Asymmetric Synthesis

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Copper-Catalyzed Preparation of Ketones Bearing a Stereogenic Center in α Position**

*Darunee Soorukram and Paul Knochel**

Dedicated to Professor K. Peter C. Vollhardt on the occasion of his 60th birthday

The enantioselective preparation of α-alkylated cyclic and acyclic ketones is important,[1] since chiral α-alkylated carbonyl moieties are present in numerous natural products.[2] Recently, we have described a highly selective *anti*-S_N2' substitution of allylic benzoates and phosphates which allows the preparation of chiral α-substituted alkenes[3,4] as well as 1,2-diols or 1,2-amino alcohols bearing a quaternary substituted carbon center.[5] Likewise, Breit et al. have reported efficient *syn*-selective S_N2' substitutions using a directing leaving group.[6]

Herein, we report the highly enantioselective preparation of chiral ketones of type **1** having a stereogenic center in the α position by two efficient oxidation procedures from the intermediate chiral cycloalkenyl lithium species **2**. These organometallic intermediates are readily obtained from the corresponding cycloalkenyl iodides **3** by I/Li exchange.[7] The enantiomerically enriched cycloalkenyl iodides **3** are prepared by a copper(I)-catalyzed *anti*-S_N2' allylic substitution with organozinc compounds starting either from allylic pentafluorobenzoates **4** or from the corresponding diethylphosphates **5** (Scheme 1 and Tables 1 and 2).

Thus, the reaction of $i\text{Pr}_2\text{Zn}$ (2.2 equiv) with (*R*)-2-iodo-2-cyclohexen-1-yl pentafluorobenzoate (98% *ee*)[3a,c] in the presence of CuCN·2 LiCl (2.2 equiv) in THF/*N*-methylpyrrolidinone (NMP) (3:1) between −30 °C and −10 °C for 20 h provided the expected iodide **3a** in 97% yield and 94% *ee*.[8] The reaction of **3a** with *t*BuLi (2 equiv) at −78 °C in THF provided the corresponding alkenyl lithium **2a**, which readily reacted with $Me_3SiOOSiMe_3$ [$(TMSO)_2$; 1.5 equiv] at −78 °C for 0.5 h. The resulting silyl enol ether was converted into the ketone **1a** using HF·pyridine in THF[9] (25 °C, 0.5 h, method A). This deprotection method provided the ketone **1a** in 93% yield and 94% *ee* (entry 1, Table 1).[10] Similarly, the

[*] Dipl.-Chem. D. Soorukram, Prof. Dr. P. Knochel
Department Chemie and Biochemistry
Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
Fax: (+49) 89-2180-77680
E-mail: paul.knochel@cup.uni-muenchen.de

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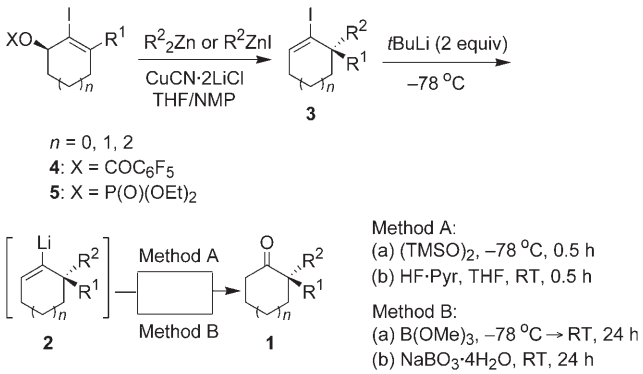


2 3 1

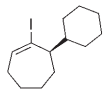
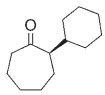
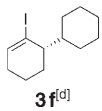
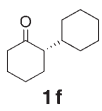
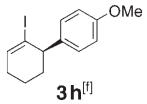
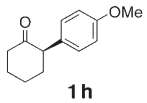
Scheme 1.

seven-membered cycloalkenyl iodide **3b** obtained in 96% *ee*[8] was converted into the chiral cycloheptanone **1b** in 76% yield and 96% *ee* (entry 2, Table 1). Five-membered cyclic ketones can also be prepared by this procedure. Thus, the cyclopentenyl iodide **3c** furnished, with the oxidation method A, (*S*)-2-pentylcyclopentanone (**1c**) in 70% yield and 93% *ee* (entry 3, Table 1). Various cyclohexanones with primary and secondary alkyl substituents were obtained in this way in 93–98% *ee* (entries 4–6, Table 1).

