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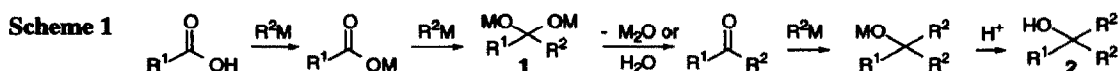
Cerium(III) Chloride Remarkably Increases the Rates of Formation and Yields of Ketones in The Reaction of Lithium Carboxylates with Organolithiums

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Abstract: The presence of CeCl_3 greatly increases the yield of ketones in the reaction of organolithiums with lithium carboxylates. The Ce^{III} suppresses the enolization of the lithium carboxylate, previously unrecognized as a competing reaction except in special cases, and the formation of tertiary alcohols. One of the reasons for the latter effect is a surprising increase in the rate of addition of the organometallic to the lithium carboxylate in the presence of Ce^{III} .

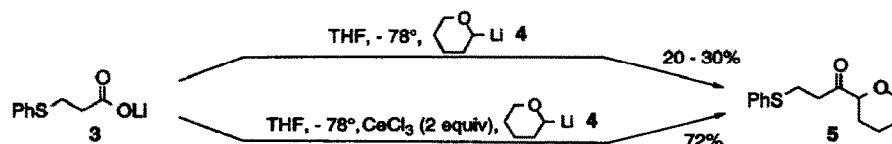
The reaction of organometals and carboxylic acids is a venerable textbook method for the synthesis of ketones.¹⁻⁵ However, this method utilizing organolithium or Grignard reagents is often marred by low ketone yields and/or simultaneous formation of tertiary alcohols 2.¹⁻³ The formation of 2 apparently occurs when ketone, produced by decomposition of the tetrahedral intermediate 1 both *before* and *during* workup, reacts with organolithium (Scheme 1).^{2a,5}



With regard to the decomposition of 1 before workup, a somewhat similar situation obtains in the addition of organometallics to lactones to give lactols accompanied by varying amounts of tertiary alcohols. Previous work from this laboratory has demonstrated that organocerium(III) compounds give far better yields of monoaddition product (lactols) than do organolithium compounds.⁶

Our original goal in the present work was to convert 2-lithiotetrahydropyran (4), prepared⁷ by reductive lithiation of 2-(phenylthio)tetrahydropyran with lithium 4,4'-di-*tert*-butylbiphenylide⁸ (LDBB), to ketone 5 as a starting material for a spiroketal synthesis.^{6,9} Although the reaction of 3-(phenylthio)propanoyl chloride, derived from the precursor of 3, with the heterocuprate¹⁰ generated from 4 gave a fair yield (48%), it was hoped that a one-pot process starting directly from the carboxylic acid would prove more efficient. However, treating the lithium carboxylate (prepared from *n*-butyllithium and the carboxylic acid) with the organolithium 4 at -78°C gave unsatisfactory yields (20-30%) of 5. Gratifyingly, a substantial increase in yield to 72% was attained by mixing 2 equiv. of CeCl_3 with the lithium carboxylate prior to the addition of 4 (Scheme 2). It is noteworthy that the yields of 5 were lower when only 1 equiv. of CeCl_3 was used either in the procedure described above (51%) or by using the preformed organocerium (57%).

Scheme 2



These observations prompted a study of the general applicability of CeCl_3 to enhance the yield of ketones in the reaction of organolithiums with lithium carboxylates. The following methods were compared.

Method A: (CeCl_3 present) R^3Li (1 equiv) is added to the carboxylic acid solution in THF at -78°C and stirred for 15 min. A suspension of CeCl_3 (2 equiv) in THF¹¹ at -78°C is cannulated to the lithium carboxylate solution and the resulting mixture is stirred for 30 min. at -78°C . R^3Li (1 equiv) is added dropwise and the mixture is stirred for the specified length of time before the addition of 5% HCl at -78°C .

Method B: (CeCl_3 absent) R^3Li (2 equiv) is added to the carboxylic acid solution in THF at -78°C and the mixture is stirred for the specified length of time before being quenched with 5% HCl at -78°C .

