A Practical Synthesis of Optically Active \( \alpha \)-Substituted Ketones in High Enantiomeric Excess

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Abstract: A highly enantioselective synthesis of optically active \( \alpha \)-substituted ketones can be achieved by using a reaction sequence involving a stereoselective anti-\( \text{SN}_2^\text{¢} \)-allylic substitution in the presence of \( \text{CuCN} \cdot 2\text{LiCl} \), followed by the oxidation of the intermediate cycloalkenyllithium species using \( \text{B(OMe)}_3/\text{NaBO}_3 \cdot 4\text{H}_2\text{O} \). The substitution reaction proceeds with a perfect transfer of chirality.

Key words: allylic substitution, organozinc, organocopper, chiral \( \alpha \)-substituted ketones

Optically active \( \alpha \)-substituted ketones are versatile building blocks for the synthesis of natural products. A number of methods for the synthesis of this class of compounds have been reported, for example stereoselective \( \alpha \)-alkylation and enantioselective protonation of enolates and enols. For the performance of alkylation reactions of ketone enolates, the regio- and stereoselectivity of enolate formation is essential for the overall selectivity of the reaction. The regioselectivity of ketone deprotonation was extensively investigated.

Here, we describe a highly regio- and enantioselective synthesis of optically active \( \alpha \)-substituted ketones using a reaction sequence involving a stereoselective anti-\( \text{SN}_2^\text{¢} \)-allylic substitution of 2-iodocycloallylic benzoates or phosphates in the presence of \( \text{CuCN} \cdot 2\text{LiCl} \) followed by the oxidation of an intermediate cycloalkenyllithium species using \( \text{B(OMe)}_3/\text{NaBO}_3 \cdot 4\text{H}_2\text{O} \). A high enantiomeric purity of \( \alpha \)-substituted ketones could be obtained via these highly stereoselective anti-\( \text{SN}_2^\text{¢} \)-allylic substitutions.

Thus, the anti-\( \text{SN}_2^\text{¢} \)-allylic substitution reaction between the chiral allylic phosphate \( 1 \) (98% ee) and dipentylzinc \( \text{Procedure 1} \) provided the desired anti-\( \text{SN}_2^\text{¢} \) product cyclohexenyl iodide \( 2 \) in 80% yield with 97% ee (Scheme 1). Similarly, treatment of the chiral allylic pentfluorobenzoate \( 3 \) (98% ee) with cyclohexylzinc iodide gave the desired anti-\( \text{SN}_2^\text{¢} \) product cycloheptenyl iodide \( 4 \) in 87% yield and 98% ee \( \text{(Procedure 2)} \). Cycloalkenyl iodides \( 2 \) and \( 4 \) were converted into ketones \( 5 \) and \( 6 \), respectively, using a one-pot oxidation reaction \( \text{(Procedure 3)} \).

The method has a broad scope for the preparation of a variety of chiral \( \alpha \)-substituted cyclohexanones and cycloheptanones in high enantiomeric purity. Furthermore, this procedure can be applied to five-membered rings as well. Thus, the stereoselective anti-\( \text{SN}_2^\text{¢} \) substitution of
the allylic phosphate 7 with dipentyldiazine gave the chiral
cyclopentenyl iodide 8 in 96% yield with 94% ee (Scheme 2). Using a one-pot oxidation reaction, the
cyclopentanone (S)-9 was obtained in 86% overall yield
with 81% ee starting from the allylic phosphate 7. This
optically pure cyclopentanone and its enantiomer are useful
perfumes with a jasmine-like odor. They are also valu-
able precursors for the synthesis of tetrahydro-6-pentyl-
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Interestingly, this method also allows a practical regiose-
lective synthesis of ketones bearing a quaternary center at
the α-position to the carbonyl group with high enantiose-
lectivity (Scheme 3). Thus, the reaction of the pentaflu-
oroobenzoate 10 with dipentyldiazine (2.4 equiv) and CuCN·2LiCl solut.
ion (1.0 M in THF, 0.56 mL, 0.56 mmol, 1.12 equiv)
and NMP (1.30 mL) and the mixture was cooled to –30 °C. CuCN·2LiCl (1.2 equiv) in THF for four hours at 25 °C
provided the anti-Sn2¢ substitution product 11 in 93% yield and 95% ee. Transmetalation of the resulting cy-
claokenyllithium species with B(OMe)3 and further oxi-
dation using NaBO3·4H2O afforded the chiral ketone
12 in 70% yield and 95% ee.²

In summary, we have developed a short, highly enantiose-
lactic synthetic sequence allowing the preparation of various chiral ketones with an α-stereogenic center.

(S)-1-Iodo-5-pentylcyclohex-1-ene (8)
[α]D20 = +13 (c = 0.31, CH2Cl2).

Synthesis of Optically Active α-Substituted Ketones

Scheme 2

Scheme 3
A flame-dried round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with a CuCN·2LiCl solution (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) and cooled to –30 °C. Cyclohexylzinc iodide (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) was added dropwise to the resulting solution. The mixture was stirred at –30 °C for 30 min, then (1S)-2-iodocyclohept-2-en-1-yl pentafluorobenzoate (3; 432 mg, 1.0 mmol) was added dropwise as a solution in NMP (1.3 mL). The mixture was stirred at –30 to –10 °C for 16 h. A sat. aq NH4Cl solution (20 mL) was stirred at 25 °C until the copper salts had dissolved, and then extracted with Et2O (3 × 25 mL). The combined organic phases were washed with brine (10 mL) and dried (Na2SO4). Purification by column chromatography (silica gel, pentane) afforded the product (R)-4 as a colorless oil; yield: 264 mg (87%); 98% ee; [a]D20 +19.4 (c = 0.31, CH2Cl2).

IR (film): 2924 (s), 2852 (s), 1702 (s), 1450 (s), 1342 (m), 1323 (m), 1166 (m), 936 cm–1 (m).

GC (Chirasil-Dex CB, 25 mm × 0.25 mm); conditions: 60 °C (1 min), ramp of 2 °C/min to 160 °C; tR (min) = 14.223 (minor), 10.991 (minor), 9.160 (major); tR (min) = 14.223 (minor), 10.991 (minor), 9.160 (major).

HRMS (EI): m/z calcd for C13H22O: 194.1671; found: 194.1740.

HRMS (EI): m/z calcd for C13H24O: 196.1827; found: 196.1831.


HRMS (EI): m/z calcd for C13H24O: 196.1837; found: 196.1837.


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References


PRACTICAL SYNTHETIC PROCEDURES

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PRACTICAL SYNTHETIC PROCEDURES

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(8) For the preparation of \(\alpha\)-chiral ketones by other methods, see for example: (a) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. J. J. Am. Chem. Soc. 1981, 103, 3081. (b) Meyers, A. I.; Williams, D. R.; White, S.; Erickson, G. W. J. Am. Chem. Soc. 1981, 103, 3088; see also references 1, 2 and 4 cited therein.
