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Design and Synthesis of Chiral *N*-Chloroimidodicarbonates: Application to Asymmetric Chlorination of Silyl Enol Ethers

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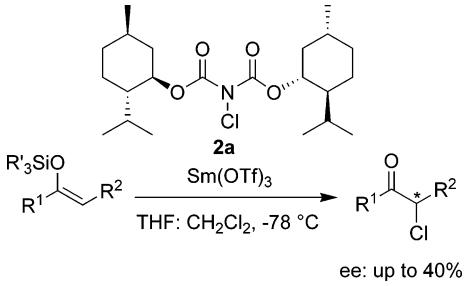
Received March 24, 2007



New chiral *N*-chloroimidodicarbonates, which function as efficient chiral chlorinating agents, were designed and synthesized. Among these, C_2-symmetric (1*R*,2*S*,5*R*)-(−)-menthyl-*N*-chloroimidodicarbonate **2a** provided moderate to good enantioselectivity (up to 40%) for the chlorination of silyl enol ethers to afford α-chloroketones only in the presence of a suitable Lewis acid such as $Sm(OTf)_3$.

Introduction

Halogenated organic compounds are important chemical intermediates for the synthesis of numerous functionalized organic compounds. In recent years, the asymmetric synthesis of halogenated compounds has been, therefore, an active area of research. We are involved in the asymmetric 1,2-halofunctionalization of alkenes and recently found that Lewis acids, in particular, metal triflates, catalyze the reactions when *N*-halosuccinimides are used as halogen sources.[1] This led us to believe that a suitable chiral *N*-haloimide might exert the enantioselective halogenation of organic compounds. Synthesis of some chiral *N*-haloamides and -imides is known from the literature; however, their utility for the asymmetric halogenation of organic compounds has not been reported.[2] Recently, Yamamoto described the synthesis and application of a chiral α,α-dichloromalonate as an efficient chlorinating agent.[3] Here, we describe the design and synthesis of new C_2-symmetric chiral *N*-chloroimidodicarbonates **2** (Figure 1) and their application to the enantioselective chlorination of silyl enol ethers.

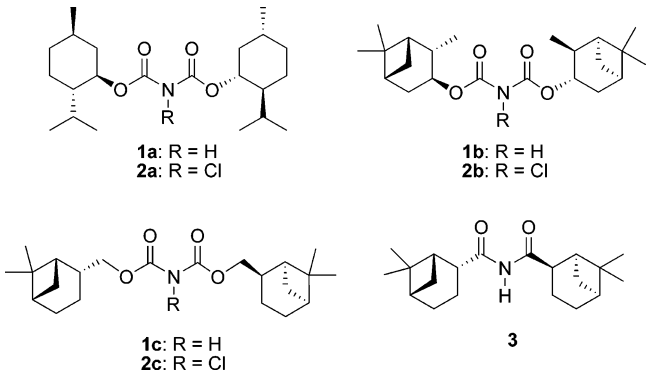


FIGURE 1. Designed C_2-symmetric imidodicarbonates and imide.

Results and Discussion

Prior to the synthesis of chiral imidodicarbonic acid esters **1**, we attempted to synthesize the chiral C_2-symmetric imide **3** (Figure 1). It was presumed that N-chlorinated **3** in its syn-dipole conformation may exert asymmetric induction. However, acylation of the corresponding amide failed to yield the imide **3** even by performing the reaction using different reagents and conditions. Steric inhibition of bulky bicyclic units might prevent the acylation reaction. This prompted us to design and synthesize the imidodicarbonates **1**, where the presence of an additional oxygen atom functions as a spacer to reduce steric inhibition.

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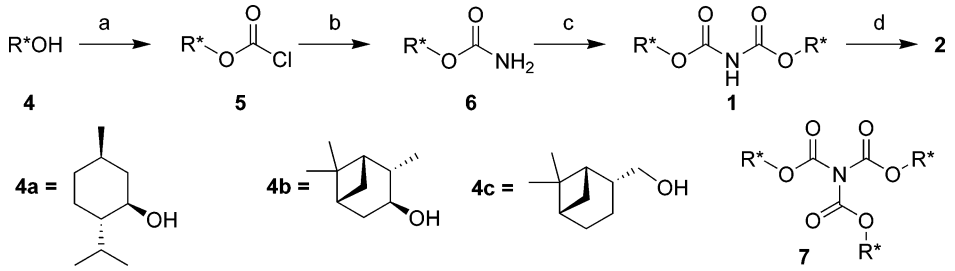
10.1021/jo070614n CCC: $37.00
Published on Web 06/02/2007

