Tetrahedron Letters,Vol.24,No.47,pp 5233-5236,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A NEW ALDOL REACTION VIA CERIUM ENOLATES

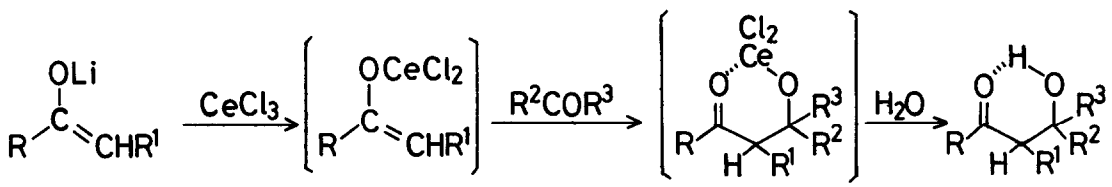
Tsuneo Imamoto*, Tetsuo Kusumoto, and Masataka Yokoyama
Department of Chemistry, Faculty of Science, Chiba University
Yayoi-cho, Chiba 260, Japan

Summary: Cerium enolates formed from cerium (III) chloride and lithium enolates undergo aldol reaction with ketones or sterically crowded aldehydes to afford the corresponding ß-hydroxyketones in high yields.

Although much progress has been made in the cross-aldol reaction of various metal enolates with aldehydes,[1,2] the analogous coupling between two different ketones has proved to be less successful except the cases in which less sterically crowded ketones such as methyl ketones are employed.[3] Recently, Mukaiyama and his co-workers reported a new aldol reaction via divalent tin enolates which is applicable to the coupling between two ketones.[4]

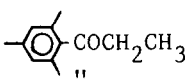
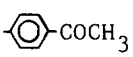
On the other hand, we have investigated the generation and reactivities of organocerium reagents and found that the reagents, prepared from cerium (III) halides and alkyllithiums, react cleanly with various carbonyl compounds to afford the corresponding 1,2-addition products in high yields, even though the substrates are susceptible to enolization or metal-halogen exchange with simple organolithiums.[5] These results prompted us to investigate the reactivities of cerium enolates toward carbonyl compounds. In this communication, we wish to report a first example of cross-aldol reaction of cerium enolates.

As is shown in the following scheme, lithium enolates prepared from ketones and lithium diisopropylamide (LDA) or lithium bistrimethylsilylamide (LBTMSA) were treated with anhydrous cerium chloride at -78 °C, and the generated cerium



enolates were allowed to react with carbonyl compounds at the same temperature for 0.5~3 h. A typical experimental procedure is described for the reaction of propiophenone with cyclohexanone. Commercially available cerium chloride ($CeCl_3 \cdot 7H_2O$)(520 mg, 1.4 mmol) was dried in vacuo at 150 °C for 2 h and was suspended in 3 ml of THF under argon. This suspension was quickly transferred by the use

Table I

Enolized Ketone	Acceptor Carbonyl Compound	Reagent	Reaction Time (h)	Yield(%)[a]	Ratio[b] Threo/Erythro
$PhCOCH_2CH_3$		LDA-$CeCl_3$	3	79	
"	"	LDA	3	28	
"		LDA-$CeCl_3$	3	45	
"	"	LDA	3	5	
"	$CH_3COCH_2CH_3$	LDA-$CeCl_3$	3	62	(40:60)[c]
"	"	LDA	3	11	(37:63)[c]
"	PhCHO	LDA-$CeCl_3$	0.5	98	18:82
"	"	LDA	0.5	95	17:83 (12:88)[d]
"		LDA-$CeCl_3$	2	93	(20:80)[e]
"	"	LDA	2	63	(20:80)[e]
		LDA-$CeCl_3$	3	56	
"	"	LDA	3	trace	
"		LDA-$CeCl_3$	3	12	
"	"	LDA	3	trace	
"	PhCHO	LDA-$CeCl_3$	1.5	94	91: 9
"	"	LDA	1.5	60	91: 9 (92: 8)[d]
"	"	LBTMSA-$CeCl_3$	1.5	89	13:87
"	"	LBTMSA	1.5	60	12:88 (12:88)[d]
"		LDA-$CeCl_3$	3	91	93: 7[f]
"	"	LDA	3	26	88:12[f]
$PhCOCH_3$		LDA-$CeCl_3$	3	60	
"	"	LDA	3	26	
	PhCHO	LDA-$CeCl_3$	1	95	50:50
"	"	LDA	1	93	55:45 (52:48)[d]