The preparation of 2-arylcyclohexanones is more difficult, since the protons in the position α to both the phenyl ring and the carbonyl group are much more acidic. Thus, the preparation of (*R*)-2-phenylcyclohexanone by method A and an S_N2 substitution mediated by the lithium cuprate $(PhMe_2CCH_2)(Ph)CuLi$ in THF[11] (−30 °C, 48 h) furnished the crude product **1g** with 90% *ee*. However, during the chromatographic purification some racemization occurred, and the ketone **1g** was obtained in pure form (70% yield) with 86% *ee* (entry 7, Table 1). Iodocyclohexene **3i** was prepared by an *anti*-S_N2' substitution using PhCu in CH_2Cl_2[12] and the corresponding phosphate as substrate (see the Experimental Section). The oxidation procedure A furnished ketone **1i** in 69% yield and 92% *ee* after chromatographic purification (entry 9, Table 1). Interestingly, the cyclohexanone bearing an α-para-methoxyphenyl substituent (**1h**) proved to be especially sensitive toward racemization, and attempts to purify the ketone **1h** by chromatography either on silica gel or alumina led to considerable racemization (5–24% *ee*). However, the recrystallization of this ketone from diethyl ether provided the pure product **1h** in 81% yield and 86% *ee*.

Although the oxidation of the alkenyl lithium derivatives of type **2** proceeded in good yields and excellent enantioselectivities, we were concerned with the scale-up and the safety of this oxidation procedure since it requires the use of the sensitive peroxide $(TMSO)_2$ (see the Experimental Section). Thus, we examined an alternative procedure in which the lithium intermediate of type **2** is transmetalated by reaction with $B(OMe)_3$ (2.5 equiv, −78 °C to 25 °C, 24 h) to give the cycloalkenyl(dimethoxy)borane, which is then oxidized with $NaBO_3·4H_2O$ (25 °C, 24 h).[13] Under these conditions, several cyclohexenyl iodides of type **3** were converted into the chiral ketones of type **1** in good yields and enantioselectivities (Scheme 1 and Table 2). A comparison of the two methods (entries 1–4 of Table 1 and Table 2) shows that similar high

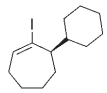
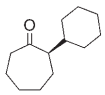
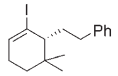
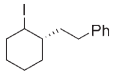
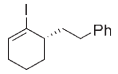
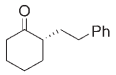
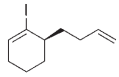
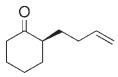
Table 1: Preparation of α-chiral ketones of type **1** by the oxidation method A using $(TMSO)_2$.

Entry	Substrate of type **3**	Yield, *ee* [%, %][a]	Product of type **1**	Yield [%][b]	*ee* [%][c]
1	 **3a**[d]	97, 94[g]	 **1a**	93	94
2	 **3b**[d]	87, 96[g]	 **1b**	76	96
3	 **3c**[e]	96, 94	 **1c**	70	93[h]
4	 **3d**[e]	90, 99	 **1d**	84	93
5	 **3e**[d]	90, 99	 **1e**	91	97
6	 **3f**[d]	90, 98[g]	 **1f**	88	98
7	 **3g**[f]	60, 93	 **1g**	70	86
8	 **3h**[f]	90, 98	 **1h**	81	86
9	 **3j**[e]	53, 96	 **1j**	69	92

