Enantio- and Diastereoselective Michael Reactions of Silyl Enol Ethers and Chalcones by Catalysis Using a Chiral Quaternary Ammonium Salt
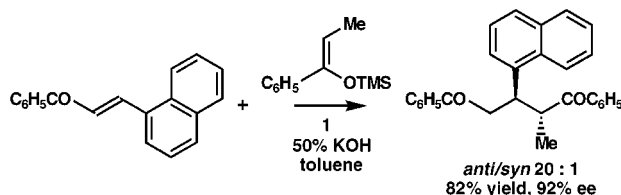
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ABSTRACT

N-(9-Anthracenylmethyl)dihydrocinchonidinium bromide (1) is an effective catalyst for enantioselective Michael additions to chalcones, as shown in the above example, using toluene/50% aqueous KOH biphasic conditions at −20 °C.

We described in a recent publication the enantioselective Michael addition of acetophenone to 4-methoxychalcone as promoted by the chiral *N*-(9-anthracenylmethyl)dihydrocinchonidinium salt **1**, in a toluene/50% aqueous KOH two-phase mixture at −10 °C, to form the (*S*)-adduct **2** in 72% yield and 80% ee.[1] The utility of this process was illustrated by the selective conversion of **2** to a chiral δ-keto acid and to a chiral 2-cyclohexenone derivative. In this manuscript
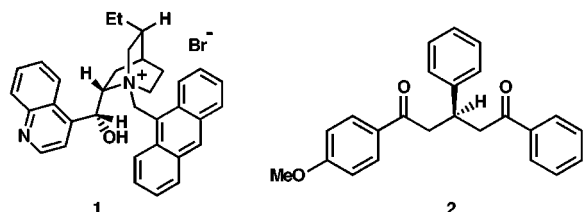

we report a modification of this chiral quaternary ammonium salt catalyzed Michael addition that leads to higher yields and enantioselectivities and also offers a wider scope with regard to nucleophilic partner.

(1) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.

Table 1 summarizes the results of a number of experiments on Michael additions of a series of chalcones **3** and trimethylsilyl enol ethers (**4**), rather than ketones, as reactants under standard conditions with **1** (10 mol %) as catalyst, toluene as organic phase, and 50% aqueous KOH as the hydroxide source. There are three advantages of the use of enol ethers **4** as reactants rather than the corresponding ketones: (1) faster reactions as compared to those of ketones, (2) higher enantioselectivities and yields, and (3) minimization of aldol side reactions. Scrutiny of the data in Table 1 reveals that for the 11 reactions studied good yields (generally in the 80−90% range) and enantioselectivities (generally 90−95% ee) could be realized using −20 °C as a convenient temperature. The procedure for this enantioselective Michael addition is simple, and the results are readily reproducible.[2,3] The (*S*)-configuration of the products **5** were assigned on the basis of previously reported results.[1] These skeletally, but not actually, C_S symmetric chiral 1,5-diketones would be difficult to synthesize by other methods.

The catalytic enantioselective Michael process can be extended to vinyloxysilanes other than the class represented by **4**. This is clearly indicated by the results summarized in

Table 1. Enantioselective Michael Reactions Catalyzed by Quaternary Ammonium Salt **1**
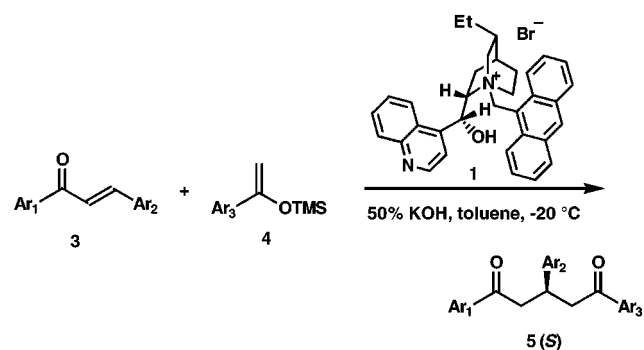
Ar$_1$	Ar$_2$	Ar$_3$	time (h)	yield (%)	ee (%)
4-F-C$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	8	85	95
4-Cl-C$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	4	91	94
4-CH$_3$O-C$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	24	80	92
4-CH$_3$-C$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	16	94	91
4-F-C$_6$H$_4$	4-Cl-C$_6$H$_4$	C$_6$H$_5$	4	87	91
4-F-C$_6$H$_4$	4-CH$_3$O-C$_6$H$_4$	C$_6$H$_5$	16	92	94
6-CH$_3$O-2-C$_{10}$H$_6$	C$_6$H$_5$	C$_6$H$_5$	24	82	94
1-C$_{10}$H$_7$	C$_6$H$_5$	C$_6$H$_5$	10	81	95
4-F-C$_6$H$_4$	C$_6$H$_5$	2-CH$_3$-C$_6$H$_4$	15	79	92
4-F-C$_6$H$_4$	C$_6$H$_5$	4-C$_6$H$_5$-C$_6$H$_4$	16	92	93
4-F-C$_6$H$_4$	C$_6$H$_5$	2-C$_{10}$H$_7$	10	81	95

