Pergamon

Tetrahedron Letters 42 (2001) 4669–4671

TETRAHEDRON LETTERS

Catalytic asymmetric aldol reaction of ketones and aldehydes using chiral calcium alkoxides

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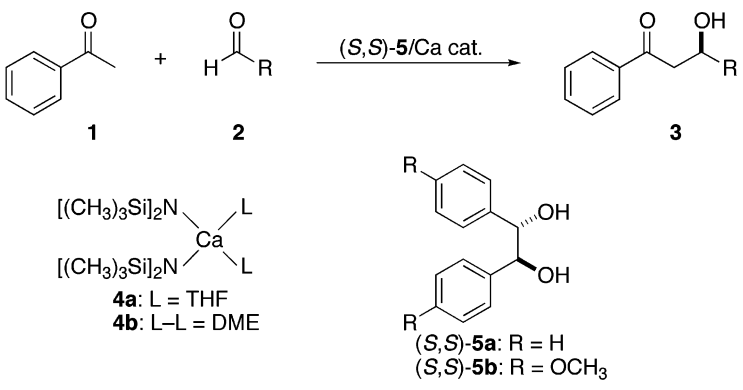
Received 24 March 2001; accepted 1 May 2001

Abstract—A chiral hydrobenzoin/Ca complex catalyzes the reaction of acetophenone and aliphatic aldehydes to give the corresponding aldol products in up to 91% ee.

The asymmetric aldol reaction is useful for constructing chiral organic frameworks.[1] Although the direct catalytic asymmetric reaction between unmodified ketones and aldehydes is highly desirable, there are only a few examples of synthetically meaningful reactions.[2–6] Certain antibodies catalyze the reaction of acetone and aromatic aldehydes giving the aldol products,[3] and proline (30–40 mol%) catalyzes an enantioselective reaction of acetone or hydroxyacetone and aldehydes (>25:1 mol ratio).[4] Metal-based catalysts are more practical. Shibasaki reported that a chiral heteropolymetallic catalyst (3–8 mol%) consisting of La, Li, and binaphthol, with the aid of $KN[Si(CH_3)_3]_2$ and H_2O, promotes the reaction of aromatic or aliphatic ketones and aldehydes (typically a 5:1 mol ratio) to afford the aldols in 30–93% ee in moderate to good yield.[5a,c] The enantioselectivity is lowered by decreasing the bulkiness of the aldehyde substrates. More recently, Trost developed chiral semi-crown/Zn catalysts that promote the reaction of acetophenone and bulky aldehydes (10:1 mol ratio; 10 mol% catalyst) with high enantioselectivity, but in moderate yield.[6] As such, there is still much room for improvement of the synthetic efficiency. The current problem in the direct aldol reaction is threefold: (1) there are few efficient chiral catalysts giving a high turnover number and frequency; (2) the thermodynamic balance between the starting carbonyl compounds and the condensation products does not always



Scheme 1. Asymmetric aldol reaction between acetophenone and aliphatic aldehydes.

Keywords: asymmetric aldol reaction; chiral Ca catalyst; CSI-MS; direct aldol reaction; hydrobenzoins.
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0040-4039/01/$ - see front matter
PII: S0040-4039(01)00819-X

favor the product formation;[7] and (3) aldehyde substrates giving high enantioselectivity are limited. We report a new protocol using a simple diol-modified Ca catalyst that gives chiral aldol products with reasonable enantiomeric excess (Scheme 1).

When a mixture of acetophenone (**1**), pivalaldehyde (**2a**), and a catalyst system prepared from $Ca[N\{Si(CH_3)_3\}_2]_2(thf)_2$ (**4a**),[8] (*S*,*S*)-hydrobenzoin [(*S*,*S*)-**5a**],[9] and KSCN (1:3:1 mol ratio)[10] in a 4:1 C_2H_5CN–THF mixed solvent (**1**:**2a**:Ca = 1000:100:3 mol ratio) was allowed to stand at −20°C for 20 h, (*R*)-3-hydroxy-4,4-dimethyl-1-phenylpentan-1-one [(*R*)-**3a**] was obtained in 74% yield with 89% ee. The reaction without KSCN gave (*R*)-**3a** in 66% yield and 73% ee. $Ca[N\{Si(CH_3)_3\}_2]_2(dme)$ (**4b**)[8] could also be used in place of **4a**.

