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Highly Enantioselective Michael Reactions Catalyzed by a Chiral Quaternary Ammonium Salt. Illustration by Asymmetric Syntheses of (*S*)-Ornithine and Chiral 2-Cyclohexenones

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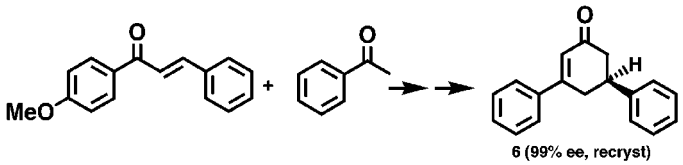
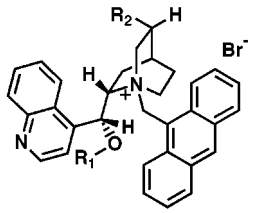
ABSTRACT



The use of the chiral quaternary ammonium salts 1a and 1b makes possible enantioselective Michael reactions which have been applied to the asymmetric syntheses of (S)-ornithine (2) and the chiral 2-cyclohexenone 6.

Chiral quaternary *N*-(9-anthracenylmethyl)cinchonidinium cations **1** have been shown to be extraordinarily effective and useful catalysts for enantioselective alkylation,[1,2] Michael,[3] aldol,[4] nitroaldol,[5] and epoxidation[6] reactions. With **1** as catalyst, enantioselectivities of >20:1 have frequently been obtained in the above reactions. In addition, the absolute configuration of the predominating enantiomer can be predicted from mechanistic models for these reactions, which are based upon the experimentally determined three-dimensional geometry of contact ion pairs of cation **1** with various anions.[1−6] For example, (*S*)-α-amino acid derivatives can be synthesized with enantioselectivities of up to 400:1 by alkylation of the *tert*-butyl glycinate Schiff base of benzophenone (O'Donnell's substrate).[7] In this case, the enolate oxygen of the glycinate ester is held in close proximity with the only sterically open face of the cation **1**, as van der Waals attractive interactions between the gegenions hold them in an energetically preferred relative



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

(1) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
(2) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000.
(3) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347.
(4) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.
(5) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1931.
(6) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.
(7) For earlier work on the enantioselective alkylation of the benzophenone Schiff base of *tert*-butyl glycinate see: (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507. (c) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991,** *56*, 5181.

