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Asymmetric protonation of silyl enolates catalyzed by chiral phosphine–silver(I) complexes*

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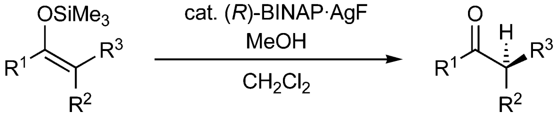
Abstract: A catalytic asymmetric protonation of trimethylsilyl enolates was achieved using a 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)–silver(I) fluoride complex as a chiral catalyst in a mixed solvent consisting of dichloromethane and methanol. Various nonracemic ketones possessing a tertiary asymmetric carbon at the α-position were prepared with high enantioselectivity up to 99 % ee.

Keywords: protonation; silyl enolate; asymmetric catalysis; alcohol; silver.

INTRODUCTION

Catalytic asymmetric protonation of prochiral enolates is a beneficial route to nonracemic carbonyl compounds, which have a tertiary asymmetric carbon at the α-position [1,2]. Various chiral catalysts have so far been developed for the reaction under basic or acidic conditions. The method under basic conditions employs reactive metal enolates as substrates. For instance, in the presence of a catalytic amount of a chiral proton source and an excess amount of an achiral proton source, lithium enolates are efficiently protonated with high enantioselectivity [3]. In contrast, silyl enolates or ketene silyl acetals can be transformed into the corresponding optically active carbonyl compounds under acidic conditions using a chiral Lewis acid or a chiral Brønsted acid as a chiral catalyst [4]. 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)•AgF has been found to catalyze asymmetric allylation of aldehydes with allylic trimethoxysilanes [5] as well as asymmetric aldol reaction with trimethoxysilyl enolates [6]. In these reactions, since the trimethoxysilyl group is obviously activated by the fluoride ion, we anticipated that the silver complex might catalyze asymmetric protonation of silyl enolates with an achiral proton source. This paper describes a novel enantioselective protonation of trimethysilyl enolates using BINAP•AgF as a chiral catalyst and methanol as an achiral proton source (Scheme 1).



Scheme 1 Asymmetric protonation of trimethylsilyl enolates with methanol catalyzed by BINAP•AgF.

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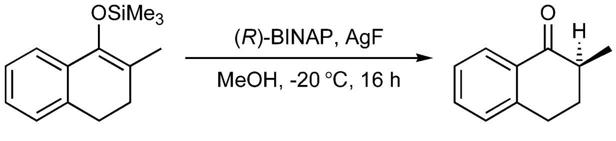
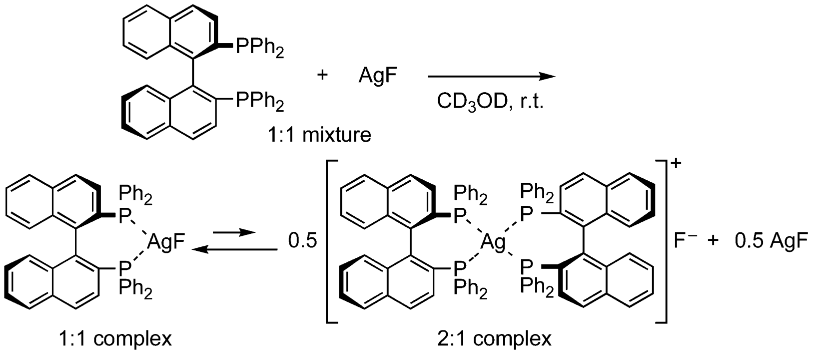
RESULTS AND DISCUSSION

First, we adopted a trimethylsilyl enolate of 2-methyl-1-tetralone as a substrate for the protonation and optimized the ratio of BINAP to AgF. As a consequence, when a 0.6:1 mixture of BINAP and AgF was used as a chiral catalyst in the protonation of the silyl enolate with MeOH at –20 °C, higher enantioselectivity was observed than that given by a 1:1 mixture (Scheme 2). We have previously found that when BINAP is added to an equimolar amount of AgF in MeOH, a considerable amount of an undesired 2:1 complex is formed in addition to a reactive 1:1 complex. We measured various ratios of the mixture in CD_3OD by ^1H NMR, and the 0.6:1 mixture was found to give the desired 1:1 complex without significant formation of the 2:1 complex (Scheme 3) [6].