Table 1 shows some examples of the direct asymmetric aldol reaction between the aromatic ketone **1** and aliphatic aldehydes **2** using the (*S*,*S*)-**5**/Ca catalysts. The reaction of aldehydes possessing a tertiary alkyl group gave the aldol products in good yield with 87–91% ee. The reactivity of the Ca catalyst is several times higher than those of the known catalyst systems.[5a–c,6] The aldol **3a** was obtained even with only 1 mol% of the Ca catalyst, albeit with a lower enantiomeric excess (82%). A gram-scale reaction of **2a** was performed without special techniques.[11] This method allowed for the synthesis of (*R*)-**3c** in 76% yield with 91% ee, which serves as a synthetic intermediate for epothilone A.[5c] Aldehydes with a secondary alkyl group can also be used as acceptors of the chiral enolate, although the extent of enantioselectivity is less satisfactory. As anticipated from the literature,[5c,6] the reaction of acetophenone and alkanal **2e** gave the cross-aldol in only 13% yield and 15% ee, along with the self-aldol products of **2e**.

The asymmetric bias is generated kinetically in the reaction of an aldehyde and an in situ-formed ketone enolate in the chiral hydrobenzoin/Ca template. Because of the reversibility of the direct ketone/aldehyde aldol reaction, however, the prolonged exposure of the chiral product to the reaction conditions significantly decreased the product enantiomeric excess. For example, reaction of **1** and **2a** under standard conditions afforded (*R*)-**3a** with the highest enantiomeric excess (92%) after 30 min (4% yield), then 89% ee after 20 h (74% yield), and 85% ee after 40 h (84% yield). Excess ketonic substrate, typically 10 mol equiv., was crucial for obtaining the aldol product in a reasonable chemical yield (>70%) and with a satisfactory enantiomeric excess, where most of the excess ketone (90%) was recovered by distillation. The reaction using an equimolar mixture of **1** and **2a** at −20°C for 163 h gave (*R*)-**3a** in only 20% yield with 77% ee. Thus, this direct catalytic asymmetric aldol reaction still has the inherent, insoluble problem. The aldol (*S*)-**3c** (89% ee) retards the reaction of **1** and **2a** catalyzed by an (*S*,*S*)- or (*R*,*R*)-**5a**-based Ca complex but does not greatly affect the enantioselectivity.

There is a notable nonlinear relationship[12] between the enantiomeric excess of the chiral source **5** and aldol product. For example, when the reaction of **1** and **2a** was conducted with the catalyst formed from **4a** and (*S*,*S*)-**5a** in 50% ee, the aldol (*R*)-**3a** was obtained in 84% ee.

Table 1. Asymmetric aldol reaction of acetophenone and aldehydes catalyzed by a chiral Ca complex[a]

Aldehyde		Diol in cat.	Time (h)	Aldol product			
No.	R			No.	Yield[b] (%)	ee[c] (%)	Config.[d]
2a	*t*-C_4H_9	(*S*,*S*)-**5a**	20	**3a**	74	89	*R*[e]
2a	*t*-C_4H_9	(*S*,*S*)-**5a**	22[f]	**3a**	87	86	*R*
2a	*t*-C_4H_9	(*S*,*S*)-**5a**	20[g]	**3a**	79	82	*R*
2a	*t*-C_4H_9	(*S*,*S*)-**5b**	16	**3a**	70	89	*R*
2b	$C_6H_5CH_2C(CH_3)_2$	(*S*,*S*)-**5a**	24	**3b**	75	87	*R*[h]
2c	$C_6H_5CH_2OCH_2C(CH_3)_2$	(*S*,*S*)-**5a**	24	**3c**	76	91	*R*[i]
2d	*cyclo*-C_6H_{11}	(*S*,*S*)-**5a**	20	**3d**	88	66	*R*[j]
2d	*cyclo*-C_6H_{11}	(*S*,*S*)-**5b**	10	**3d**	71	69	*R*
2e	$C_6H_5CH_2CH_2$	(*S*,*S*)-**5a**	14	**3e**	13	15	*S*[k]

[a] Unless otherwise stated, the reaction was conducted at −20°C using 5.20 mmol of acetophenone and 0.520 mmol of an aldehyde in 4:1 C_2H_5CN–THF mixed solvent (0.21 M) containing 3 mol% of the catalyst.

[b] Isolated yield.