SCHEME 1. Synthesis of Imidodicarbonates 1 and *N*-Chloroimidodicarbonates 2[a]

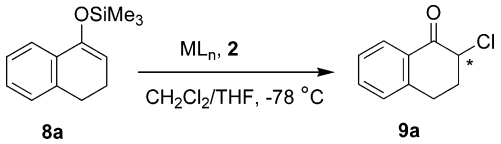


[a] Reagents: (a) triphosgene, C_5H_5N, CCl_4, quantitative; (b) aq NH_3, 0 °C, quantitative; (c) NaH, THF, **5**, 0 °C, 1 min; and (d) *t*-BuOCl (5 equiv), 30−40 °C.

Three different imidodicarbonates **1a**−**c** were synthesized from easily available chiral alcohols (1*R*,2*S*,5*R*)-(−)-menthol **4a**, (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheol **4b**, and (1*S*,2*R*,5*S*)-(−)-myrtanol **4c** (Scheme 1). Alcohols **4** on reaction with triphosgene and pyridine in CCl_4/toluene gave alkyl chloroformate **5** in quantitative yields.[4] Without further purification, chloroformate **5** was stirred with 50% aqueous ammonia solution at 0 °C to afford the carbamate **6** in high yields. When the sodium salt of carbamate **6**, generated on reaction with NaH, was treated with the corresponding chloroformate **5** followed by immediate quenching with saturated NH_4Cl solution, imidodicarbonates **1** were produced in 20−60% yield. It is to be noted that when the reaction was continued for >20 min, it exclusively yielded the imidotricarbonate **7**. The competition between **1** and **7** could not be controlled even by varying the different ratios of sodium salts of **6** and **5**. *N*-Chloroimidodicarbonates **2a**−**c** were prepared by treatment with excess *tert*-butyl hypochlorite at 30−40 °C. Formation of *N*-chloroimidodicarbonates **2** has been revealed by the disappearance of a broad singlet of NH of **1** in the ^{1}H NMR spectra.

α-Halogenated carbonyl compounds, in particular, α-chloro/bromo compounds, are versatile intermediates in organic synthesis. Few methods for the enantioselective synthesis of α-halogenated carbonyl compounds are known in the literature.[3,5−9] Lectka reported a catalytic and enantioselective synthesis of α-haloester via tandem halogenation/esterification of acyl halides.[5] In recent years, many research groups have made important contributions to organocatalytic and enantioselective α-halogenation of aldehydes[6] and ketones.[7] Jørgensen and Bernardi[8] and Togni et al.[9] independently described the catalytic and enantioselective α-halogenation of carbonyl compounds using NCS and $ArICl_2$ as chlorinating agents, respectively. Chiral α,α-dichloromalonates have efficiently been used by Yamamoto et al. for the enantioselective chlorination of silyl enol ethers to afford α-chloroketones.[3] Herein, we describe the utility of the new chiral chlorinating agents **2** for the enantioselective chlorination of silyl enol ethers to provide α-chloroketones.

TABLE 1. Screening of Lewis Acids for Enatioselective Chlorination of 8a with 2



entry	chlorinating agent	ML_n	ee of **9a** (%)[a]	yield (%)[b]
1	**2a**	none	ne[c]	92
2	**2b**	none	ne	90
3	**2c**	none	ne	93
4	**2a**	$CuCl_2$	ne	84
5	**2a**	$TiCl_4$	ne	78
6	**2a**	$MgBr_2$	ne	75
7	**2a**	$La(OTf)_3$	ne	88
8	**2a**	$Y(OTf)_3$	ne	86
9	**2a**	$Mg(OTf)_2$	ne	81
10	**2a**	$Sc(OTf)_3$	ne	84
11	**2a**	$Cu(OTf)_2$	ne	80
12	**2a**	$Yb(OTf)_3$	18	87
13	**2a**	$Sm(OTf)_3$	22	88
14	**2b**	$Sm(OTf)_3$	4	84
15	**2c**	$Sm(OTf)_3$	ne	87

[a] Determined by HPLC analysis. [b] Isolated yields. [c] ne: No ee.

