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CaF_2 catalyzed S_N2 type chlorodehydroxylation of chiral secondary alcohols with thionyl chloride: a practical and convenient approach for the preparation of optically active chloroalkanes

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ABSTRACT

A CaF_2 catalyzed chlorodehydroxylation of chiral secondary alcohols with thionyl chloride has been developed. The chlorination reaction is effective for a wide range of alcohols, generating the corresponding chloroalkanes in good yield with high optical purity with inversion of the original configuration of the alcohol.

Optically active alkyl chlorides are commonly used as both very useful synthetic intermediates and valuable end products.[1] For example, they can be used as electrophiles and are converted, by nucleophilic displacement, to various valuable chiral synthons including amines, thiols, or ethers.[2] Since alcohols are one of the most common and versatile compounds for transformation into other classes of chemicals, an overwhelming approach to the alkyl chlorides and other halide analogues is the replacement of the hydroxyl group of the corresponding alcohols. Consequently, chlorination of alcohols has been accepted as a general and basic transformation pathway in organic synthesis.[3] The conversion can be accomplished using a two-step procedure where the alcohol is first converted into a leaving group (generally a sulfonate) followed by nucleophilic displacement with the appropriate halide or in a single flask where both steps are performed in situ. Not surprising, the direct chlorodehydroxylation of alcohols is more preferable than the former. Although the hydroxyl moiety is hardly substituted due to its lower leaving ability, numerous chlorination reagents have been developed during the past several decades. Among them, the most important reagents for such a displacement of the hydroxyl group by chlorine in a stereospecific manner are thionyl chloride,[4] phosphorus compounds, such as PCl_3,[5] PCl_5,[6] R_3PCl_2,[7] Ph_3P/CCl_4,[8] $Ph_3P/Cl_3CCOCCl_3$,[9] or Ph_3P/R_2SeCl_2[10] system. Other methods, such as the use of 2-chlorobenzoxazolium salt,[11] *N*,*N*-diphenylchlorophenyl-methyleniminium chloride,[12] or *N*,*N*′-diisopropylcarbodiimide/AcCl/CuCl[13] as the chlorination reagents were also developed. Recently, the first triphenylphosphine oxide-catalyzed Appel-type chlorination[14] reaction has been realized using oxalyl chloride as the chlorination reagent.[15] In case of Ph_3P in combination with an electrophilic halogen source as the chlorination reagent, the concomitant generation of stoichiometric phosphine oxide by-products impacts severely on the atom efficiency and large-scale applicability of these reactions. Furthermore, purification of the product is not always straightforward. The use of phosphorus chloride, oxalyl chloride, benzoxazolium phenylmethyleniminium salt, or *N*,*N*′-diisopropylcarbodiimide/AcCl/CuCl system suffers from some disadvantages with respect to reaction conditions, availability, or purification issues. Generally, the use of thionyl chloride demonstrated great advantage on purification and large-scale applicability because only two gaseous byproducts were generated in this process. With respect to the stereochemical outcome of the reaction, the reaction proceeds with retention of the original configuration of the alcohol via an internal nucleophilic substitution (S_Ni) when $SOCl_2$ alone was employed as the chlorination reagent, while the introduction of chlorine occurred with inversion of stereochemistry by an S_N2 fashion in the presence of pyridine.[16] The main drawback of the latter process is the addition of at least stoichiometric odorous pyridine. Although Kellogg has reported an S_N2-type chlorodehydroxylation of ethyl L-lactate with thionyl chloride in the presence of catalytic amount of DMF, the generality of the reaction has not been examined.[17] Therefore, the development of an alternative process for the chlorodehydroxylation of chiral alcohols by thionyl chloride with inversion of the configuration avoiding the use of pyridine will be of great interest and remains a challenging task. Herein, we report the development of a practical and convenient approach for the preparation of optically active chloroalkanes via CaF_2 catalyzed S_N2 type chlorodehydroxylation of chiral secondary alcohols with thionyl chloride.