CeCl_3 greatly increases the yield of 5-decanone from *n*-butyllithium and hexanoic acid (**6a**) (Table 1). One of the reasons is evident from entries 1-6. The reaction of **6a** with *n*-butyllithium gives a much higher ratio of ketone to tertiary alcohol in the presence of CeCl_3 , suggesting that the cerium(III) leads to a decreased rate of decomposition of the tetrahedral diolate intermediate **1** relative to its rate of formation. In the absence of CeCl_3 , some tertiary alcohol is formed before and some during workup as indicated by the increase in the ratio of ketone to alcohol when the butyllithium is destroyed by silylation before workup⁵ (compare entries 4 and 5). In view of the finding (entries 1-6) that when CeCl_3 is used the carboxylic acid is almost completely utilized in 4 hr while in its absence most of the acid is recovered in the same time period, it appears that the presence of Ce^{III} greatly enhances the addition rate. Its effect on the rate of decomposition of **1** is not known.

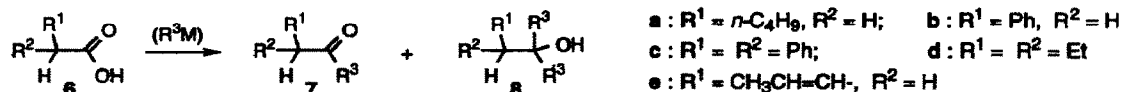
However, one possible reason for the recovery of most of the acid in the experiments in the absence of Ce^{III} is that the lithium carboxylate may have been deprotonated by the butyllithium. That some deprotonation has indeed occurred is indicated by the 15% - 37% (depending on the quantity of butyllithium used) deuterium incorporation in the recovered acid when the reaction was quenched with 5% $\text{DCl}/\text{D}_2\text{O}$ (entries 3-6). This is a surprising finding since deprotonation has only been suspected as a serious competing reaction to ketone formation when the lithium carboxylate has an allylic or benzylic proton.¹

Thus, a second reason for the improved yields of ketone in the presence of Ce^{III} is that the latter suppresses enolization of the lithium carboxylate salt. This may explain why the organolithiums that have been used in this ketone forming reaction are generally restricted to the less basic methyl-, vinyl-, and aryllithium when an enolizable acid is used.^{3,4} It is well known that organocerium reagents cause less enolization than organolithiums or Grignard reagents in the reaction with carbonyl groups.¹²

In order to examine the effect of enolization, we chose readily enolizable phenylacetic acid **6b** and diphenylacetic acid **6c** as substrates to compare the ketone formation to enolization in the presence and absence of CeCl_3 (Table 1). In the case of lithium phenylacetate, the primary alkylmetallic reagent gave high yields of ketone in the presence of Ce^{III} and only negligible amounts in its absence (entries 7-11). It is noteworthy that the recovered acid from the reaction in the presence of CeCl_3 showed no sign of enolization while in its absence almost complete enolization occurred (entries 10-11). In the case of the secondary alkylmetallic, the product yield was not as high as in the primary case in the presence of CeCl_3 , but still far higher than in its absence (entries 12-13). The tertiary alkylmetallic reagents showed no ketone formation in the presence or absence of CeCl_3 . The almost quantitatively recovered starting acid from the *t*-BuLi reaction showed nearly complete enolization, whereas in the presence of Ce^{III} none of the recovered acid had been enolized (entries 14-16). The most striking comparison was in the case of PhLi, in which the yield improved from less than 1% to 95% (entries 17-18) when CeCl_3 was used. Further dramatic results were evident in entries 21-27; the ketone was formed even from the highly enolizable diphenylacetic acid **6c** in the presence of CeCl_3 , whereas in its absence only traces of ketone were detected.

A few other interesting aspects can be gleaned from the table. The use of preformed *n*-butylcerium gives the same result as the addition of *n*-butyllithium to the mixture of the lithium carboxylate and CeCl_3 (entries 21-22), possibly implying that an organocerium reagent is being generated in method A. Raising the temperature from -78 to -60°C results in a huge increase in the yield of tertiary alcohol (entries 21, 24) probably due to an increase in the rate of decomposition of the tetrahedral intermediate **1** relative to its rate of formation. 1-Cyclohexenyllithium gives a modest yield of ketone in the presence of CeCl_3 even in the case of the readily ionized phenylacetate ion (entry 19) but, in this particular case, some of the resulting enone is destroyed by conjugate addition of thiophenoxide produced in the reductive lithiation of the 1-cyclohexenyl phenyl sulfide used to prepare the organolithium.¹³ In the presence of CeCl_3 , even the very basic *sec*-butyllithium gives some enone with a carboxylic acid salt that bears an allylic proton (entry 31); presumably, *sec*-organolithiums would give satisfactory yields with less acidic lithium carboxylates. Finally, as may be expected for the addition of an organometallic to a quasicarbonyl group, steric hindrance inhibits the reaction substantially (compare entry 10 with entries 12, 14, 29).

