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Highly Enantioselective Chlorination of β-Keto Esters and Subsequent S_N2 Displacement of Tertiary Chlorides: A Flexible Method for the Construction of Quaternary Stereogenic Centers

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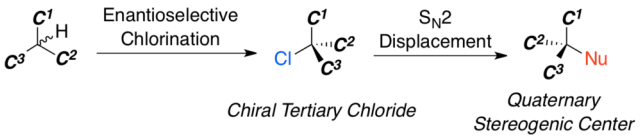
Supporting Information

ABSTRACT: Highly enantioselective chlorination of β-oxo esters and subsequent stereospecific substitution of tertiary chlorides are described. Enantioselective chlorination of β-keto esters and malonates was performed using a chiral Lewis acid catalyst prepared from $Cu(OTf)_2$ and the newly developed spirooxazoline ligand **2** to yield the desired α-chlorinated products with high enantioselectivity (up to 98% ee). Nucleophilic substitution of the resulting chlorides proceeded smoothly to afford a variety of chiral molecules such as α-amino, α-alkylthio, and α-fluoro esters, without loss of enantiopurity. The results of X-ray crystallographic analysis proved that Walden inversion occurs at the chlorinated tertiary carbon center. These results supported the fact that the substitution proceeds via an S_N2 mechanism.

The S_N2 reaction, one of the most fundamental reactions in organic transformation, can be used for the construction of enantioenriched chiral carbon centers because the substitution proceeds with complete inversion of stereochemistry. Optically active tertiary chlorides could be useful intermediates for the preparation of a variety of chiral molecules having a quaternary stereogenic center if S_N2 substitution were to occur at the chlorinated tertiary carbon. However, this process has not been successful to date except in a rare instance[1] because of two major underlying problems: First, as described in organic chemistry textbooks, tertiary halides (particularly tertiary chlorides) rarely undergo S_N2 substitution.[2] Second, there are relatively few catalytic methods that afford highly enantioenriched tertiary chlorides, and the development of such a reaction with broad substrate scope remains a challenge.[3−5] We describe herein the highly enantioselective chlorination of a wide range of β-keto esters in the presence of a newly synthesized chiral spirooxazoline ligand and subsequent unimpeded S_N2 substitution at the chlorinated tertiary carbon. The present method yields a variety of chiral molecules having a quaternary stereogenic center (Scheme 1).

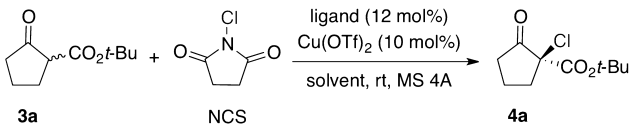
We began by focusing on the development of an efficient catalyst for the enantioselective chlorination. Our recent research revealed that the chiral pyridyl spirooxazoline ligand **1**, which we call SPYMOX, shows high asymmetric induction ability in the palladium-catalyzed allylic alkylation[6a] and copper(II)-catalyzed asymmetric fluorination of β-keto esters.[6b]

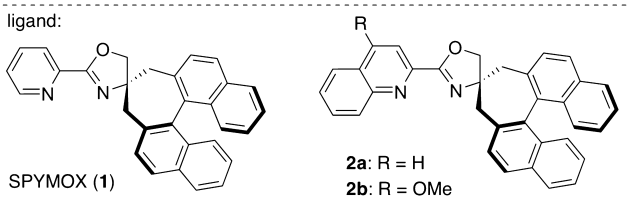
Scheme 1



We first applied SPYMOX to the asymmetric chlorination of β-keto esters using *N*-chlorosuccinimide (NCS) as the chlorination reagent. Chlorination of **3a** in the presence of the SPYMOX/$Cu(OTf)_2$ complex afforded the desired product **4a** in high yield but with moderate enantioselectivity (78% ee; Table 1, entry 1). To enhance the enantioselectivity in this chlorination, we designed new chiral spirooxazoline ligands **2** with a quinoline backbone. Specifically, we expected the steric repulsion between the substrate and the additional benzene

Table 1. Optimization of the Reaction Conditions[a]





entry	ligand	solvent	time (h)	% yield[b]	% ee[c]
1	**1**	benzene	1	93	78
2	**2a**	benzene	1	97	95
3	**2b**	benzene	1	96	95
4	**2a**	toluene	1	96	94
5	**2a**	CH_2Cl_2	1	93	93
6	**2a**	THF	2	91	71

[a]All of the reactions were carried out using 1.5 equiv of NCS in the presence of a Lewis acid catalyst prepared from 12 mol % chiral ligand and 10 mol % $Cu(OTf)_2$. [b]Isolated yields. [c]Determined by chiral GC analysis.