In the literature report, CaF_2 has proven to be an efficient catalyst for the chlorination of *O*,*O*-dimethyl methylphosphonate with thionyl chloride, generating the corresponding methylphosphonodichloride in excellent yields.[18] We envisioned that this

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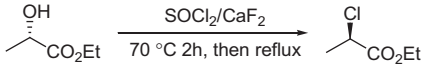
Table 1
Optimization of the reaction condition[a]



Entry	CaF_2 (mol %)	$SOCl_2$ (equiv)	Time (h)	Yield[b] (%)	ee[c] (%)
1	10	1.0	4	74	94
2	10	1.1	7	85	95
3	10	1.2	9	82	94
4	5	1.1	8	80	94
5	1	1.1	11	74	89
6	0	1.1	15	60	−70

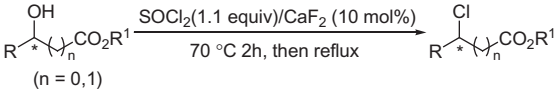
[a] All the reactions are performed on a 20 mmol scale.
[b] Isolated yield.
[c] Determined by chiral GC analysis.

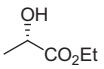
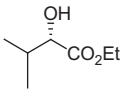
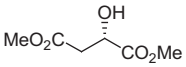
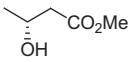
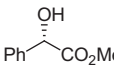
chlorination system may be applied for the preparation of the chiral alkyl chloride from optically active secondary alcohols via an S_N2 type displacement of hydroxyl group with chlorine.

We first optimized the chlorination reaction using ethyl L-lactate as the test substrate and the selected results are shown in Table 1. Screening of an appropriate solvent was first performed upon treatment of ethyl L-lactate with 1 equiv thionyl chloride in the presence of 10 mol % of CaF_2. The formation of the corresponding ethyl (*R*)-2-chloropropionate was not detected when the reaction mixture was refluxed for 48 h in conventional solvents, such as chloroform, 1,2-dichloroethane, and toluene. It was gratifying that decomposition of the corresponding chlorosulfinic ester preformed at 70 °C for 2 h was observed at refluxing (appr. 170 °C) under solvent free condition, providing the chlorinated product with inversion of configuration in 74% yield with ee value of 94% (Table 1, entry 1). Increasing the amount of thionyl chloride from 1.0 to 1.1 equiv gave rise to a slightly increased enantioselectivity and yield (Table 1, entry 2). The use of 1.2 equiv of chlorination reagent failed to further improve the optical purity of the product (Table 1, entry 3). Adjusting the catalyst loading demonstrates an obvious influence on the reaction. Reducing the amount of CaF_2 to 5 mol % led to a slightly decreased yield and ee value. Further reducing the catalyst loading to 1 mol % resulted in a slower reaction and marked decease in enantioselectivity. In addition, some control experiments were performed to elucidate the important role of CaF_2 in this transformation. Under indentical conditions, the chlorodehydroxylation product was obtained in 60% yield with the retention of stereochemistry in the absence of CaF_2 (Table 1, entry 6, −70% ee). The use of other calcium salts, such as $CaCl_2$ and $CaSO_4$, resulted in both decrease in yield and enantioselectivity ($CaCl_2$: 20% yield, 40% ee; $CaSO_4$: 30% yield, 85% ee), while Bu_4NF was not active at all in this process.

With a protocol for catalytic chlorination in hand we examined a range of optically active hydroxyl substituted carboxylate substrates, such as (*S*)-methyl 3-methyl-2-hydroxybutanoate, (*S*)-dimethyl 2-hydroxysuccinate, (*R*)-methyl 3-hydroxybutanoate, and (*S*)-methyl mandelate, under the optimal conditions (Table 2).[18] In general, the corresponding configuration inversed chlorination products can be obtained in good yields with high optical purity for chiral alkyl substituted acetate regardless of the hydroxyl group's location (Table 2, entries 1–4). In the case of the aryl substituted substrate, (*S*)-methyl mandelate, the reaction occurred with partial racemization, which indicated that the existence of a competition of the type S_N1 versus S_Ni in the decomposition process of the chlorosulfinic ester (Table 2, entry 5). This may be attributed to the unusual stability of the benzylic carbocation. Nevertheless, it is noteworthy that, in all cases, the corresponding

Table 2
Catalytic chlorination of hydroxyl substituted carboxylate[a]