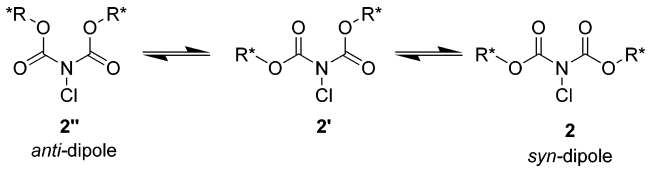


FIGURE 2. Plausible rotamers of *N*-chloroimidodicarbonates **2**.

All three *N*-chloroimidodicarbonates **2** reacted very well with enol ether **8a** even at −78 °C and afforded α-chlorotetralone **9a** in high yields, and no enantioselectivity (ee) was observed (Table 1, entries 1−3). It seems that a number rotamers of **2** might be acting as chlorinating agents (Figure 2) and that led overall to no asymmetric induction. So, the complexation of **2** with a suitable Lewis acid could restrict it to the syn-dipole conformation **2** (Figure 2) and might exert asymmetric induction,

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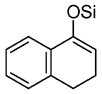
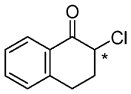
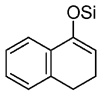
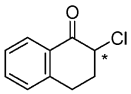
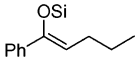
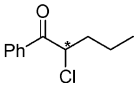
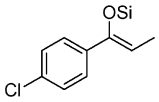
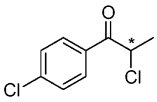
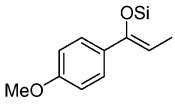
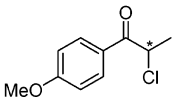
TABLE 2. $Sm(OTf)_3$ Mediated Asymmetric Chlorination of Silyl Enol Ether 8 with 2a

entry	substrate		SiR_3	product	% ee[a]	yield[b] (%)
1		**8a**	$SiMe_3$		22	88
2		**8b**	$SiMe_2Bu^t$		4[c]	85
3		**8c** *(Z:E 3:1)*	$SiMe_3$		10	87
4		**8d**	$SiMe_2Bu^t$		40	89
5		**8e**	$SiMe_2Bu^t$		32	91
6		**8f**	$SiMe_2Bu^t$		32	89
7		**8g**	$SiMe_2Bu^t$		20	81

[a] Determined by HPLC analysis. [b] Isolated yields after column chromatography. [c] Opposite enantiomer.

as was speculated earlier. A variety of Lewis acids was, therefore, screened for the chlorination of **8a** with **2** (Table 1). Among these, $Sm(OTf)_3$ was found to be a suitable Lewis acid and **2a** as an efficient chlorinating agent to induce the chirality. Better enantioselectivity was only observed in homogeneous reaction conditions (i.e., when the reaction was carried out in CH_2Cl_2/THF (3:1)). It is worth mentioning that in 100% CH_2Cl_2 (partial solubility of the Lewis acid), no ee was found, and only in THF did chlorinating agent **2** undergo fast decomposition. So, when a solution of **2a** (1.0 equiv) and $Sm(OTf)_3$ (1.1 equiv)[10] in CH_2Cl_2/THF (3:1) at −78 °C was treated with trimethylsilyl enol ether of tetralone **8a** (1.0 equiv), within 10 min, it gave α-chlorotetralone **9a** with 22% ee (Table 1, entry 13), whereas chlorinating agents **2b** and **2c** showed 4 and 0% ee, respectively (Table 1, entries 14 and 15).[11]

To generalize the previous findings, chlorination of other silyl enol ethers was studied using **2a** as a chiral chlorinating agent in the presence of $Sm(OTf)_3$ (Table 2). It is to be noted that the silyl group has an important role in asymmetric induction. $Sm(OTf)_3$ assisted chlorination of trimethylsilyl (TMS) enol ether **8a** afforded 22% ee with **2a** (Table 2, entry 1) and under the same reaction conditions, *tert*-butyldimethylsilyl (TBDMS) enol ether **8b** provided the reverse but low enantioselectivity (Table 2, entry 2). This is might be due to the bulkiness of the silyl group in the cyclic *E*-enol ether that led to the competitive face selectivity. Unlike cyclic *E*-enol ethers, acyclic *Z*-enol ethers showed different effects. TMS enol ether **8c** showed 10% ee (Table 2, entry 3), but TBDMS enol ether **8d** provided 40% ee (Table 2, entry 4). Other TBDMS enol ethers of acyclic ketones also showed moderate enantioselectivity (Table 2, entries 5−7).

