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Highly Enantioselective Dimerization of α,β-Enones Catalyzed by a Rigid Quaternary Ammonium Salt

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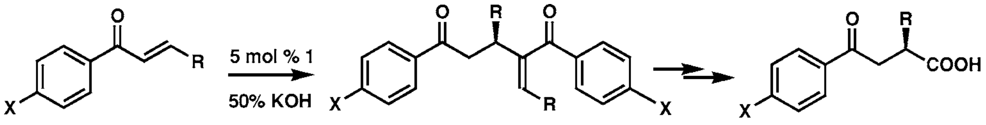
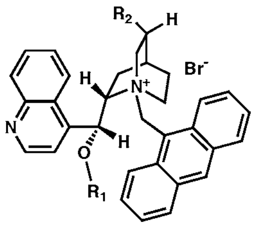
ABSTRACT



Up to 98% ee

The chiral quaternary ammonium salt 1 served as a phase-transfer catalyst for the enantioselective dimerization of α,β-enones, providing a route for the asymmetric syntheses of chiral 1,5-dicarbonyl compounds and α-alkylated γ-keto acids.

Enantioselective phase-transfer catalysis by chiral quaternary ammonium salts is an attractive and important approach for organic synthesis in both academia and industry because of the advantages of mild conditions, simple reaction procedures, safe and inexpensive reagents and solvents, and metal-free conditions. Among all developed chiral phase-transfer catalysts, chiral quaternary *N*-(9-anthracenylmethyl)cinchonidium cations **1** and **2** have been shown to be especially useful and versatile catalysts for a variety of enantioselective reactions, for example, alkylation,[1−3] Michael,[4] aldol,[5] and epoxidation[6] processes. With these catalysts, enantioselectivities of >20:1 have frequently been observed in the above reactions. In addition, these chiral catalysts have been applied to control diastereoselectivity in nitro aldol reactions of aldehydes with nitromethane.[7] These methodologies have been demonstrated for the syntheses of several different types of compounds including chiral α-amino acids, γ-amino acids, α-hydroxy ketones, and β-hydroxy ketones as well as a highly efficient and practical synthesis of the HIV protease inhibitor amprenavir. We have recently described the enantioselective Michael addition of acetophenone to chalcones catalyzed by a chiral quaternary *N*-(9-anthracenylmethyl)-cinchonidium cation **1** to form the Michael adduct with 80% ee.[8] The enantioselectivity of this Michael addition has further been improved to 95% ee using trimethylsilyl enol ethers as reactants.[9] The utility of this transformation was illustrated by syntheses of chiral δ-keto acids and chiral 2-cyclohexenones. In continuing this work, we found that α,β-enones with a γ-proton can be dimerized under chiral phase-transfer conditions to provide chiral 1,5-dicarbonyl compounds in high yield and high enantioselectivity through an enantioselective Michael reaction−double-bond transposition sequence. This process with the chiral quaternary ammonium salt **1** as catalyst and its application to the syntheses of chiral γ-keto acids are described herein.



1 $R_1 = H$, $R_2 = C_2H_5$
2 $R_1 = CH_2CH{=}CH_2$, $R_2 = H_2C{=}CH$

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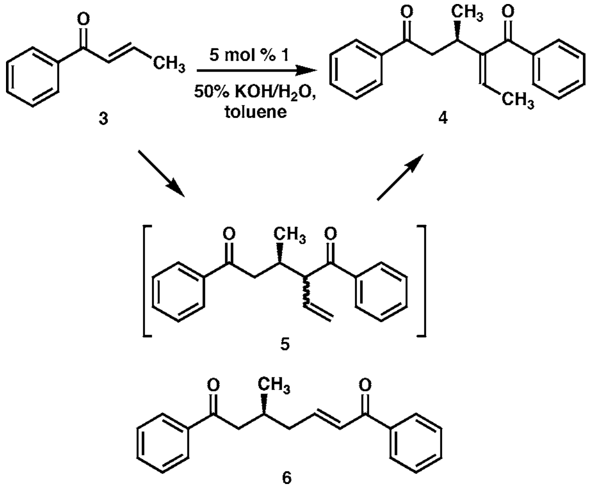
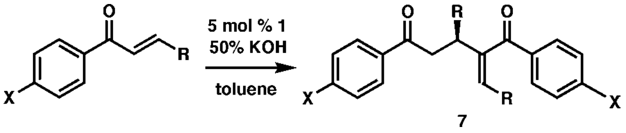
Treatment of 1-phenyl-2-buten-1-one (**3**) with 5 mol % of catalyst **1** in toluene and 50% aq KOH led to the formation of a chiral coupling product in 87% yield and with 89% enantiomeric purity (ee) as determined by HPLC analysis using a chiral column. The structure of this compound was shown to be **4** by ^{1}H NMR, ^{13}C NMR, NOE, and MS analysis. This dimerization of 1-phenyl-2-buten-1-one clearly occurs via an enantioselective Michael reaction to form **5**, followed by base-catalyzed $\beta,\gamma-\alpha,\beta$-double bond transposition (Scheme 1). None of the isomeric dimer **6** could be detected.