Entry	Substrate	Time (h)	Yield (%) [b,c]	ee[c] (%)
1		7	85 (81)	95 (93)[d]
2		13	78 (72)	92 (88)[e]
3		6	86 (81)	95 (91)[f]
4[g]		25	77 (74)	95 (92)[h]
5[g]		12	85 (80)	58 (45)[i]

[a] All the reactions are performed on a 20 mmol scale.
[b] Isolated yield.
[c] Data in parenthesis are those obtained from $SOCl_2$/pyridine system.
[d] βDEX120, R_t = 29.8 (minor) and 30.5 min (major).
[e] βDEX120, R_t = 9.42 (major) and 10.60 min (minor).
[f] Chiralpak AS–H column, hexane/2-propanol = 95/5, flow rate = 1 mL/min, wavelengh = 220 nm: R_t = 10.19 (minor) and 11.20 (major).
[g] The reaction is conducted at 70 °C.
[h] γ-DEX225, R_t = 43.9 (minor) and 44.9 min (major).
[i] Chiralpak OD–H column, hexane/2-propanol = 99/1, flow rate = 1 mL/min, wavelengh = 220 nm: R_t = 7.40 (major) and 11.20 (minor).

chloro-ester was obtained both with higher yield and optical purity than those obtained from $SOCl_2$/pyridine system.

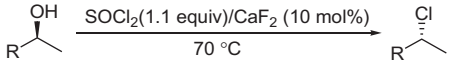
To further extend the scope of this catalytic chlorination protocol, a plethora of optically active simple secondary alcohol were prepared from the ring-opening of (*S*)-2-methyloxirane with Grignard reagent and subjected to the CaF_2 catalyzed chlorodehydroxylation with thionyl chloride. The results are collected in Table 3.

In the case of simple secondary alcohols, the optimal temperature of the decomposition of the chlorosulfinic ester is 70 °C.[19] Either increasing or decreasing the temperature will lead to a decrease of the specific rotation value of the chloroalkane. As shown in Table 3, the reaction tolerated alkyl, branched alkyl, phenyl and alkenyl substituted chiral secondary alcohols, generating the corresponding alkyl chloride with inversion of the original configuration of the alcohol. Compared with the results obtained for $SOCl_2$/pyridine system, better or comparable yields and stereochemistry outcomes were obtained for this newly developed CaF_2 catalyzed chlorination system.

To demonstrate the potential of this method for preparative purposes, the chlorodehydroxylation of (*S*)-ethyl lactate is also carried out on a large scale giving (*R*)-ethyl 2-chloropropionate without any erosion in both chemical yield and optical purity (Scheme 1). In view of the latter being the key intermediate for the synthesis of L-alanyl-L-glutamide which is currently used as part of total parenteral nutrition protocols in hospital settings, this efficient and environmental benign stereoselective chlorodehydroxylation process will be of great importance for the synthesis of L-alanyl-L-glutamide and related fine chemicals.

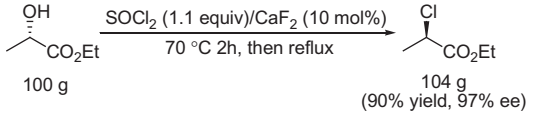
In conclusion, a CaF_2 catalyzed chlorodehydroxylation of chiral secondary alcohols with thionyl chloride has been developed. The stereochemistry outcome indicates that the S_N2 process leading to the inversion of configuration is involved in this developed reagent system. Compared with the literature reported $SOCl_2$/pyridine

Table 3
Catalytic chlorination of chiral secondary alcohols[a]



Entry	Substrate	Time (h)	Yield[b,c] (%)	$[\alpha]_D^{25}$ (*c* 1.0 $CHCl_3$)[c]
1	Et	3	82 (77)	−33.6 (−32.8)[d]
2	Pr	3	86 (84)	−28.9 (−28.7)[e]
3	^{i}Bu	4	87 (83)	−34.2 (−33.6)
4	Pentyl	4	82 (81)	−34.8 (−32.5)
5	Octyl	5	89 (85)	−27.4 (−26.7)[f]
6	Bn	2.5	68 (74)	−32.9 (−33.8)[g]
7	$BnCH_2$	3	71 (80)	−43.8 (−42.6)
8	$BnCH_2CH_2$	3	74 (78)	−35.7 (−36.4)
9	Allyl	3	65	−22.7[h]
10	$CH_2{=}CHCH_2CH_2$	3	68	−23.6[i]