[c] The ee was determined by chiral HPLC (Chiralpak AS).

[d] The absolute configurations of **3a**, **3b**, **3d**, **3e** were determined by the sign of optical rotation of products. The absolute configuration of **3c** was determined by the sign of optical rotation of the corresponding β-hydroxy esters after Baeyer–Villiger oxidation of **3c**.[5c]

[e] $[\alpha]_D^{16}$ +73.2° (*c* 1.38, $CHCl_3$);[13a] 89% ee.

[f] Reaction using 344 mmol of **1** and 35 mmol of **2a** aldehyde in 4:1 C_2H_5CN–THF mixed solvent (0.44 M).

[g] Reaction using 1 mol% of the catalyst (3.0 M).

[h] $[\alpha]_D^{23}$ +56.8° (*c* 1.18, $CHCl_3$);[13b] 87% ee.

[i] $[\alpha]_D^{23}$ +53.3° (*c* 2.36, $CHCl_3$); 91% ee.

[j] $[\alpha]_D^{21}$ +44.2° (*c* 2.22, $CHCl_3$);[13a] 66% ee.

[k] $[\alpha]_D^{22}$ +2.32° (*c* 0.34, $CHCl_3$);[13a] 15% ee.

Although the detailed structure of alkaline earth catalysts remains unclear, coldspray ionization mass spectrometry (CSI-MS)[14] provided useful information regarding the atomic constitution of the chiral Ca alkoxides. The sample prepared from **4a** and 3 equiv. of (*S*,*S*)-**5a** [H_2(HB)] gave the CSI-MS data, demonstrating that the major species is oligomeric. The eminent peak at *m*/*z* 1922 corresponds to $[Ca_5H_9(HB)_8O]^+$. This assignment is consistent with the result obtained with the di-*p*-methoxy auxiliary (*S*,*S*)-**5b**[15] [H_2(HB*)], where the major peak is shifted to *m*/*z* 2402 due to $[Ca_5H_9(HB^*)_8O]^+$. The Ca complex formed from **4a**, 3 equiv. of H_2(HB), and 1 equiv. of KSCN in a 4:1 C_2H_5CN–THF mixture gave a spectrum that exhibits a strong peak at *m*/*z* 2019 due to $[Ca_5KH_9(HB)_8O(SCN)]^+$. These results indicate that Ca, HB, and KSCN contribute to the formation of the highly aggregated chiral complex. Despite the C_2-symmetry of the auxiliary, (*S*,*S*)-**5**, the Ca complex has a high degree of complexity. Although the less aggregated Ca species might be responsible for the asymmetric aldol reaction, such oligomeric catalysts must participate directly or indirectly in the asymmetric reaction in view of significant asymmetric amplification.

In summary, the newly devised Ca complexes catalyze the asymmetric aldol reaction of acetophenone and aliphatic aldehydes directly without structural modification. The properties of the Ca catalysts are further modifiable, hopefully, leading to more efficient catalysts, because various chiral hydrobenzoin derivatives are available.[9,15] Although the catalytic utility of Ca salts has not been extensively explored,[16] this environmentally benign and abundant alkaline earth metal might be useful for contemporary organic synthesis.

Acknowledgements

This work was supported by the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Grant No. 07CE2004).

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10. No reaction occurred with a 1:1:1 mixture of **4a**, (*S*,*S*)-**5a**, and KSCN.
11. Experimental procedure: A solution of **4a** (671 mg, 3.13 mmol) in THF (16 mL) was added to a stirred solution of (*S*,*S*)-**5a** (671 mg, 3.13 mmol) and KSCN (101 mg, 1.04 mmol) in C_2H_5CN (63 mL) over 30 min at room temperature. The mixture was stirred overnight at room temperature and the insoluble materials were removed by filtration. Compounds **1** (40.0 mL, 344 mmol) and **2a** (3.80 mL, 35.0 mmol) were added to this catalyst solution (3 mol%) at −20°C, and the mixture was stirred at −20°C for 22 h. Then 1 M aqueous HCl was added. The mixture was extracted with ether and washed with aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and distilled (50°C/2 mmHg) to afford **1** (33.7 g, 90% recovery). The residue was subjected to silica-gel column chromatography (12:1 hexane–ether) to give (*R*)-**3a** (6.26 g, 87% yield, 86% ee) and (*S*,*S*)-**5a** (610 mg, 91% recovery).
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