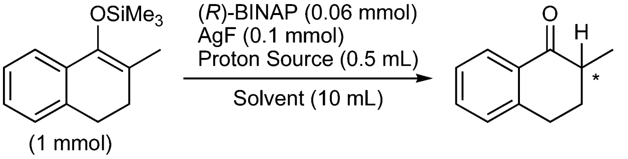
(*R*)-BINAP (mol %)	AgF (mol %)	Yield, %	% ee
10	10	82	4
6	10	26	20

Scheme 2 The optimum ratio of BINAP to AgF in the asymmetric protonation.



Scheme 3 Detection of a 2:1 complex of BINAP and AgF by ^1H NMR.

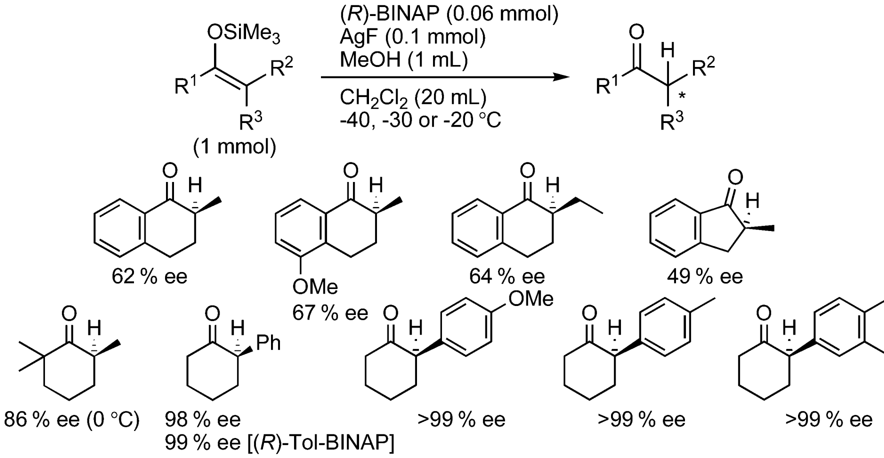
We then investigated the effects of the solvent and achiral proton source on the isolated yield and enantioselectivity. Some results are given in Scheme 4. Among the solvents examined, ethereal solvents and chlorinated hydrocarbons showed higher ee than did methanol, and dichloromethane gave the best result. For instance, when a 20:1 mixture of dichloromethane and methanol was used as a solvent in the protonation, (*S*)-enriched 2-methyl-1-tetralone with 56 % ee was formed in good yields. As for the achiral proton source, although we tested various achiral alcohols except methanol, this simple alcohol was found to be the most effective in terms of enantioselectivity.



Solvent	Proton Source	Conditions	Yield, %	% ee (confign)
MeOH	MeOH	-20 °C, 16 h	26	20 (*S*)
THF	MeOH	-40 °C, 6 h	87	38 (*S*)
Et_2O	MeOH	-40 °C, 6 h	74	26 (*S*)
$CHCl_3$	MeOH	-20 °C, 20 h	47	38 (*S*)
CH_2Cl_2	MeOH	-20 °C, 20 h	68	56 (*S*)
CH_2Cl_2	EtOH	-20 °C,15 h	75	14 (*S*)
CH_2Cl_2	*i*-PrOH	-20 °C, 7 h	97	34 (*R*)

Scheme 4 Optimization of the reaction conditions.