We also investigated the asymmetric chlorination of **8d** using chiral non-C_2-symmetric *N*-chloroimidodicarbonate **11a** and *N*-acylcarbamates **11b** and **11c** (Scheme 2). Under the same reaction conditions (i.e., in the presence of $Sm(OTf)_3$) **11a** and **11b** showed enantioselectivity of 16 and 10%, respectively, whereas **11c** did not provide any induction even in the presence of a strong Lewis acid such as $TiCl_4$, $SnCl_4$, or Et_3Al. Thus, the asymmetric chlorination of silyl enol ethers using chiral *N*-chloroimidodicarbonates **2** in the presence of a Lewis acid might be attributed to the chelated transition state (Scheme 3).[3,12]

Conclusion

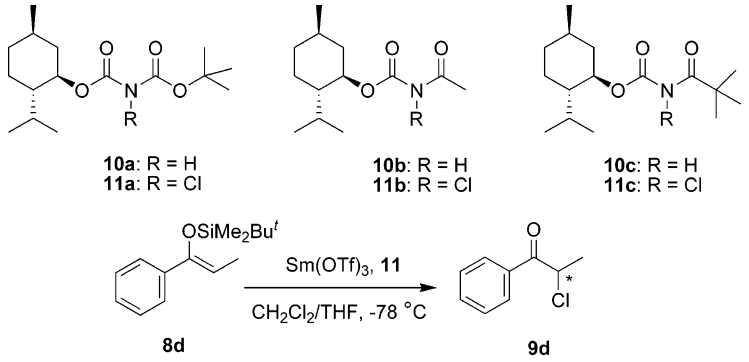
In conclusion, we have designed and synthesized new chiral *N*-chloroimidodicarbonates, which function as efficient chiral chlorinating agents. Among these, C_2-symmetric (1*R*,2*S*,5*R*)-(−)-menthyl-*N*-chloroimidodicarbonate **2a** provided moderate to good enantioselectivity (up to 40%) for the chlorination of silyl enol ethers to afford α-chloroketones only in the presence of suitable Lewis acid such as $Sm(OTf)_3$. The nature of the silyl

(10) 0.1 equiv of excess $Sm(OTf)_3$ was used, only to avoid the presence of unchelated rotamers.

(11) Since it showed modest enantioselectivity, no further attempt was made to determine the absolute stereochemistry of chiral α-chloroketones **9**.

(12) From the TS, the absolute srereochemistry of cyclic α-chloroketone **9a** (from **8a**) and acyclic α-chloroketones **9c**/**9d** and **9e**−**g** might be predicted as S and R, respectively.

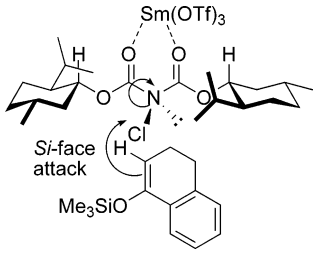
SCHEME 2. Asymmetric Chlorination of 8d using Chiral Non-C_2-Symmetric Chlorinating Agents 11



chlorinating agent	ee (%)	yield[a]
11a	16	85%
11b	10	82%
11c	00	76%

[a] Isolated yields after column chromatography.

SCHEME 3. Proposed TS



groups plays an important role in the enantioselectivity of the reaction. Asymmetric induction was also observed for non-C_2-symmetric chiral chlorinating agents such as (1*R*,2*S*,5*R*)-(−)-menthyl-*N*-chloroimidodicarbonate and (1*R*,2*S*,5*R*)-(−)-menthyl-*N*-acetyl-*N*-chlorocarbamate. Further application of this chemistry is underway in our laboratory.

Experimental Procedures

All reactions were conducted with oven-dried glassware under an atmosphere of argon (Ar). Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Flash chromatography was carried out using silica gel (230−400 mesh). TLC was performed on aluminum-backed plates coated with silica gel 60 with a F_{254} indicator.