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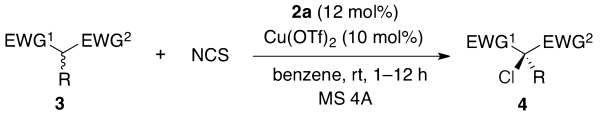
ring in **2** to push the reaction center closer to the chiral binaphthyl backbone. As expected, the enantioselectivity of the reaction dramatically increased to 95% ee when **2** was used under the same reaction conditions (entries 2 and 3). Screening of various solvents showed that benzene afforded the best enantioselectivity and reactivity.

With the optimized reaction conditions, we attempted to expand the substrate scope of the asymmetric chlorination. As summarized in Table 2, various cyclic and acyclic β-keto esters, including both aliphatic and aromatic keto esters, were successfully chlorinated with high enantiopurity. It was found that a bulky ester substituent is essential for obtaining high selectivity (entry 6 vs entry 7). Chlorination of α-alkylmalonates also proceeded with good-to-high enantioselectivity (entries 19–22).[7] On the other hand, chlorination of α-cyanoacetate and β-ketophosphonates gave poor enantioselectivity (entries 23–25). In the chlorination process, certain functional groups such as carbamate, alkene, nitrile, and an additional ketone were well-tolerated (entries 4, 5, 13–15, 21, and 22). The sense of stereoselection in the chlorination was controlled by the chiral ligand even when α-chloro-β-keto esters **4i** and **4j**, which have a menthyl ester as a chiral auxiliary, were used in the reaction (entries 9 and 10). The absolute configuration of the chlorinated chiral carbon in **4j** was determined to be *S* by X-ray structural analysis (see the Supporting Information).

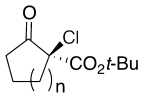
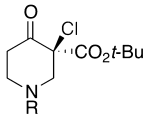
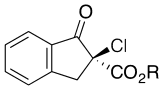
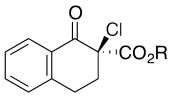
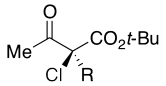
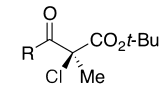
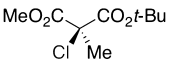
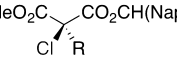
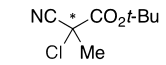
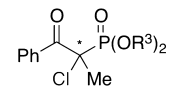
Encouraged by the high asymmetric induction ability of the new chiral ligands, we next focused on the S_N2 substitution of α-chloro-β-oxo esters.[8] First, we attempted to use sodium azide as the nucleophile. The resulting azide could be converted into a primary amine by subsequent palladium-catalyzed hydrogenolysis. For all of the substrates used, the reaction proceeded smoothly to yield the corresponding α-azido esters **5** and α-amino esters **6** in high yield (Table 3). Notably, when the palladium loading was increased to 20 mol % in the hydrogenation of **5f** and **5h**, reduction of the ketone carbonyl proceeded simultaneously with the hydrogenolysis to yield β-hydroxy-α-amino esters **7f** and **7h** in a highly diastereoselective manner (96–99% de; entries 5 and 6).[9] Most importantly, the enantiopurity of **5** was exactly the same as that of the starting compound **4** in all cases. Furthermore, single-crystal X-ray crystallographic analysis revealed that the nucleophilic substitution of **4** to give **5** involved a Walden inversion (see the Supporting Information for details). These results strongly suggested that this nucleophilic substitution proceeds via a rigorous S_N2 mechanism. The electron-withdrawing nature of the two carbonyl groups next to the chlorinated tertiary carbon probably enables the unusual S_N2 substitution of the tertiary chloride.[2b] Thus, this method will be useful for the preparation of highly substituted α-amino acid derivatives.