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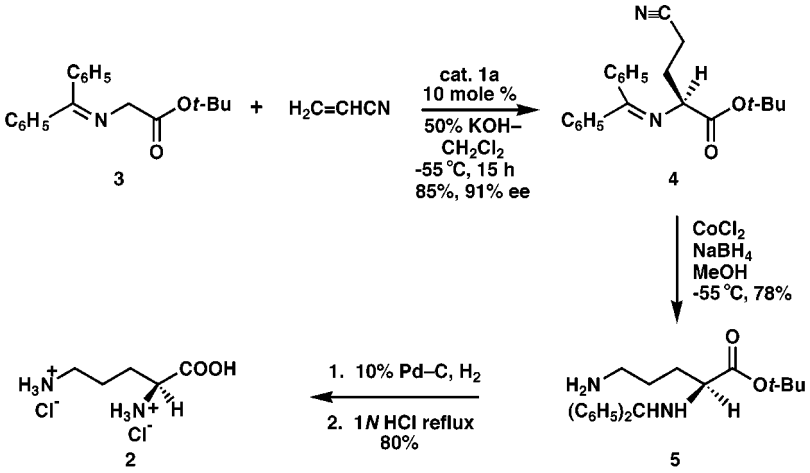
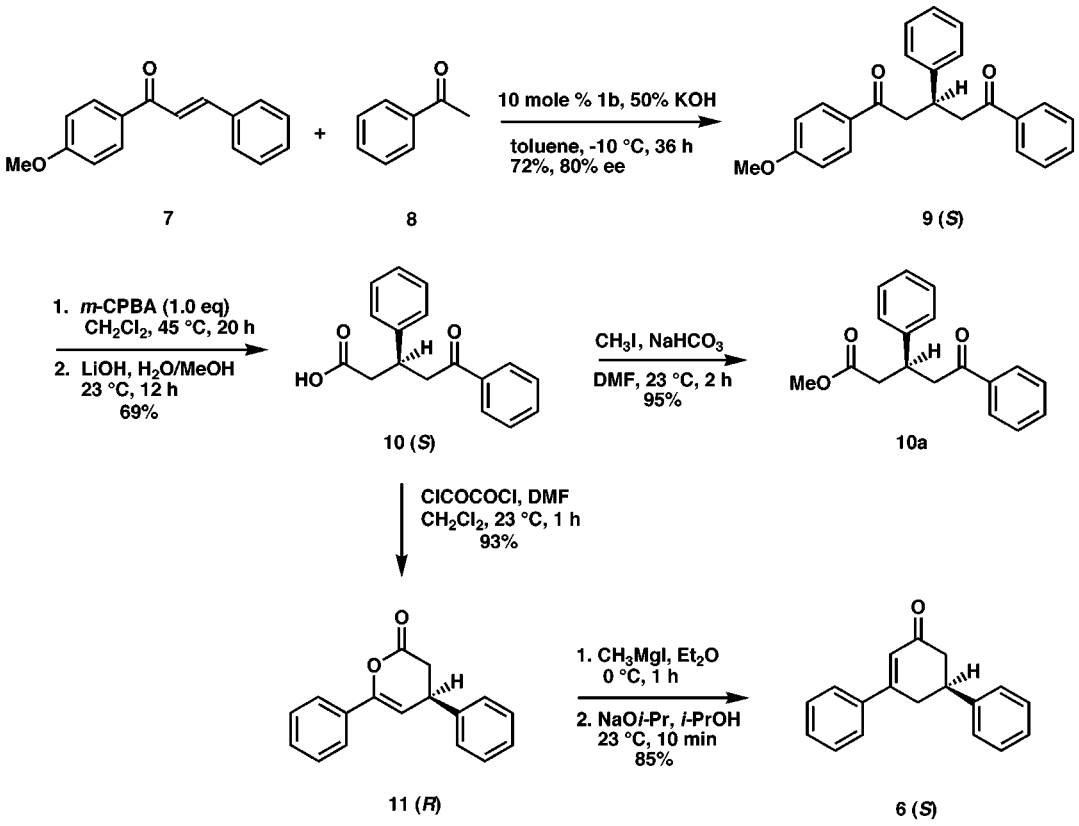
Scheme 1



orientation that favors alkylation to form the *S* product.[1] A variation on this pathway is observed in the hypochlorite-mediated epoxidation of α,*β*-enones, such as benzalacetophenone, in which the contact ion pair of **1** with hypochlorite can bind the enone substrate so that the nucleophilic oxygen of ClO^- is in proximity with the *β*-carbon of the enone. Here, the Michael addition is facilitated not only by the favorable alignment of the two reactants but also by charge acceleration of the conjugate addition of ClO^- due to stabilization of the developing enolate (by the proximate N^+) of the Michael adduct. In this paper, we describe the application of these two mechanistic modes of reaction to novel enantioselective Michael additions.

The first type of asymmetric Michael reaction has been utilized for a remarkably simple synthesis of the natural α-amino acid (*S*)-ornithine (**2**) from glycine and acrylonitrile using the chiral catalyst **1a**, as outlined in Scheme 1. Reaction