Scheme 1



Various other α,β-enones possessing a γ-C-H subunit were also tested as substrates for this dimerization. Table 1 summarizes the results of experiments with these α,β-enones under the standard chiral phase-transfer conditions with **1** (5 mol %) as catalyst, toluene as the organic phase, and 50% aqueous KOH as base.

Table 1. Enantioselective Dimerization of α,β-Enones Catalyzed by **1**



entry	X	R	prod	*T* (°C), time (h)	yield[a] (%)	ee (%),[b] config
1	H	CH_3	**4**	23, 0.5	92	83, *R*
2	H	CH_3	**4**	−40, 12	87	89, *R*
3	F	CH_3	**7a**	−40, 12	89	90, *R*
4	Cl	CH_3	**7b**	−40, 12	97	88, *R*
5	OMe	CH_3	**7c**	−40, 48	80	86, *R*
6	H	Isopropyl	**7d**	−40, 36	81	98, *S*
7	H	Cyclohexyl	**7e**	−40, 48	79	97, *S*

[a] Isolated yield after chromatography. [b] ee was determined by HPLC analysis using chiral columns (Chiralcel OB-H and OJ).

The data in Table 1 reveal some noteworthy features of the dimerization reaction: (1) in general, good yields (80−90% range) and high enantioselectivities (86−98% ee) were achieved at −40 °C under the standard conditions using a simple and reproducible procedure; (2) α,β-enones with an electron-withdrawing substituent on the phenyl ring provided higher enantioselectivities than those with an electron-donating substituent (entries 3 and 4 vs 5), which is consistent with the previous experience in Michael and epoxidation reactions with catalyst **2**;[6,9] (3) higher enantioselectivity was observed for α,β-enones having a bulkier substituent than methyl at C(β) of the α,β double bond (entries 6 and 7 vs 1 and 2), although the dimerization reaction was relatively slower; (4) as usual, higher enantioselectivity was observed at lower reaction temperatures (entry 2 vs 1).

The absolute configurations for the chiral products (**4** and **7a**−**e**) were verified to be as predicted by the previously described mechanistic model[6,8] by comparison of the optical rotation with literature data after conversion of the products **4** and **7d** to the γ-keto acids **9**[10] and **10**.[11] The face selectivity of the dimerization is in agreement with the results previously

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[16] **Preparation of 4.** To a cold (−40 °C) mixture of 1-phenyl-2-buten-1-one (**3**) (67.0 mg, 0.5 mmol) and chiral quaternary salt **1** (14.4 mg, 0.025 mmol) in toluene (2.5 mL) was added 0.5 mL of 50% KOH aqueous solution. After being stirred at −40 °C for 12 h, the reaction mixture was treated with 10 mL of diethyl ether and 5.0 mL of water. The organic phase was separated, concentrated, and purified by flash chromatography (silica gel, 9:1 hexanes−ethyl acetate) to afford **4** (58.3 mg, 87% yield, 89% ee) as a thick oil. Found for **4**: $[\alpha]^{23}_{D} = -6.2$ ($c = 2.0$, CH_2Cl_2); FTIR (film) 2928.5, 1685.2, 1645.5, 1597.8, 1271.7 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.97−7.35 (m, 10H), 6.18 (q, $J = 7.0$ Hz, 1H), 3.60 (m, 2H), 3.34 (m, 1H), 1.94 (d, $J = 7.0$ Hz, 3H), 1.33 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 199.5, 144.5, 139.9, 139.5, 137.3, 132.9, 131.7, 129.6, 128.5, 128.1, 128.0, 43.4, 29.7, 29.2, 19.4, 14.1 ppm; HRMS (CI$^+$) calcd $[C_{20}H_{20}O_2 + H]^+$ 293.1540, found 293.1541. The ee of product **4** was determined by HPLC analysis with a Chiralcel OB-H column, 1% isopropyl alcohol in hexanes, 1.0 mL per min, $\lambda = 254$ nm, retention times of the enantiomers of **4**: 12.4 min (minor), 23.5 min (major).

