonation reaction to afford the desired adduct along with regeneration of the catalyst.

The present reaction could be extended to a catalytic enantioselective version using a chiral ligand. Indeed, using a chiral ligand **7**, the desired product **2k** was obtained in 73% yield with 33% ee. Although the enentioselectivity is not satisfactory, the possiblity of a direct-type, catalytic enantioselective aldol reaction of amides with aldehydes has been demonstrated (eq 3).



In summary, we have developed the first highly *anti*-selective direct-type catalytic aldol reactions of amides with aldehydes. The reactions proceeded smoothly in the presence of a catalytic amount of barium phenoxide under mild conditions (at 0 °C for 24−48 h in most cases). The use of (*N*-Boc)acylanisidides is key, and a wide range of aromatic, heterocyclic, α,β-unsaturated aldehydes were applicable to afford the desired adducts in high yields with high *anti*-selectivities. Further investigations to clarify the precise mechanism of this reaction as well as to improve the enantioselectivity of the asymmetric version are now in progress.

Scheme 1. Assumed Catalytic Cycle



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Supporting Information Available: Experimental procedures and product characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) Evans *et al.* reported that aldol reactions of esters proceeded in excellent yields and diastereoselectivity using more than stoichiometric amounts of chiral auxiliaries, silylating reagents, and amines without preconversion of ester equivalents (See ref 4). In other cases, excess amounts of α-oxy carbonyl compounds (2.0 equiv), which have relatively low pK_a values of α-protons of ester equivalents, are generally used as suitable substrates (See ref 5). Thus, a breakthrough in this field is strongly desired.
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(10) Similar *N*- to *O*-Boc migrations were reported. Bew, S. P.; Bull, S. D.; Davies, S. G.; Savory, E. D.; Watkin, D. J. *Tetrahedron* **2002**, *58*, 9387.

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