^{1}H NMR spectra were measured at 200 and 400 MHz and ^{13}C NMR spectra were measured at 50 and 100 MHz using $CDCl_3$ and C_6D_6 as solvents. ^{1}H NMR chemical shifts were expressed in parts per million (δ) downfield to $CHCl_3$ ($\delta = 7.26$); ^{13}C NMR chemical shifts were expressed in parts per million (δ) relative to the central $CDCl_3$ resonance ($\delta = 77.0$) and C_6D_6 resonance ($\delta = 128.0$). Coupling constants in ^{1}H NMR were expressed in hertz.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methyl-cyclohexane-1-chloroformate or (1*R*,2*S*,5*R*)-(−)-Menthyl-chloroformate (5a).[4] A suspension of triphosgene (2.34 g, 7.88 mmol) in pyridine (1.80 mL, 22.11 mmol) and carbon tetrachloride (90 mL) was added to a stirred solution of (1*S*,2*S*,3*S*,5*R*)-(−)-menthol **4a** (3.0 g, 19.23 mmol) in carbon tetrachloride (90 mL). The resulting solution was stirred at 55−60 °C for 6 h. The reaction mixture was cooled to ambient temperature, and dichloromethane (150 mL) was added. The solution was washed with water (2 × 75 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated to afford the title compound as a colorless oil in quantitative yield (4.15 g). This was used directly for the next step without further purification. $[\alpha]_D^{25}$ −74.43 (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}): 690, 833, 945, 1145, 1170, 1458, 1776 (CO), 2959; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, $J = 7.0$ Hz, 3H), 0.92 (d, $J = 7.0$ Hz, 3H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.85−1.30 (m, 3H), 1.30−1.60 (m, 2H), 1.60−1.80 (m, 2H), 1.80−2.05 (m, 1H), 2.05−2.25 (m, 1H), 4.73 (dt, $J = 4.5$, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 20.5, 21.8, 23.3, 26.2, 31.4, 33.7, 40.1, 46.8, 83.9, 149.9.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methyl-cyclohexylcarbamate (6a). A solution of chloroformate **5a** (1.5 g, 6.86 mmol) in THF (15 mL) was cooled in an ice bath. 50% aqueous ammonia solution (15 mL) was dropwise added with vigorous stirring. The reaction mixture was stirred at rt overnight to remove the excess ammonia. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). Combined organic layers were washed with water (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, and evaporated to afford the title carbamate in quantitative yield (1.34 g), which may be directly used for the next step without any purification. Recrystallization from ethanol/water gave pure **6a** as a white solid. mp 155−157 °C; $[\alpha]_D^{25}$ −75.16 (*c* 1.0, CH_2C1_2); IR (KBr, cm^{-1}): 569, 787, 1049, 1340, 1408, 1612, 1684(CO), 2952, 3261, 3442; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.79 (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.5$ Hz, 6H), 0.85−1.14 (m, 3H), 1.15−1.52 (m, 2H), 1.60−1.70 (m, 2H), 1.85−2.10 (m, 2H), 4.53 (dt, $J = 4.3$, 10.8 Hz, 1H), 4.61 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.4, 20.7, 22.0, 23.5, 26.2, 31.3, 34.3, 41.3, 47.3, 74.9, 157.1; Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.10; H, 10.75; N, 6.95.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methyl-cyclohexylimidodicarbonate or (1*R*,2*S*,5*R*)-(−)-Menthyl-imidodicarbonate (1a). To a stirred suspension of NaH (0.12 g, 60% in oil, 3.01 mmol) in dry THF (15 mL) under argon was dropwise added a solution of carbamte **6a** (0.50 g, 2.51 mmol) in dry THF (15 mL) at 0 °C. The reaction mixture was allowed to come to room temperature (25 °C) and was stirred for 2 h. The reaction mixture was again cooled at 0 °C. Then, a solution of chloroformate **5a** (0.60 g, 2.76 mmol) in dry THF (15 mL) was added rapidly at 0 °C and immediately quenched with an aqueous saturated NH_4Cl solution (15 mL). The reaction mixture was extracted with diethyl ether (4 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude **1a**. Flash chromatography over a silica gel column (diethyl ether/petroleum ether = 10:90) yielded 0.58 g (60%) as a white solid. mp 64−70 °C; $[\alpha]_D^{33}$ −89.02 (*c* 0.4, CH_2Cl_2); IR (KBr, cm^{-1}): 1093, 1176, 1495, 1713 (CO), 1795 (CO), 2957; ^{1}H NMR (200