Table 2, which reveal not only strong enantiocontrol but also good diastereocontrol for (Z)-1-phenyl-1-(trimethylsilyloxy)-

1-propene (**6**) as nucleophilic component with a variety of chalcones **3**. In general the enantioselectivities were found to be high (92−99% ee) for the predominating *anti* diastereomer (**7a**−**7h** in Table 2). The assignment of absolute configuration to the products was based on the rigorous determination of structure for the Michael adducts shown in Table 2, entry 7. For this case the *syn* diastereomer **8g** is a crystalline solid, mp 142−144 °C, which was subjected to X-ray crystallographic analysis, revealing the molecular structure shown in Figure 1.[4] Treatment of this *syn* adduct
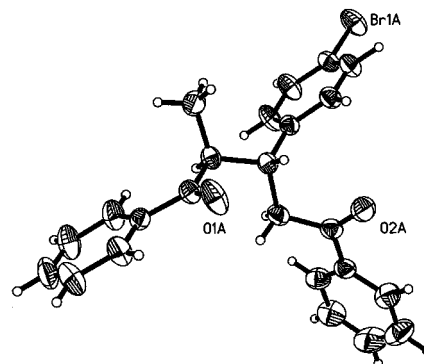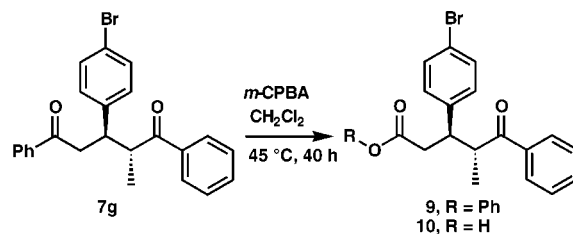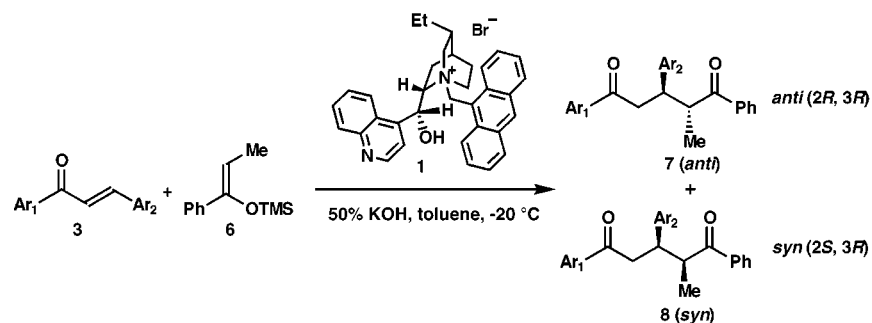

Figure 1. X-ray crystal structure of compound **8g**.

(**8g**) with alcoholic base effected equilibration to a chromatographically separable mixture of diastereomers **7g** (*anti*; obtained as an oil) and **8g** (*syn*) in a ratio of ca. 2:1. The *anti* diastereomer was identical in all respects with the *anti* product obtained directly from the Michael reaction of **3** and **6** in the presence of the catalyst **1**. The face selectivity with regard to the chalcone component must therefore be the same for the formation of the major *anti* adduct **7g** and the minor *syn* adduct **8g**. The face selectivity for addition to the chalcone is identical for the Michael additions shown in Table 1 and Table 2. Furthermore, this same face selectivity has previously been observed for other Michael-type reactions of chalcones and other α,β-enones, for which a clear mechanistic rationale has been provided.[1,5] The stereochemistry of the other products listed in Table 2, entries 1−6 and 8, was assigned by analogy with the configurations of adducts **7g** and **8g**.[6]

The enantioselective Michael reaction summarized in Table 2 is advantageous not only for the synthesis of chiral