[a] Yield of isolated produce. The enantiomeric excess was determined by either HPLC or GC analysis. In each case the racemic compound was also prepared for calibration. [b] Overall yield after oxidation and desilylation. [c] The enantiomeric excess was determined by either HPLC or GC analysis. In each case the racemic compound was also prepared for calibration. [d] Prepared from the corresponding pentafluorobenzoate (see the Supporting Information). [e] Prepared from the corresponding diethylphosphate (see the Supporting Information). [f] Prepared from the corresponding acetate (S_N2 substitution; see the Supporting Information). [g] Determined from the corresponding ketone. [h] Determined from the corresponding lactone (see the Supporting Information).

enantioselectivities were obtained for cyclohexanones and cycloheptanones, whereas for the cyclopentanone **1c** an enantioselectivity of only 81% *ee* was obtained with method B (entry 3, Table 2). Various chiral cyclohexanones bearing either a primary or a secondary alkyl substituent in α position were prepared in this way in 46–65% yield and 90–98% *ee* (entries 5–8, Table 2). Interestingly, ketones bearing a quaternary center in the position α to the carbonyl center were obtained by this method. Thus, the reaction of the pentafluorobenzoate **6** with $Pent_2Zn$ (2.4 equiv) and CuCN·2 LiCl (1.2 equiv) in THF for 4 h at 25 °C provided the S_N2'-substitution product **7** in 93% yield and 95% *ee*. Less than 5% of the S_N2-substitution product was found. Application of

Table 2: Preparation of α-chiral ketones of type **1** by method B by transmetalation with $(MeO)_3B$ and further oxidation with $NaBO_3 \cdot 4H_2O$.

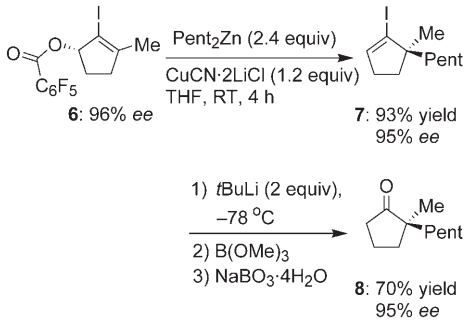
Entry	Substrate of type **3**	Yield, *ee* [%, %][a]	Product of type **1**	Yield [%][b]	*ee* [%][c]
1	 **3a**[d]	97, 97[f]	 **1a**	90	97
2	 **3b**[d]	87, 98[f]	 **1b**	86	98
3	 **3c**[e]	96, 94	 **1c**	90	81[g]
4	 **3d**[e]	90, 99	 **1d**	86	98
5	 **3j**[e]	95, 98[f]	 **1j**	56	98
6	 **3k**[e]	95, 98	 **1k**	65	97
7	 **3l**[d]	85, 99	 **1l**	61	95
8	 **3m**[d]	85, 98	 **1m**	46	90

[a] Yield of isolated product. The enantiomeric excess was determined by either HPLC or GC analysis. In each case the racemic compound was also prepared for calibration. [b] Overall yield of the two-step oxidation procedure. [c] The enantiomeric excess was determined by HPLC or GC analysis. In each case the racemic compound was also prepared for calibration. [d] Prepared from the corresponding pentafluorobenzoate (see the Supporting Information). [e] Prepared from the corresponding diethylphosphate (see the Supporting Information). [f] Determined from the corresponding ketone. [g] Determined from the corresponding lactone (see the Supporting Information).

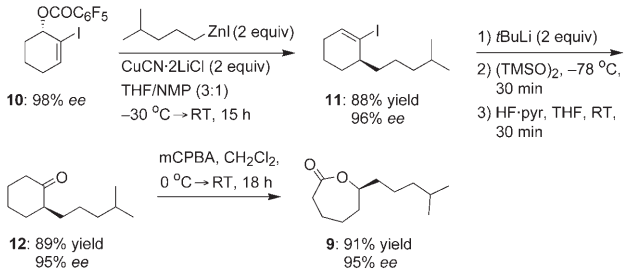
method B provided the ketone **8** in 70% yield and 95% *ee* (Scheme 2).