Table 1. Formation of Ketones from Carboxylic Acids 6



Entry	Acid	Reagent (equiv)	Method	Time (h)	R ³	Ketone	Yield ^a % (% D) ^b	Alcohol	Yield ^a (%)	Recovered % (% D) ^b
	6					7		8		
1	6a	<i>n</i> -BuLi/CeCl ₃ (1:2)	A	16	<i>n</i> -Bu	7a	83	8a	8	<i>c</i>
2		<i>n</i> -BuLi/CeCl ₃ (1:2)	A	4	<i>n</i> -Bu	7a	82	8a	7	3
3		<i>n</i> -BuLi (2)	B ^d	16	<i>n</i> -Bu	7a	15 (80)	8a	6	79 (15)
4		<i>n</i> -BuLi (2)	B ^d	4	<i>n</i> -Bu	7a	7 (76)	8a	7	82 (17)
5		<i>n</i> -BuLi (2)	B ^e	4	<i>n</i> -Bu	7a	12 (=100)	8a	4	78 (12)
6		<i>n</i> -BuLi (3)	B ^d	4	<i>n</i> -Bu	7a	7 (36)	8a	15	71 (37)
7	6b	MeLi/CeCl ₃ (1:2)	A	16	Me	7b	62	8b	<i>f</i>	<i>c</i>
8		MeLi/CeCl ₃ (1:2)	A ^g	4	Me	7b	61	8b	<i>f</i>	<i>c</i>
9		MeLi (2)	B ^g	4	Me	7b	0.6	8b	<i>f</i>	<i>c</i>
10		<i>n</i> -BuLi/CeCl ₃ (1:2)	A ^h	24	<i>n</i> -Bu	7b	74 (0)	8b	<i>f</i>	14 (0)
11		<i>n</i> -BuLi (2)	B ^d	4	<i>n</i> -Bu	7b	trace	8b	<i>f</i>	<i>i</i> (100)
12		<i>s</i> -BuLi/CeCl ₃ (1:2)	A ^d	4 ⁱ	<i>s</i> -Bu	7b	36 ^k	8b	<i>f</i>	58 (24)
13		<i>s</i> -BuLi (2)	B ^d	4	<i>s</i> -Bu	7b	trace	8b	<i>f</i>	>99 (48)
14		<i>t</i> -BuLi/CeCl ₃ (1:2)	A	4 ^l	<i>t</i> -Bu	7b	0	8b	<i>f</i>	<i>c</i>
15		<i>t</i> -BuLi/CeCl ₃ (1:2)	A ^{d,m}	0.25 ⁿ	<i>t</i> -Bu	7b	0	8b	<i>f</i>	100 (0)
16		<i>t</i> -BuLi (2)	B ^d	4	<i>t</i> -Bu	7b	0	8b	<i>f</i>	100 (100)
17		PhLi/CeCl ₃ (1:2)	A	16 ^o	Ph	7b	95	8b	<i>f</i>	<i>c</i>
18		PhLi (2)	B	4	Ph	7b	trace	8b	<i>f</i>	>99
19		1-cyclohexenylLi/CeCl ₃ (1:2)	A	0.5 ^p	1-cyclohexenyl	7b	24 ^q	8b	<i>f</i>	<i>c</i>
20		1-cyclohexenylLi (2)	B	4	1-cyclohexenyl	7b	trace	8b	<i>f</i>	<i>c</i>
21	6c	<i>n</i> -BuLi/CeCl ₃ (1:2)	A ^r	16	<i>n</i> -Bu	7c	39	8c	<i>f</i>	<i>c</i>
22		<i>n</i> -BuLi/CeCl ₃ (1:2)	A ^{m,r}	16	<i>n</i> -Bu	7c	39	8c	<i>f</i>	<i>c</i>
23		<i>n</i> -BuLi/CeCl ₃ (1:2)	A ^{d,r}	4	<i>n</i> -Bu	7c	30 (9) ^s	8c	<i>f</i>	28 (11)
24		<i>n</i> -BuLi/CeCl ₃ (1:2)	A ^{r,t}	16	<i>n</i> -Bu	7c	25	8c	30	<i>c</i>
25		<i>n</i> -BuLi/CeCl ₃ (1:1)	A ^r	16	<i>n</i> -Bu	7c	15	8c	<i>f</i>	<i>c</i>
26		<i>n</i> -BuLi/CeCl ₃ (1:4)	A ^r	16	<i>n</i> -Bu	7c	5	8c	<i>f</i>	<i>c</i>
27		<i>n</i> -BuLi (2)	B ^{d,r,u}	4	<i>n</i> -Bu	7c	trace	8c	<i>f</i>	<i>i</i> (100)
28	6d	<i>n</i> -BuLi/CeCl ₃ (1:2)	A	16	<i>n</i> -Bu	7d	21	8d	8	63
29		<i>n</i> -BuLi/CeCl ₃ (1:2)	A ^d	4	<i>n</i> -Bu	7d	8	8d	2	86 (0)
30		<i>n</i> -BuLi (2)	B	4	<i>n</i> -Bu	7d	0	8d	0	100
31	6e	<i>s</i> -BuLi/CeCl ₃ (1:2)	A	4	<i>s</i> -Bu	7e	29	8e	<i>f</i>	<i>c</i>
32		<i>s</i> -BuLi (2)	B	4	<i>s</i> -Bu	7e	trace	8e	<i>f</i>	<i>c</i>