(2) The following procedure is illustrative. To a cold (−20 °C) mixture of 4-fluorochalcone (113 mg, 0.5 mmol), 1-phenyl-1-(trimethylsilyloxy)-ethylene (115 mg, 0.6 mmol), and chiral quaternary ammonium salt **1**[3] (28.7 mg, 0.05 mmol) in toluene (2.5 mL) was added 0.5 mL of 50% KOH aqueous solution. After stirring at −20 °C for 16 h, the reaction mixture was diluted with 10 mL of Et$_2$O and 5 mL of water. The toluene phase was concentrated, and the product was purified by flash chromatography (silica gel, 6:1 hexanes/ethyl acetate) to afford (S)-**5**, Ar$_1$ = 4-F-C$_6$H$_4$, Ar$_2$ = Ar$_3$ = C$_6$H$_5$, (147 mg, 85% yield, 95% ee) as an oil. [α]$^{23}_D$ = −1.1 (c 2.0, CH$_2$Cl$_2$); FTIR (film) 1683.5 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.00−7.94 (m, 4H), 7.57−7.07 (m, 10H), 4.06 (m, 1H), 3.48 (m, 2H), 3.65 (dd, J = 16.5 and 6.5 Hz, 1H), 3.31 (dd, J = 16.5 and 7.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.8, 197.2, 165.9 (d, J = 253.0 Hz), 143.9, 137.1, 133.5 (d, J = 3.0 Hz), 133.4, 131.0 (d, J = 11.4 Hz), 129.0, 128.8, 128.4, 127.7, 127.0, 115.9 (d, J = 22.1 Hz), 45.1, 45.0, 37.4 ppm; HRMS (CI) calcd [C$_{23}$H$_{19}$FO$_2$ + H]$^+$ 347.1447, found 347.1448. The ee value was determined by HPLC analysis at 23 °C with a Chiralcel OD column, 5% isopropyl alcohol in hexanes, 1.0 mL/min, λ = 254 nm; retention times, minor 26.7 min; major 36.9 min.

(3) Quaternary ammonium salt **1** was synthesized by the following procedure; see Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. A suspension of dihydrocinchonidine (2.96 g, 10.0 mmol) and 9-(bromomethyl)anthracene (2.85 g, 10.5 mmol) in toluene (20 mL) was heated at reflux for 3 h. The resulting mixture was cooled to ambient temperature, poured into 300 mL of diethyl ether, and filtered to give **1** as a yellow powder (5.55 g, 98% yield): mp 180 °C (dec); [α]$^{23}_D$ = −253 (c 1.0, MeOH); FTIR (film) 1620.4, 1699.4, 1509.1, 1420.3, 1265.9, 1065.6 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) 9.00 (d, J = 4.8 Hz, 1H), 8.82 (s, 1H), 8.78 (d, J = 9.2 Hz, 1H), 8.60 (m, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.16 (m, 1H), 8.07 (d, J = 4.8 Hz, 1H), 7.90 (m, 2H), 7.80 (m, 2H), 7.62 (m, 2H), 7.12 (m, 2H), 6.46 (d, J = 14.0 Hz, 1H), 5.83 (d, J = 14.0 Hz, 1H), 4.67 (m, 1H), 4.63 (s, 1H), 4.44 (t, J = 9.2 Hz, 1H), 3.62 (m, 1H), 3.18 (m, 1H), 2.71 (m, 1H), 2.26 (m, 2H), 2.11 (m, 1H), 1.88 (m, 1H), 1.57 (m, 1H), 1.43 (m, 1H), 1.26 (m, 3H), 0.68 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD$_3$OD) δ 149.9, 147.6, 146.7, 133.6, 132.5, 131.8, 130.1, 130.0, 129.9, 129.2, 128.7, 128.1, 128.0, 127.9, 125.4, 125.3, 125.2, 125.1, 124.6, 123.9, 123.3, 120.4, 118.2, 68.6, 66.0, 64.4, 55.5, 52.2, 36.5, 26.3, 25.6, 23.8, 21.6, 10.4 ppm.