Scheme 2



of the benzophenone Schiff base of *tert*-butyl glycinate with acrylonitrile in the presence of 10 mol % of cinchonidinium bromide **1a** in CH_2Cl_2 and 50% aqueous potassium hydroxide at −55 °C for 15 h produced the Michael adduct **4** of 91% enantiomeric purity in 85% yield after chromatography on silica gel. The determination of ee of **4** was made by HPLC analysis using a Regis Whelk-O1 column with 20% isopropyl alcohol in hexane for elution at 23 °C and UV detection at 254 nm (retention times at flow rate 1 mL/min: minor enantiomer, 9.3 min; major, 11.0 min). The catalyst **1a** was recovered (82%) during workup. Reduction of **4** with the cobalt boride−$NaBH_4$ reagent[8] in methanol at 55 °C afforded the diamino ester **5** (78% yield). Cleavage of the benzhydryl group from **5** (H_2, Pd−C) followed by acid-catalyzed hydrolysis (aqueous HCl) of the *tert*-butyl ester produced the dihydrochloride of (*S*)-ornithine, identified by comparison with an authentic sample: mp 194−196 °C; $[\alpha]^{23}_D$ +16.7 (c = 2, 6 N HCl). The absolute configuration of the key chiral intermediate **4** in this synthesis of (*S*)-ornithine agrees with the prediction based on the previous described mechanistic model.[1−3] A typical experimental procedure for the synthesis of **4** is provided.[9]

The application of the chiral quaternary ammonium salt **1b** to an enantioselective Michael reaction leading to the chiral Robinson annulation product **6** is depicted in Scheme 2. Michael reaction of 4-methoxychalcone (**7**) and acetophenone (**8**) in toluene at −10 °C in the presence of 10 mol % of catalyst **1b** and 50% aqueous potassium hydroxide for 36 h gave the *S* adduct **9** in 72% yield and 80% ee. Determination of enantioselection was made by HPLC analysis using a Chiracel OD column (Daicel Technologies), 10% isopropyl alcohol in hexane, UV detection at 254 nm, and a flow rate of 1.0 mL/min (retention times: *ent*-**9**, 36.2 min; **9**, 54 min). The *S* absolute configuration of the dominant Michael adduct (**9**) was established by Baeyer−Villiger oxidation (selective for the 4-methoxybenzoyl subunit of **9**) and subsequent saponification with lithium hydroxide in aqueous methanol, which gave the known dextrorotatory keto acid **10** (*S*-form).[10] Recrystallization of **10** from ethyl acetate−hexane provided 99% enantiomerically pure material, $[\alpha]^{23}_D$ +2.8 (c = 1.0, CH_2Cl_2), mp 158−160 °C, as

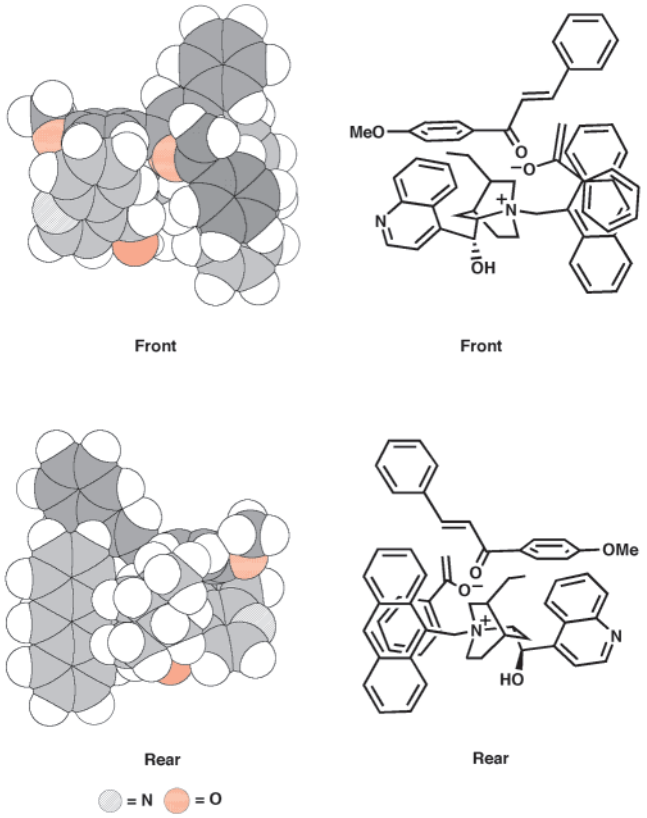


Figure 1.