^a Isolated yield. ^b The figures in parentheses are the percentages of deuteration for one α -H. The extent of deuteration was determined by the ¹H NMR analyses of the isolated compounds from the reaction which was quenched with 5% DCI/D₂O or with 10% AcOD at the reaction temperature. ^c Present but not recovered. ^d The reaction was quenched with 5% DCI/D₂O. ^e The reaction mixture was quenched⁵ with TMSCl at -78°C, then warmed to RT before 5% DCI/D₂O addition. ^f Insignificant yield. ^g The reaction mixture was quenched with TMSCl at -78°C, then warmed to RT before 5% HCl addition.³ ^h The reaction mixture was quenched with 10% AcOD. ⁱ The amount of recovery was not measured. ^j Longer and shorter reaction times gave lower product yields (16 h, 23%; 0.25 h, 19%). ^k The product ketone showed 30% deuteration for one of the 2° α -H, and 25% deuteration for the 3° α -H. ^l No product was obtained upon increasing the time to 16 h. ^m The organolithium was added to the CeCl₃ (2 equiv) suspension in THF at -78°C. After being stirred for 30 min., the mixture was cannulated to the lithium carboxylate solution at -78°C. ⁿ No product was obtained upon increasing the time to 4 h. ^o A similarly high yield of the product (91%) was obtained upon decreasing the time to 4 h. ^p Longer reaction times did not improve the yield. ^q 2-(Phenylthio)cyclohexyl benzyl ketone, the thiophenoxide adduct of the product enone, was also obtained in 13% yield. ^r Because of the low solubility of **6c** in THF at -78°C, *n*-BuLi (1 equiv. in Method A; 2 equiv. in Method B) was added to the THF solution of **6c** at 0°C, and the mixture was stirred for 15 min. before being cooled to the reaction temperature. ^s The product ketone was deuterated at the 3° α -H. ^t The reaction temperature was -60°C. ^u The reaction temperature was 0°C. 4 Equiv. of *n*-BuLi also gave no product.

In conclusion, CeCl_3 is highly effective at increasing the yield of ketone produced in the reaction of an organolithium with a lithium carboxylate at a low temperature. Its effect is to increase the rate of production of the tetrahedral intermediate so that tertiary alcohol formation is suppressed and, in cases in which an enolizable proton is present, to suppress enolization, a previously unrecognized (except in special cases) competing process. We suspect that the enhanced addition rate is due to greater carbonyl character in cerium vs lithium carboxylates, due to the increased strength of the Ce-O as opposed to the Li-O bond.

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