(4) The coordinates of the *syn* diastereomer **8g**, Ar$_1$ = C$_6$H$_5$, Ar$_2$ = 4-Br-C$_6$H$_4$, can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Table 2. Enantio- and Diastereoselective Michael Additions of Propiophenone Enolate to Chalcones

entry	Ar$_1$	Ar$_2$	product	time (h)	anti/syn	7 (anti) yield (%)	ee (%)	8 (syn) yield (%)	ee (%)
1	C$_6$H$_5$	C$_6$H$_5$	a	10	9:1	81	99	9	90
2	4-F-C$_6$H$_4$	C$_6$H$_5$	b	10	10:1	86	99	9	94
3	4-Br-C$_6$H$_4$	C$_6$H$_5$	c	10	10:1	80	99	8	84
4	4-CH$_3$O-C$_6$H$_4$	C$_6$H$_5$	d	40	4:1	75	98	18	90
5	C$_6$H$_5$	4-CH$_3$-C$_6$H$_4$	e	15	10:1	78	99	7	81
6	C$_6$H$_5$	4-NO$_2$-C$_6$H$_4$	f	40	3:1	65	97	22	95
7	C$_6$H$_5$	4-Br-C$_6$H$_4$	g	10	7:1	82	92	12	95
8	C$_6$H$_5$	1-C$_{10}$H$_7$	h	15	20:1	82	92		

1,5-diketones of type **7** but also for a variety of products that can readily be produced therefrom. For instance, the large difference in reactivity of the two carbonyl groups of **7** (due to differences in steric shielding) allows selective Baeyer–Villiger oxidation, which leads in the case of **7g** to the phenyl ester **9** in 90% yield using 1.7 equiv of *m*-chloroperbenzoic acid in CH$_2$Cl$_2$ at reflux for 40 h. Saponification of **9** (LiOH in CH$_3$OH/H$_2$O at 0 °C for 10

min) produced the corresponding free acid **10**. δ-Keto acid derivatives such as **9** or **10** are not otherwise accessible by catalytic enantioselective routes as far as we are aware.

The enantioselective methodology outlined herein is novel and promising and, we believe, practical for more general synthetic purposes.

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(5) (a) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (b) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1247.

(6) The following experimental procedure for the case of entry 7 of Table 2 is illustrative. To a cold (−20 °C) mixture of 4′-bromochalcone (144 mg, 0.5 mmol), (Z)-1-phenyl-1-(trimethylsilyloxy)-1-propylene (124 mg, 0.6 mmol), and chiral quaternary ammonium salt (28.7 mg, 0.05 mmol) in toluene (2.5 mL) was added 0.5 mL of 50% KOH aqueous solution. After stirring at −20 °C for 10 h, the reaction was diluted with of 10 mL of Et$_2$O and 5 mL of water. The product from the organic phase was purified by flash chromatography (silica gel, 9:1 hexanes/ethyl acetate) to afford the product **7g** (*anti*, 2R,3R) (207 mg, 82% yield, 92% ee) and **8g** (*syn*, 2S,3R) (30.0 mg, 12% yield, 95% ee). For **7g** (*anti*, 2R,3R): [α]$^{23}_D$ = −28.8 (*c* 2.0, CH$_2$Cl$_2$); FTIR (film) 1682.4 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.86–7.14 (m, 14H), 3.92 (m, 1H), 3.44 (d, J = 6.0 Hz, 2H), 1.28 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.2, 198.4, 142.2, 137.1, 136.8, 133.4, 131.7, 130.0, 128.9, 128.8, 128.3, 128.2, 120.6, 45.9, 42.6, 40.4, 14.9 ppm; HRMS (CI) calcd. [C$_{24}$H$_{21}$BrO$_2$ + H]$^+$ 421.0803, found 421.0790. The ee value was determined by HPLC analysis with a Whelk

O1 column, 10% isopropyl alcohol in hexanes, 1.0 mL/min, λ = 254 nm; retention times, minor 39.7 min, major 43.6 min. For **8g** (*syn*, 2S,3R): mp 142−144 °C; [α]$^{23}_D$ = +17.9 (*c* 1.0, CH$_2$Cl$_2$); FTIR (film) 1678.7 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 8.05−7.84 (m, 4H), 7.62−7.09 (m, 10H), 3.92−3.81 (m, 2H), 3.38 (dd, J = 16.5 and 4.5 Hz, 1H), 3.23 (dd, J = 16.0 and 10.0 Hz, 1H), 1.01 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.7, 198.4, 140.9, 136.9, 136.8, 133.6, 133.3, 131.8, 130.4, 129.1, 128.8, 128.6, 128.4, 120.8, 45.7, 44.0, 43.5, 16.9 ppm. The ee value was determined by HPLC analysis with a Chiralcel OD column, 10% isopropyl alcohol in hexanes, 1.0 mL/min, λ = 254 nm; retention times, minor 10.5 min, major 12.4 min. The absolute configurations of the chiral centers were determined by X-ray analysis, which demonstrated the structure shown in Figure 1.