established by conversion to the corresponding methyl ester **10a** and HPLC analysis. Treatment of keto acid **10** with excess oxalyl chloride and a catalytic amount of dimethylformamide at 23 °C for 1 h furnished cleanly the enol δ-lactone **11** (93%), which upon sequential reaction with methylmagnesium iodide in ether (to form the corresponding methyl ketone) and sodium isopropoxide in isopropyl alcohol (to effect aldol cyclization) produced the (*S*)-α,β-enone **6**: $[\alpha]^{23}_D$ +36.9 (c = 2, CH_2Cl_2), mp 91−93 °C; FTIR (film)

(8) Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801.

(9) To a solution of **3** (502 mg, 1.7 mmol) and chiral quaternary ammonium salt **1a** (103 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) was added dropwise 1 mL of 50% aqueous potassium hydroxide solution. After being cooled to −55 °C, the mixture was treated with acrylonitrile (1.1 mL, 17 mmol), stirred at −55 °C for 15 h, concentrated, and diluted with 50 mL of Et_2O and 10 mL of hexanes. The solid quaternary ammonium salt **1a** was collected by filtration and the solid was dissolved in 20 mL of CH_2Cl_2, washed with water and dried over $MgSO_4$. After evaporation of solvent, the catalyst **1a** was recovered (84 mg, 82% yield). The filtrate was washed with water and brine, dried and purified by flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) to afford the product **4** (503 mg, 85% yield) as colorless crystals: mp 57−58 °C; $[\alpha]^{23}_D$ = −120.5 (c = 1.0, $CHCl_3$); FTIR (film) 3061.5, 3001.3, 2977.7, 2246.8, 1732.0, 1624.7, 1598.0, 1446.4, 1369.0, 1289.3, 1151.6 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.71−7.18 (m, 10H), 4.06 (m, 1H), 2.46 (m, 2H), 2.32−2.17 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 169.8, 139.1, 136.0, 130.6, 128.9, 128.8, 128.6, 128.1, 127.6, 119.4, 81.8, 63.7, 29.4, 27.9, 13.7 ppm; HRMS (EI^+) calcd $[C_{22}H_{24}N_2O_2]^+$ 348.1838, found 348.1827. The ee value was determined by HPLC analysis with a Regis Whelk-O1 column, 20% isopropyl alcohol in hexane, 1.0 mL/min, l = 254 nm, retention times: minor, 9.3 min; major, 11.0 min.

(10) (*S*)-3,5-Diphenyl-5-oxopentanoic acid (**10**) has previously been synthesized from a chiral starting material; see: Diaz-Ortiz, A.; Diez-Barra, E.; de la Hoz, A.; Prieto, P.; Moreno, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 259.

