Asymmetric Catalysis

Enantioselective Protonation of Silyl Enolates Catalyzed by a Binap·AgF Complex**

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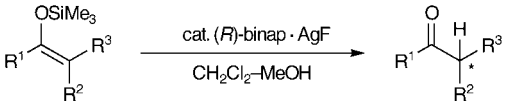
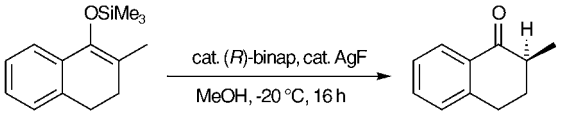
Enantioselective protonation of prochiral enolates and enantioselective alkylation of enolates are efficient methods to prepare optically active carbonyl compounds with a tertiary asymmetric carbon center at the α-position.[1,2] The catalytic enantioselective protonation reactions of metal enolates already reported are performed either under basic or under acidic conditions. The method under basic conditions involves, for example, the protonation of a reactive metal enolate, such as lithium enolate, with a catalytic amount of a chiral acid and an excess of an achiral acid.[3] In contrast, the method under acidic conditions uses silyl enolates or ketene silyl acetals as substrates which, in the presence of a chiral Lewis acid or a chiral Brønsted acid catalyst, are converted into optically active carbonyl compounds.[4] Binap·AgF is an efficient chiral catalyst for the asymmetric aldol reaction of silyl enolates[5] and also for the asymmetric allylation of aldehydes with allylsilane.[6] Because the activation of a trimethoxysilyl group by the fluoride ion is remarkable, we envisioned that the silver fluoride complex could also act as a chiral catalyst for the asymmetric protonation of silyl enolates with an appropriate achiral proton source such as methanol. We report here a new catalytic asymmetric protonation of silyl enolates with methanol using binap·AgF as a chiral catalyst [Eq. (1)].



(1)

We initially examined the protonation of a 2-methyl-1-tetralone-derived trimethylsilyl enolate with methanol to find the optimal reaction conditions. We attempted the reaction employing diverse ratios of binap and AgF at −20 °C and found that a 0.6:1 mixture yielded a nonracemic product with higher enantioselectivity than a 1:1 mixture [Eq. (2)]. As we have reported previously, various ratios of binap and AgF were examined by ^{1}H NMR spectroscopy and the 0.6:1 mixture was found to give the desired 1:1 complex without formation of the unreactive 2:1 complex.[5]

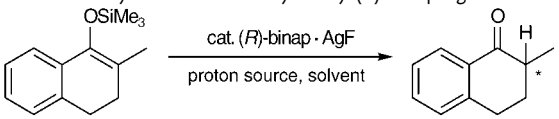


(2)

10 mol% (*R*)-binap, 10 mol% AgF — 82%, 4% *ee* (*S*)
6 mol% (*R*)-binap, 10 mol% AgF — 26%, 20% *ee* (*S*)

We then studied the influence of the solvent on yield and enantioselectivity (Table 1). Among the solvents tested, THF or chlorinated hydrocarbons gave better enantioselctivities than methanol, and dichloromethane was the solvent of choice. When the protonation was performed in a 20:1 mixture of dichloromethane and methanol, (*S*)-enriched 2-methyl-1-tetralone was obtained with 56% *ee* (entry 7). A further improvement in the enantiomeric ratio was achieved when twice as much solvent was used (entries 8 and 9). We also investigated the enantioselectivity of this catalytic protonation with other achiral alcohols but methanol proved most efficient (entries 7, 10, and 11).

Table 1: Optimization of the asymmetric protonation of the trimethylsilyl enolate of 2-methyl-1-tetralone catalyzed by (*R*)-binap·AgF.[a]



Entry	Solvent	Proton source	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%]	Config.[c]
1	MeOH	MeOH	−20	16	26	20	*S*
2	THF	MeOH	−40	6	87	38	*S*
3	DMF	MeOH	−40	5	60	30	*S*
4	toluene	MeOH	−20	13	18	13	*S*
5	Et_2O	MeOH	−40	6	74	26	*S*
6	$CHCl_3$	MeOH	−20	20	47	38	*S*
7	CH_2Cl_2	MeOH	−20	20	68	56	*S*
8[d]	CH_2Cl_2	MeOH	−20	20	44	60	*S*
9[d]	CH_2Cl_2	MeOH	−20	36	72	62	*S*
10	CH_2Cl_2	EtOH	−20	15	75	14	*S*
11	CH_2Cl_2	*i*PrOH	−20	7	97	34	*R*

[a] Unless otherwise noted, the reaction was carried out with (*R*)-binap (0.06 mmol), AgF (0.1 mmol), the trimethylsilyl enolate of 2-methyl-1-tetralone (1 mmol), and the specified proton source (0.5 mL) in the specified solvent (10 mL). [b] Yield of isolated product. [c] The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H). [d] MeOH (1 mL) and CH_2Cl_2 (20 mL) were used.