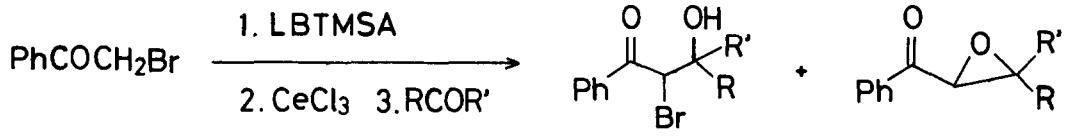
a) Isolated yield. All products gave satisfactry ^1H NMR and IR spectra.
b) Aldol ratio was determined by 100 MHz ^1H NMR, unless otherwise stated.
c) Isomer ratio was determined by 270 MHz ^1H NMR, but each isomers (threo/erythro) could not be assigned. Reference 6). d) Reference 7).
e) Each isomer (threo/erythro) could not be assigned. Reference 8).
f) Reference 9).

of a squirt to a solution of lithium enolate of propiophenone which was prepared by the reaction of propiophenone (161 mg, 1.2 mmol) with LDA (1.2 mmol) in THF-hexane(5:1) (6 ml) at -78 °C for 1 h. After stirring for 30 min, cyclohexanone (108 mg, 1.1 mmol) was added and stirring was continued for an additional 3 h at the same temperature. Then, the usual work-up of the reaction mixture gave 2-(1-hydroxycyclohexyl)-1-phenylpropan-1-one in 79% yield.

In a similar manner, various carbonyl compounds were subjected to aldol addition, and furthermore, the same couplings were conducted in the absence of cerium chloride for comparison. These results are summarized in Table 1.

It is emphasized that cerium enolates achieved higher yields of aldols than lithium enolates, although similar stereoselectivities were observed in both methods. These results can be reasonably interpreted by assuming that the transmetallation of lithium enolates with cerium chloride proceeds without change of the geometry of enolates, and that the generated cerium enolates react with carbonyl compounds via well-recognized six-membered transition state. The stereochemistry of the products, therefore, originates from the geometry of the initially formed lithium enolates; (Z)-enolates lead to erythro aldols and (E)-enolates to threo isomers. Cerium (III) ion plays a role for the effective interception of intermediacy aldol adduct by chelate formation more tightly than lithium ion, suppressing retro-aldol and/or cross enolization, and hence the aldols are produced in high yields.

On the basis of the facts mentioned above, we next tried to prepare α-bromo-β-hydroxyketones which are important intermediates to α,β-epoxyketones.[10] Our preliminary experiments showed that the desired products could be obtained in good yields, as is depicted below. This method is favorably compared with the reaction using LBTMSA only.



R = Ph , R' = H	74%[11]	21%
(none $CeCl_3$	36	55)
R, R' = $-(CH_2)_5-$	75[12]	8
(none $CeCl_3$	trace	trace)

References and Notes

1) For reviews, see; a) C.H. Heathcock in "Comprehensive Carbanion Chemistry" T. Durst and E. Buncel, Eds. Vol. II. Elsevier, Amsterdam, 1981; b) P.A. Bartlett, Tetrahedron, 36, 2 (1980); c) T. Mukaiyama, Org. Reactions, Vol. 28, p. 208 (1982).

2) For recent notable examples of aldol reactions, see; C.H. Heathcock, J.P. Hagen, E.T. Jarvi, M.C. Pirrung, and S.D. Young, J. Am. Chem. Soc., 103, 4972 (1981); D.A. Evans, J.V. Nelson, E. Vogel, and T.R. Taber, ibid., 103, 3099 (1981); D.A. Evans and L.R. NcGee, ibid., 103, 2876 (1981); A.I. Meyers and Y. Yamamoto, ibid., 103, 4278 (1981); R. Noyori, I. Nishida, and J. Sakata, ibid., 103, 2106 (1981); S. Masamune, W. Choy, F.A.J. Kerdesky, and A. Imperiali, ibid., 103, 1566 (1981); S. Masamune, T. Kaiho, and D.S. Garvey, ibid., 104, 5521 (1982), and references cited therin.