(11) Experimental procedure for **7** + **8** → **9**: To a cold (−10 °C) mixture of 4-methoxychalcone (**7**) (119 mg, 0.5 mmol), acetophenone (**8**) (120 mg, 1.0 mmol), and chiral quaternary ammonium salt **1b** (28.3 mg, 0.05 mmol) in toluene (2.5 mL) was added 0.5 mL of 50% KOH aqueous solution. After the mixture was stirred at −10 °C for 36 h, the reaction was quenched by addition of 10 mL of Et_2O and 5 mL of water. The organic phase was purified by flash chromatography (silica gel, 3:1 hexanes/ethyl acetate) to afford the product (*S*)-**9** (129 mg, 72% yield, 80% ee) as an oil: $[\alpha]^{23}_D$ = −2.1 (c = 1.5, CH_2Cl_2); FTIR (film) 2923.4, 2851.7, 1680.1, 1600.1, 1510.0, 1449.4, 1260.6, 1170.6 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.94 (m, 4H), 7.54 (m, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.28 (m, 4H), 7.17 (m, 1H), 6.91 (m, 2H), 4.06 (dt, J = 14.0, 7.5 Hz, 1H), 3.86 (s, 3H), 3.50 (dd, J = 16.5, 6.5 Hz, 1H), 3.43 (dd, J = 16.5, 7.0 Hz, 1H), 3.34 (dd, J = 16.5, 7.0 Hz, 1H), 3.29 (dd, J = 16.5, 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 197.4, 163.7, 144.1, 137.2, 133.3, 130.7, 130.2, 128.9, 128.8, 128.4, 127.7, 126.9, 114.0, 55.7, 45.2, 44.9, 37.6 ppm; HRMS (CI^+) calcd $[C_{24}H_{22}O_3 + H]^+$ 359.1647, found 359.1631. The ee value was determined by HPLC analysis with a Chiralcel OD column, 10% isopropyl alcohol in hexane, 1.0 mL/min, λ = 254 nm, retention times: minor, 36.2 min; major, 54.0 min.

1662.0, 1605.7, 1496.6, 1447.2, 1260.7 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.57−7.26 (m, 10H), 6.52 (d, J = 2.0 Hz, 1H), 3.47 (s, 1H), 3.07 (dd, J = 17.6, 4.4 Hz, 1H), 2.94 (ddd, J = 17.6, 11.2, 2.4 Hz, 1H), 2.79 (dd, J = 16.4, 5.2 Hz, 1H), 2.73 (dd, J = 16.4, 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 158.9, 143.4, 138.6, 130.4, 129.1, 129.0, 127.3, 127.0, 126.4, 125.4, 44.3, 41.4, 36.7 ppm. The ee value was determined by HPLC analysis with a Chiralcel OJ column, 10% isopropyl alcohol in hexane, 1.0 mL/min, λ = 254 nm (retention times: **6**, 20.5 min; *ent*-**6**, 23.0 min).[11]

The correct absolute configuration for the chiral products (**6**−**11**) shown in Scheme 2 are those predicted by the previously described mechanistic model for the Michael epoxidation of α,β-enones using potassium hypochlorite as reagent with the chiral catalyst **1a**.[6] Two different views of the three-dimensional arrangement of 4-methoxychalcone, acetophenone enolate ion and the chiral quaternary ammonium ion **1b** are shown in Figure 1 which corresponds to the mechanistic model.[6] In Figure 1, the two views shown are related by a 180° rotation about the vertical axis. The acetophenone enolate is contact ion paired with N^+ of the quaternary ammonium catalyst. The α,β-enone is wedged between the ethyl and quinoline substituents on the quinuclidine ring and the carbonyl oxygen is so positioned that close ion pairing with N^+ of the catalyst can occur in the Michael transition state. The phenyl group of acetophenone enolate is positioned to π-stack with the 9-anthracenyl subunit of the catalyst.

On the basis of this mechanistic model and previous results on the cinchonidinium cation accelerated Michael epoxidation of α,β-enones, it was expected that 4-fluorochalcone would undergo highly enantioselective Michael reaction with acetophenone enolate. Indeed, it was determined experimentally that such was the case since the (*S*)-4-fluoro analogue of **9** was produced in 87% ee and 84% yield, i.e., with >14:1 enantioselection.

The synthesis of (*S*)-ornithine described herein is the simplest catalytic asymmetric synthesis developed thus far.[12] The enantioselective Michael process outlined in Scheme 2 is also novel.

Acknowledgment. This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

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(12) The only other catalytic route for the asymmetric synthesis of ornithine reported utilized Knowles−Monsanto-type reduction of an α-*N*-benzoylaminoacrylic acid derivative with a chiral Rh(I) catalyst; see: Baldwin, J. E.; Merritt, K. D.; Schofield, C. J. *Tetrahedron Lett.* **1993**, *34*, 3919.