As an application of this methodology, we prepared (*R*)-10-methyl-6-undecanolide (**9**), a caprolactone recently isolated from a marine streptomycete (isolate B6007)[14] (Scheme 3). Thus, the reaction of $(CH_3)_2CH(CH_2)_3ZnI$ (2 equiv) with compound **10** (98% *ee*)[3a,c] in the presence of CuCN·2 LiCl (2 equiv) in THF/NMP (3:1) between −30 °C and room temperature for 15 h provided the *anti*-S_N2'-substitution product **11** in 88% yield and 96% *ee*. The oxidation procedure A furnished the ketone **12** in 89% yield and 95% *ee*. Baeyer–Villiger oxidation of **12** with *m*-chloroperbenzoic acid in CH_2Cl_2 gave the caprolactone **9** in 91% yield and 95% *ee*.

In summary, we have developed a short synthetic sequence for the enantioselective preparation of various



Scheme 2. Application of method B to provide **8**.



Scheme 3. Application to the preparation of **9**. *m*CPBA = *m*-chloroperbenzoic acid.

chiral ketones with an stereogenic center in α position. Extensions of this method to more complex substrates are underway in our laboratory.

Experimental Section

Typical procedure for the preparation **1a** (entry 1, Table 1) with $(TMSO)_2$ (method A): A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with **3a** (125 mg, 0.5 mmol, 1 equiv) and THF (4 mL). The mixture was cooled at −78 °C, then *t*BuLi (1.6 M in pentane, 0.63 mL, 1 mmol, 2 equiv) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min, then $(TMSO)_2$ (neat, 0.16 mL, 0.75 mmol, 1.5 equiv) was added (**Caution: Explosive!**[15] The reagent must be transferred with a plastic syringe and teflon needle and added slowly). The reaction mixture was stirred continuously at −78 °C for 30 min, and then poured into water, extracted with pentane, and dried over $MgSO_4$. The solvents were removed, and the crude product was used in the next step without purification.

A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with dry pyridine (0.4 mL) and HF·pyridine complex (70%) (0.02 mL, 0.5 mmol, 1 equiv). A solution of the previously prepared silyl enol ether (see above) in THF (2 mL) was added dropwise at room temperature. The reaction mixture was stirred for 30 min, poured into water, extracted with Et_2O, washed with brine, and dried over $MgSO_4$. The solvents were removed, and the crude product was purified by column chromatography (silica gel, 10% Et_2O/pentane) to yield the chiral ketone **1a** (65 mg, 93% yield, 94% *ee*) as a colorless oil.

Typical procedure for the preparation of **1a** with $B(OMe)_3$ (method B): A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with **3a** (125 mg, 0.5 mmol, 1 equiv) and THF (4 mL). The mixture was cooled at −78 °C, then *t*BuLi (1.6 M in pentane, 0.63 mL, 1 mmol, 2 equiv) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min, then $B(OMe)_3$ (neat, 0.14 mL, 1.25 mmol, 2.5 equiv) was added dropwise. The reaction mixture was slowly warmed up to RT

and stirred for 24 h, then a suspension of $NaBO_3 \cdot 4H_2O$ (10 equiv, 769 mg, 5 mmol) in H_2O (6 mL) was added. After the mixture had been stirred at RT for 24 h, it was poured into water, extracted with Et_2O, washed with brine, and dried over $MgSO_4$. The solvents were removed, and the crude product was purified by column chromatography (silica gel, 10% Et_2O/pentane) to yield the chiral ketone **1a** (63 mg, 90% yield, 97% *ee*) as a colorless oil.

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