This asymmetric protonation was applied to a variety of trimethylsilyl enolates; the results with 2-methyl-1-tetralone and related ketone derivatives are summarized in Table 2. Both the 5-methoxy and the 2-ethyl derivatives gave good optical purities similar to that of 2-methyl-1-tetralone (entries 1–3). However, to our surprise, use of the 2,2,6-trimethylcyclohexanone-derived silyl enolate resulted in a

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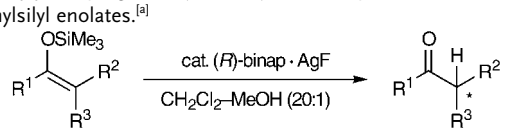
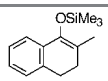
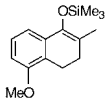
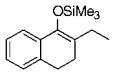
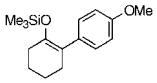
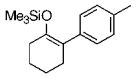
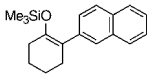
Table 2: (*R*)-binap·AgF-catalyzed asymmetric protonation of various trimethylsilyl enolates.[a]



Entry	Trimethylsilyl enolate	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%]	Config.[c]
1		−20	36	72	62	*S*
2		−20	48	82	67	*S*
3		−20	48	75	64	*S*
4		0	48	82	87[d]	*S*
5		−30	24	96	98	*R*
6[e]		−30	24	75	99	*R*
7		−30	48	95	97	*R*
8		−40	48	93	>99	*R*
9		−40	48	96	>99	*R*
10		−40	48	89	>99	*R*

[a] Unless otherwise noted, the reaction was carried out with (*R*)-binap (0.06 mmol), AgF (0.1 mmol), the trimethylsilyl enolate (1 mmol), and MeOH (1 mL) in anhydrous CH_2Cl_2 (20 mL). [b] Yield of isolated product. [c] The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H). See Table 3 in the Experimental Section for details. [d] The enantioselectivity was determined by GLC analysis on a chiral column (G-TA). [e] (*R*)-*p*-Tol-binap was used.

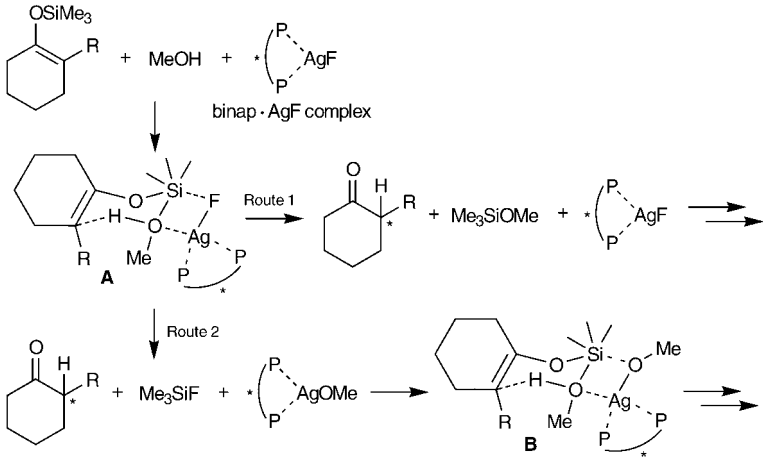


Figure 1. Plausible reaction mechanisms for the asymmetric protonation catalyzed by binap·AgF.

high enantioselectivity of more than 80% *ee* (entry 4). In general, simple ketones with no aromatic substituent at the α-carbon lead to unsatisfactory results in the catalytic asymmetric protonation under acidic conditions.[4b] Gratifyingly, a quite high enantiomeric ratio was obtained with the silyl enolate of 2-phenylcyclohexanone (entry 5), and the use of *p*-Tol-binap with the same silyl enolate afforded 99% *ee* (entry 6). 2-Arylcycloalkanones are also good substrates for the present asymmetric protonation: for instance, the trimethylsilyl enolate of 2-phenylcycloheptanone showed high enantioselectivity and reactivity (entry 7). As for *p*-methoxyphenyl, *p*-tolyl, and 2-naphthyl derivatives, almost perfect enantioselectivity was attained and *R*-enriched products were formed essentially quantitatively in every case (entries 8–10).