3) T. Mukaiyama, K. Banno, and K. Narasaka, J. Am. Chem. Soc., 96, 7503 (1974); E.J. Corey and D. Enders, Chem. Ber., 111, 1362 (1978); F. Gaudermar-Bardone and M. Gaudermar, J. Organomet. Chem., 104, 281 (1976); T. Inoue, T. Uchimaru, and T. Mukaiyama, Chem. Lett., 1977, 153, and refernce 1c.

4) T. Mukaiyama, R.W. Stevens, and N. Iwasawa, Chem. Lett., 1982, 353; R.W. Stevens, N. Iwasawa, and T. Mukaiyama, ibid., 1982, 1459; R.W. Stevens and T. Mukaiyama, ibid., 1983, 595.

5) T. Imamoto, T. Kusumoto, and M. Yokoyama, J. Chem. Soc., Chem. Commun., 1982, 1042.

6) 270MHz ^{1}H NMR ($CDCl_3$); major isomer δ 7.94-7.97(m,2H), 7.44-7.61(m,3H), 3.87(s,1H), 3.57(q,J=6.9Hz,1H), 1.45-1.78(m,2H), 1.25(d,J=7.3Hz,3H), 1.19(s,3H), 0.94(t,J=7.9Hz,3H); minor isomer δ 7.94-7.97(m,2H), 7.44-7.61(m,3H), 3.70(s,1H), 3.57(q,J=6.9Hz,1H), 1.45-1.78(m,2H), 1.28(d,J=6.9Hz,3H), 1.20(s,3H), 0.87(t,J=7.6Hz,3H).

7) C.H. Heathcock, C.T. Buse, W.A. Kleschick, M.C. Pirrung, J.E. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (1980).

8) ^{1}H NMR (CCl_4); major isomer δ 7.86-8.02(m,2H), 7.34-7.54(m,3H), 6.71(s,2H), 5.46(d,J=10Hz,1H) 3.94-4.30(m,1H), 2.83(s,1H), 2.44(s,6H), 2.22(s,3H), 0.83(d,J=8Hz,3H); minor isomer δ 7.43-7.68(m,2H), 7.07-7.30(m,3H), 6.31(s,2H), 5.10(d,J=9Hz,1H), 3.94-4.30(m,1H), 2.83(s,1H), 2.35(s,6H), 2.09(s,3H), 1.30(d,J=7Hz,3H).

9) ^{1}H NMR ($CDCl_3$); threo isomer δ 6.83(s,2H), 6.80(s,2H), 5.67(d,J=10Hz,1H), 3.56-3.92(m,1H), 2.70(s,1H), 2.10-2.64(m,18H), 0.78(d,J=7Hz,3H); (erythro isomer δ 5.25(d,J=8Hz), 1.27 (d,J=7Hz)).

10) S. Shoda and T. Mukaiyama, Chem. Lett., 1981, 723; T. Mukaiyama, T. Haga, and N. Iwasawa, ibid., 1982, 1601.

11) IR (KBr); 3480 cm^{-1} (-OH), 1675 cm^{-1} (C=O); 270MHz ^{1}H NMR ($CDCl_3$); δ 7.83-8.10(m,2H), 7.23-7.62(m,8H), 5.20-5.39(m,2H), 3.40-3.90(br,1H); Exact mass (M^++1); m/e 305.0154: calcd. for $C_{15}H_{14}BrO_2$: 305.0177. Isomer ratio could not be determined.

12) IR (neat); 3475 cm^{-1} (-OH), 1670 cm^{-1} (C=O); ^{1}H NMR (CCl_4); δ 7.80-8.15(m,2H), 7.15-7.65(m, 3H), 5.08(s,1H), 3.73(s,1H), 0.80-2.30(m,10H); Exact mass (M^++1); m/e 297.0523: calcd. for $C_{14}H_{18}BrO_2$: 297.0490.

(Received in Japan 8 August 1983)