We next used alkylthiols as nucleophiles. As shown in Table 4, nucleophilic substitution of α-chloro-β-keto esters proceeded smoothly in the presence of triethylamine to yield the corresponding α-alkylthio-β-keto esters **8**,[10] and the enantiopurity was maintained in all cases (entries 1–7). On the other hand, the reaction of α-chloromalonate **4t** with benzylthiol did not afford the desired product at all. Finally, we attempted to carry out a much more challenging reaction, nucleophilic substitution with fluorides for the construction of fluorinated stereogenic centers. After screening several fluorides such as NaF, KF, and tetrabutylammonium fluoride, we found that a combination of CsF and 18-crown-6 efficiently promotes the nucleophilic fluorination of **4f** to afford the desired α-fluoro-β-keto ester **9f** in high yield with complete Walden inversion (entry 8). The reaction of **4h** also gave the desired product **9h** without loss of enantiopurity, but the yield was disappointingly low (35%), and *tert*-butyl 1-hydroxy-2-naphthoate, which was probably generated by the elimination of hydrogen chloride and subsequent aromatization,[11] was obtained as a byproduct in

Table 2. Enantioselective Chlorination of Active Methine Compounds[a]



EWG = electron-withdrawing group

entry	product		%yield[b]	%ee[c]
1		**4a**: n = 1	90	95
2		**4b:** n = 2	92	98
3		**4c:** n = 3	92	98
4		**4d**: R = Cbz	90	90
5		**4e**: R = Boc	93	88
6		**4f:** R = *t*-Bu	94	96
7		**4g:** R = Me	97	63
8[d]		**4h**: R = *t*-Bu	98	90
9		**4i**: R = *l*-menthyl	99	84[e]
10		**4j**: R = *d*-menthyl	96	89 (*S*)[e,f]
11		**4k**: R = Me	99	95
12		**4l**: R = Bn	94	92
13[g]		**4m**: R = allyl	96	94
14		**4n**: R = CH_2CN	84	95
15		**4o**: R = CH_2COPh	90	91
16		**4p**: R = Et	72	90
17[g]		**4q**: R = $(CH_2)_2Ph$	92	86
18[g,h]		**4r**: R = Ph	78	96
19[d,h]		**4s**	93	80
20[d,g,h]		**4t**: R = Me	93 (97[i])	91 (85[i])
21[d,g,h]		**4u**: R = CH_2CN	83	90
22[d,g,h]	Nap = 1-naphthyl	**4v**: R = allyl	80	81
23[j]		**4w**	91	0
24		**4x**: R = Et	81	37
25		**4y**: R = *i*-Pr	83	18

[a]All of the reactions were carried out using 1.5 equiv of NCS in the presence of a Lewis acid catalyst prepared from 12 mol % **2a** and 10 mol % $Cu(OTf)_2$, unless otherwise noted. [b]Isolated yields. [c]Determined by chiral HPLC or GC analysis. [d]Ligand **2b** was used instead of **2a**. [e]Diastereomeric excess. [f]Absolute configuration of the chlorinated carbon. [g]The reaction was carried out for 48–60 h. [h]36 mol % **2** and 30 mol % $Cu(OTf)_2$ were used. [i]The reaction was carried out under reflux conditions for 24 h with 12 mol % **2b** and 10 mol % $Cu(OTf)_2$. [j]The reaction was carried out under reflux conditions.

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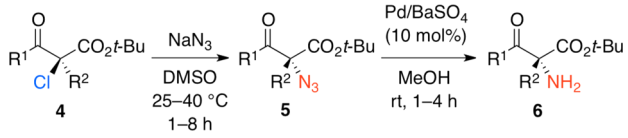
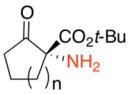
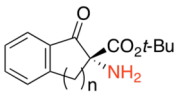
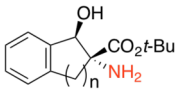
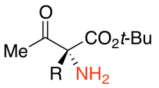
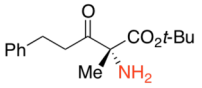
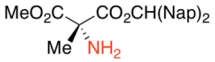
Table 3. S_N2 Substitution with Sodium Azide and Subsequent Hydrogenolysis To Give α-Amino Acid Derivatives[a]



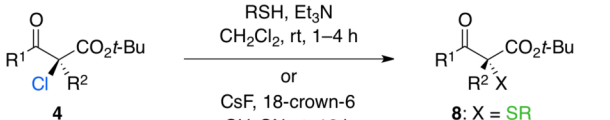
entry	4 (%ee)	product		%yield[b]	%ee[c]
1	**4a** (95)		**6a**: n = 1	85 (91)	95
2	**4b** (98)		**6b:** n = 2	92 (95)	98
3	**4f** (96)		**6f**: n = 1	97 (99)	96
4	**4h** (90)		**6h:** n = 2	69 (90)	90
5[d]	**4f** (96)		**7f**: n = 1	99[e] (99)	96
6[d]	**4h** (90)		**7h:** n = 2	90[f] (90)	90
7	**4k** (95)		**6k**: R = Me	93 (95)	95
8	**4l** (92)		**6l**: R = Bn	89 (90)	92
9	**4q** (86)		**6q**	91 (94)	86
10	**4t** (91)		**6t**	86 (99)	91