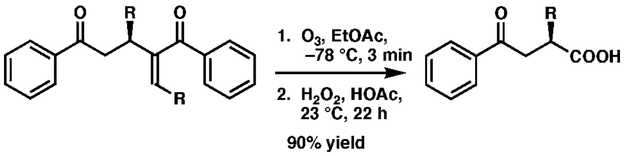
[17] **Conversion of 4 to 9.** A cold (−78 °C) solution of **4** (58.4 mg, 0.2 mmol) in ethyl acetate was treated with a stream of ozone until a blue color appeared (ca. 3 min). The excess of ozone was removed by sparging with nitrogen, and 0.5 mL of 30% hydrogen peroxide and 0.5 mL of glacial acetic acid were added at −78 °C. This mixture was warmed to ambient temperature and was stirred at this temperature for 22 h. The reaction mixture was extracted with ethyl acetate (10 mL) and then washed with brine. After evaporation of solvent, the residue was purified by preparative TLC (silica gel, 9:1 CH_2Cl_2−MeOH) to give 34.6 mg of **9** as a colorless solid (90% yield). Found for **9**: $[\alpha]^{23}_{D} = +28.4$ ($c = 1.0$, $CHCl_3$); FTIR (film) 1706.8, 1681.1, 1216.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.97−7.44 (m, 5H), 3.47 (dd, $J = 17.5$, 7.5 Hz, 1H), 3.17 (m, 1H), 3.07 (d, $J = 17.5$ Hz, 1H), 1.32 (d, $J = 6.5$ Hz, 3H). The configuration of **9** was assigned by comparison of the optical rotation with literature data.[10] The γ-keto acid **10** was prepared similarly. Data for **10**: $[\alpha]^{23}_{D} = +31.8$ ($c = 1.0$, MeOH); FTIR (film) 2990.2, 1706.9, 1689.5, 1224.8 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.97−7.46 (m, 5H), 3.47 (dd, $J = 17.2$, 7.2 Hz, 1H), 3.30 (m, 2H), 0.98 (d, $J = 7.6$ Hz, 6H). The configuration of **10** was assigned by comparison of the optical rotation with literature data.[11]

observed for other types of Michael reactions of α,β-enones, for which a clear mechanistic rationale has been provided.

The products of this dimerization are useful intermediates for the syntheses of chiral γ-keto acids, important chiral backbones for the preparation of peptide mimetics (peptide isosteres) in drug discovery, such as, human neutrophile elastase inhibitors[11] and angiotensin converting enzyme inhibitors.[12] Preparation of chiral γ-keto acids was previously problematic.[13−15] To our knowledge, no catalytic asymmetric route to these compounds has been reported previously. The chiral γ-keto acids **9** and **10** were easily synthesized by ozonolysis of **4** and **7d** at −78 °C in ethyl acetate, followed by oxidation with hydrogen peroxide at ambient temperature in 90% yield (Scheme 2).

In summary, we have developed a novel catalytic asymmetric dimerization of α,β-enones having a proton at C(γ) involving an enantioselective Michael reaction with an initial *N*-(9-anthracenylmethyl)cinchonidium hydroxide as a chiral catalyst. Using this methodology, we have demonstrated a simple and practical pathway to chiral α-alkylated γ-keto acids, which are important intermediates for preparation of peptide isosteres. The following procedures are illustrative.[16,17]

Scheme 2



4, R = CH$_3$
7d, R = *i*-Pr

9, R = CH$_3$
10, R = *i*-Pr

Supporting Information Available: Physical data are given for compounds **7a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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