MHz, $CDCl_3$): δ 0.78 (d, J = 7.0 Hz, 6H), 0.89 (d, J = 7.0 Hz, 6H), 0.90 (d, J = 6.5 Hz, 6H), 0.85−1.20 (m, 6H), 1.20−1.55 (m, 4H), 1.55−1.75 (m, 4H), 1.75−2.0 (m, 2H), 2.0−2.20 (m, 2H), 4.66 (dt, J = 4.4, 10.8 Hz, 2H), 6.92 (br s 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.3 (2C), 20.7 (2C), 21.9 (2C), 23.3 (2C), 26.1 (2C), 31.3 (2C), 34.0 (2C), 40.8 (2C), 47.0 (2C), 76.3 (2C), 150.6 (2C). Anal. Calcd for $C_{22}H_{39}NO_4 + 0.25\ H_2O$: C, 68.45; H, 10.31; N, 3.63. Found: C, 68.60; N, 10.37; N, 3.68.

Di-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methyl-cyclohexyl-*N*-chloroimidodicarbonate or Di-(1*R*,2*S*,5*R*)-(−)-menthyl-*N*-chloroimidodicarbonate (2a). *tert*-Butyl hypochlorite was added in excess (5 equiv) to the imidodicarbonate **1a** under argon atmosphere. The resulting reaction mixture was stirred at 30−40 °C for 30 min. Excess hypochlorite was removed under reduced pressure (using a liquid nitrogen trap) to afford the *N*-chloroimidodicarbonate **2a**, which was directly used for chlorination. Gummy liquid, IR (KBr, cm^{-1}): 753, 947, 1095, 1222, 1457, 1734 (CO), 1759 (CO), 2871, 2957; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.79 (d, J = 6.7 Hz, 6H), 0.92 (d, J = 6.4 Hz, 12H), 0.85−1.35 (m, 6H), 1.35−1.80 (m, 8H), 1.80−2.25 (m, 4H), 4.72 (dt, J = 3.7, 10.8 Hz, 2H). ^{13}C NMR (50 MHz, C_6D_6): δ 16.3 (2C), 20.9 (2C), 22.0 (2C), 23.4 (2C), 26.3 (2C), 31.4 (2C), 34.2 (2C), 40.8 (2C), 47.3 (2C), 80.0 (2C), 151.3 (2C).

Chlorination of Silyl Enol Ether 8d with 2a. To a solution of *N*-chloroimidodicarbonate **2a** (0.041 g, 0.1 mmol) in DCM/THF (2:1, 4 mL) was added $Sm(OTf)_3$ (0.066 g, 0.11 mmol) at −78 °C under argon atmosphere. The reaction mixture was stirred at −78 °C for 15 min, and a solution of enol ether **8d** (0.025 g, 0.1 mmol) in DCM (1 mL) was added dropwise. After 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with DCM (2 × 7 mL), and evaporation of the solvent under reduced pressure gave the chlorinated product along with imidodicarbonate. This mixture was directly used for HPLC analysis. Flash chromatography over a silica gel (230−400 mesh) column using ethyl acetate/petroleum ether as an eluent yilded 0.015 g (89%) of the pure α-chlorinated product **9c**/**9d**.

2-Chloro-1-phenyl-propan-1-one (9c/9d). Light yellow oil, IR (KBr, cm^{-1}): 652, 687, 954, 1200, 1253, 1449, 1597, 1693 (CO), 2984; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.75 (d, J = 6.6 Hz, 3H), 5.26 (q, J = 6.7 Hz, 1H), 7.40−7.65 (m, 3H), 8.02 (dd, J = 2.1, 7.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.6, 52.7, 128.6 (2C), 128.8 (2C), 133.6, 133.9, 193.4. Enantiomeric excess was determined to be 10% ee from TMS enol ether **8c** and 40% ee from TBDMS enol ether **8d** by HPLC analysis with a Chiracel OD-H column (4.6 mm ø × 150 mm), 0.5% *i*-PrOH/hexanes (isocratic), 1 mL/min, 210 nm.

Acknowledgment. We thank DST (SR/S1/OC-13/2004), New Delhi for providing financial support. M.B., B.M., and D.S. thank IIT, Kharagpur; UGC, New Delhi; and CSIR, New Delhi, respectively, for their fellowships.

Supporting Information Available: Synthesis and characterization data of other compounds **1b**, **1c**, **5b**, **5c**, **6b**, **6c**, **7**, **9a**, **9c**/**9d, 9e−g**, **10a−c**, and **11a−c**; ^{1}H and ^{13}C NMR and DEPT spectra for all the compounds; and HPLC traces of crude reaction mixture. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070614N