[a] All the reactions are performed on a 20 mmol scale.
[b] Isolated yield.
[c] Data in parenthesis are those obtained from $SOCl_2$/pyridine system.[20]
[d] $[\alpha]_D^{20}$ −31.2 (neat).[21]
[e] $[\alpha]_D^{20}$ −38.1 (methanol).[22]
[f] $[\alpha]_D^{20}$ +33.0 (*c* 0.97, CH_2Cl_2) for *S* enantiomer.[23]
[g] $[\alpha]_D^{25}$ −20.0 (*c* 5, $CHCl_3$)[24] and $[\alpha]_D^{16}$ −22.6 (neat).[25]
[h] $[\alpha]_{587.5}^{25}$ −5.1 (calculated value).[26]
[i] $[\alpha]_D^{25}$ −61.8 (calculated value).[27]



Scheme 1. Large-scale preparation of (*R*)-ethyl 2-chloropropionate.

method, the great advantage of this chlorination system is that only catalytic amount of CaF_2 is sufficient to ensure the conversion of the alcohol into the corresponding alkyl chloride with high optical purity in an S_N2 fashion, avoiding the use of at least stoichiometric environmentally hazardous pyridine. Moreover, the new reaction described here offers a practical and inexpensive method for the synthesis of the key intermediate for the synthesis of L-alanyl-L-glutamide.

Acknowledgments

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19. *General procedure for the CaF_2 catalyzed chlorodehydroxylation of chiral secondary alcohols*: To a mixture of thionyl chloride (1.6 mL, 22 mmol) and CaF_2 (156 mg, 2 mmol) was added dropwise the chiral secondary alcohols at room temperature. After stirring at 70 °C for 2 h, the reaction mixture was heated to refluxing or maintain the same temperature for the depicted time. Then the reaction mixture was cooled to room temperature, neutralized with saturated aqueous $NaHCO_3$ solution, extracted with methylene chloride, and dried over anhydrous $MgSO_4$. After removal of solvent in vacuum, the crude product was purified either by column chromatograph on silica gel or distillation under reduced pressure. *2-Methyl-4-chloropentane*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 1.40–1.47 (m, 1 H), 1.51 (d, *J* = 6.6 Hz, 3 H), 1.64–1.74 (m, 1 H), 1.83–1.88 (m, 1 H), 4.03–4.15 (m, 1 H). *2-Chloroheptane*: ^{1}H NMR ($CDCl_3$, 400 MHz): 0.90 (t, *J* = 6.4 Hz, 3 H), 1.26–1.35 (m, 4 H), 1.37–1.43 (m, 1 H), 1.45–1.50 (m, 1 H), 1.51 (d, *J* = 6.4 Hz, 3 H), 3.99–4.07 (m, 1 H). *1-(3-Chlorobutyl)benzene*: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.54 (d, *J* = 6.4 Hz, 3 H), 1.99–2.06 (m, 2 H), 2.72–2.79 (m, 1 H), 2.83–2.90 (m, 1 H), 3.96–4.05 (m, 1 H). 7.21–7.22 (m, 3 Harom), 7.29–7.32 (m, 2 Harom). *1-(4-Chloropentyl)benzene*: ^{1}H NMR ($CDCl_3$, 400 MHz): 1.50 (d, *J* = 6.4 Hz, 3 H), 1.74–1.78 (m, 3 H), 1.82–1.89 (m, 1 H), 2.63–2.68 (m, 2 H), 4.01–4.09 (m, 1 H), 7.18–7.21 (m, 3 Harom), 7.27–7.31 (m, 2 Harom).
20. *General procedure for the chlorodehydroxylation of chiral secondary alcohols with Py/$SOCl_2$*: To a solution of alcohol (0.02 mol) and pyridine (0.022 mol) in chloroform (20 mL) was added dropwise a solution of $SOCl_2$ (0.022 mol) in chloroform (10 mL) at 0 °C. Then resulting mixture was heated to 60 °C until the full conversion of the alcohol. After cooling to room temperature, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The organic phase was separated and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified either by column chromatograph on silica gel or distillation under reduced pressure.
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