The reaction mechanism has not been fully elucidated; however, two mechanisms can be suggested for the catalytic asymmetric protonation (Figure 1).[7] From the aforementioned fact that AgF obviously activates the trimethylsilyl group of the substrates, the cyclic model **A** can be postulated as an initial transition-state structure for the reaction. In this assembly, the binap·AgF complex acts as a chiral Lewis acid and MeOH coordinates to both the silver(I) complex and the silyl enolate to form a six-membered cyclic structure, which is further stabilized by the adjacent four-membered ring formed by AgF and the trimethylsilyl group. As a probable catalytic mechanism for the next stage, the binap·AgF complex is regenerated from the assembly **A** accompanied by the formation of the protonated product and methoxytrimethylsilane (route 1). However, an alternative mechanism (route 2), which generates binap·AgOMe[8] and fluorotrimethylsilane from **A** by a transmetallation step, cannot be ruled out. In the second cycle and thereafter, binap·AgOMe is recycled and behaves as a chiral catalyst in the transition-state structure **B**.

In conclusion, we have developed a novel catalytic asymmetric protonation system. The use of a binap·AgF complex as the chiral catalyst and MeOH as the proton source allows the synthesis of various nonracemic ketones with enantioselectivities of up to 99% *ee*. Further studies on the application of this protonation to other substrates and extension of the present catalytic system to other reactions are currently underway.

Experimental Section

Typical procedure for asymmetric protonation of trimethylsilyl enolates with methanol catalyzed by (*R*)-binap·AgF.

Synthesis of (*R*)-2-phenylcyclohexanone[2a,4b,9] (entry 5 in Table 2): A mixture of AgF (13.5 mg, 0.106 mmol) and (*R*)-binap (38.5 mg, 0.062 mmol) was dissolved in anhydrous MeOH (1 mL) under argon in the dark, and stirred at room temperature (20 °C) for 10 min. After addition of anhydrous CH_2Cl_2 (20 mL) to the solution, the mixture was stirred for another 10 min at room temperature. (2-Phenylcyclohex-1-enyloxy)trimethylsilane (214.9 mg, 0.88 mmol) was added dropwise to the resulting mixture at −78 °C. The mixture was stirred for 24 h at −30 °C and then treated with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted twice with diethyl ether (10 mL each), and the

combined organic extracts were washed with saturated brine (20 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel (1/7 ethyl acetate/hexane as the eluent) to give (*R*)-enriched 2-phenylcyclohexanone (146.5 mg, 96% yield) as a white solid.

Details on the products and the determination of their *ee* values are listed in Table 3.

Table 3: HPLC analysis of the chiral ketone products.[a]

Entry	Product	*ee* [%]	hexane/ *i*PrOH	t_{minor} [min]	t_{major} [min]
1	(*S*)-3,4-dihydro-2-methyl-naphthalen-1(2*H*)-one[2a,10]	62	99:1	12.3	13.3
2[b]	(*S*)-3,4-dihydro-5-methoxy-2-methylnaphthalen-1(2*H*)-one[11,12]	67	20:1	24.9	18.9
3	(*S*)-2-ethyl-3,4-dihydro-naphthalen-1(2*H*)-one[11,13]	64	99:1	13.9	14.9
4[c]	(*S*)-2,2,6-trimethyl-cyclohexanone[3,14]	87	–	26.3	27.1
5	(*R*)-2-phenylcyclo-hexanone[2a,4b,9]	98	9:1	13.9	14.8
6		99	9:1	14.0	15.0
7[d]	(*R*)-2-phenylcyclo-heptanone[4b,11,15]	97	20:1	9.1	7.1
8	(*R*)-2-(4-methoxyphenyl)-cyclohexanone[4b,9b,16]	>99	20:1	7.4	9.2
9	(*R*)-2-*p*-tolylcyclo-hexanone[4b,9b,16]	>99	20:1	15.4	16.8
10	(*R*)-2-(naphthalen-2-yl)-cyclohexanone[4b,9b,16]	>99	20:1	24.2	29.5

[a] HPLC analysis: Chiralcel OD-H, Daicel Chemical Industries, Ltd., flow rate = 0.5 mL min^{-1} unless stated otherwise. The entry numbers are the same as in Table 2. [b] Chiralcel OB, flow rate = 0.5 mL min^{-1}. [c] GC analysis on a chiral column (Chiraldex G-TA, Astec, 80°C, 50 Pa). [d] Chiralpak AS, flow rate = 1.0 mL min^{-1}.

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