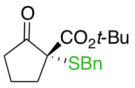
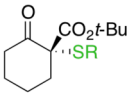
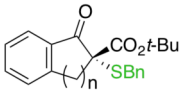
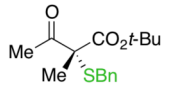
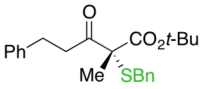
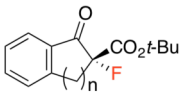
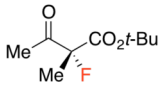
[a]All of the reactions were carried out using 3 equiv of NaN_3. [b]Isolated yields of amine **6** or **7** for two steps. Yields in parentheses are the isolated yields of azide **5**. [c]Enantiomeric excess of **5** determined by chiral HPLC or GC analysis. [d]Azidation was carried out at 25 °C for 6–20 h with 20 mol % Pd catalyst. [e]96% de. [f]99% de.

45% yield (entry 9). Surprisingly, fluorination of **4k** (95% ee) yielded the corresponding product **9k** with decreased enantiopurity (84% ee; entry 10),[12] probably because of the competitive S_N1 pathway. Furthermore, the enantiopurity of the starting chloride decreased during the course of the reaction (7% of **4k** was recovered, with 84% ee). This partial racemization, which may be due to the nucleophilic substitution (S_N2 and/or S_N1) of **4k** by CsCl generated in situ, was also the reason for the isolation of **9k** with lower enantiopurity. Unfortunately, fluorination of other substrates (**4a**, **4b**, **4p**, **4r**, and **4t**) afforded only trace amounts of the desired product under similar reaction conditions, and significant amounts of byproduct were formed. Nevertheless, an important feature of this fluorination method is that a highly enantioenriched fluorinated stereogenic center can be constructed by using the combination of an inexpensive oxidant (NCS) and a nucleophilic fluorination reagent (CsF) instead of a commonly used electrophilic fluorinating reagent[13] such as *N*-fluorobenzenesulfonimide.

In conclusion, we have successfully carried out the highly enantioselective α-chlorination of β-keto esters and malonates with a chiral spirooxazoline ligand. Substitution of the resulting chlorides with some nucleophiles successfully afforded the corresponding α-heteroatom-substituted β-oxo esters without loss of enantiopurity. The results of X-ray crystallographic analysis proved that the nucleophilic substitution with sodium azide involved a Walden inversion. These results strongly

Table 4. S_N2 Reaction with Alkylthiols and Cesium Fluoride[a]



entry	4 (%ee)	product		%yield[b]	%ee[c]
1[d]	**4a** (95)		**8a**	90	95
2	**4b** (98)		**8ba**: R = Bn	88	98
3[d]	**4b** (98)		**8bb:** R = CH_2(2-furyl)	88	97
4[d]	**4f** (96)		**8f**: n = 1	88	96
5	**4h** (90)		**8h**: n = 2	91	90
6	**4k** (95)		**8k**	96	95
7	**4q** (86)		**8q**	98	86
8	**4f** (96)		**9f**: n = 1	80	96 (*R*)
9[e]	**4h** (90)		**9h**: n = 2	35	90
10[f]	**4k** (95)		**9k**	43(80)[g]	84

[a]Sulfenylation was carried out using 3 equiv of alkylthiol and 6 equiv of Et_3N in CH_2Cl_2. Fluorination was carried out using 3 equiv of CsF and 1 equiv of 18-crown-6 in acetonitrile, unless otherwise noted. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]The reaction was carried out at 0 °C. [e]The reaction was carried out at 80 °C for 24 h. [f]Reaction was carried out at 0 °C for 168 h with 6 equiv of CsF and 1 equiv of 18-crown-6. [g]The yield in parentheses was determined by ^1H NMR analysis using 2,2,2-trifluoroethanol as an internal standard. The isolated yield was low because of the volatility of the product.

suggest that the substitution proceeds via the S_N2 mechanism, although the reaction occurred at a tertiary carbon. An advantage of our method is that it allows for the formation of multiple optically active compounds with a quaternary stereogenic center from a single intermediate.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, HPLC and GC enantiomer analyses, and NMR spectra (^1H, ^{13}C, and ^{19}F) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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