This asymmetric protonation was applied to various trimethylsilyl enolates, and some of the results with 2-methyl-1-tetralone derivatives and other cyclic ketones are shown in Scheme 5 [7]. In addition to the 5-MeO derivative, the 2-ethyl derivative also gave good enantiomeric excess (ee) similar to that of 2-methyl-1-tetralone. Moderate asymmetric induction was also observed in the protonation of the silyl enolate of 2-methyl-1-indanone. Noteworthy was the fact that the use of 2,2,6-trimethylcyclohexanone-derived silyl enolate resulted in high enantioselectivity of more than 85 % ee. The simple substrates possessing no aromatic groups, in general, give unsatisfactory results in the catalytic asymmetric protonation under acidic conditions [4b]. To our pleasure, a quite high enantioselectivity was observed for the silyl enolate of 2-phenylcyclohexanone. By use of *p*-Tol-BINAP, the level of asymmetric induction at last reached 99 % ee. 2-Arylcycloalkanones are more suitable substrates for the present asymmetric protonation and, for example, trimethylsilyl enolate of 2-phenylcycloheptanone also provided high chemical yield and ee. As for the substrates having a *p*-methoxyphenyl, *p*-tolyl, or 2-naphthyl group, nearly enantiomeric pure (*R*)-ketones were obtained in each case.



Scheme 5 (*R*)-BINAP•AgF-catalyzed asymmetric protonation of various trimethylsilyl enolates.

Two reaction pathways are proposed for the catalytic asymmetric protonation of trimethylsilyl enolates (Fig. 1). Based on the fact that the trimethylsilyl group of the enolates was undoubtedly activated by a BINAP•AgF complex, the bicyclic structure **A** is considered to be a possible initial transition-state model for the protonation. In this assembly, the AgF complex plays an important role as a chiral Lewis acid. A silyl enolate and MeOH form a chair-like six-membered cyclic transition-state structure, which is further stabilized by the adjacent four-membered ring containing a BINAP•AgF complex. As a subsequent reaction pathway, the BINAP•AgF complex is liberated from the assembly **A** accompanied by the formation of the protonated product and methoxytrimethylsilane (route 1). However, an alternative pathway (route 2) including a transmetallation step is also possible, which produces BINAP•AgOMe and fluorotrimethylsilane from the transition-state structure **A**. In the next transition-state structure **B**, BINAP•AgOMe acts as a chiral catalyst and is recycled thereafter.

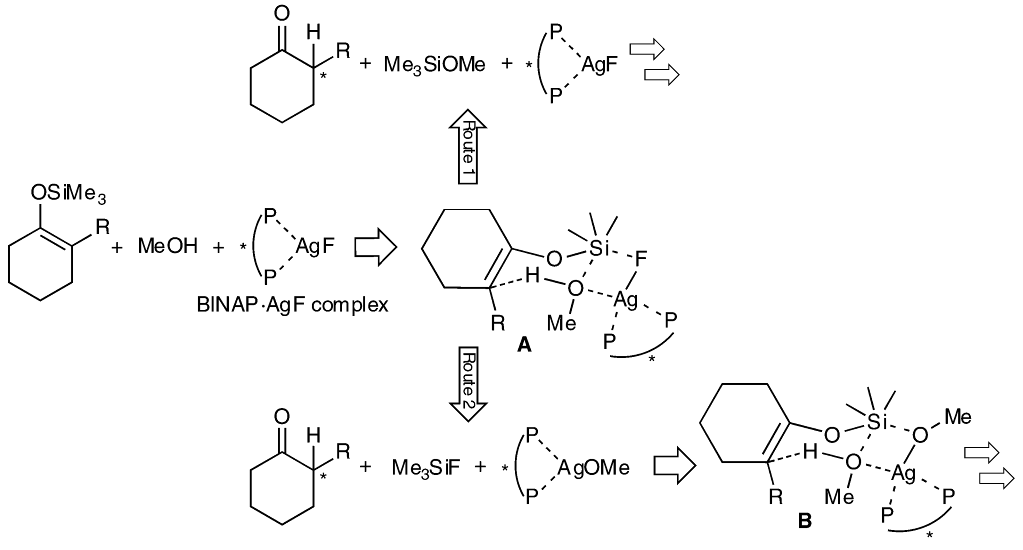


Fig. 1 Working hypotheses for the BINAP•AgF-catalyzed asymmetric protonation.

In summary, we have developed a new catalytic asymmetric proton transfer reaction. By employing a BINAP•AgF complex as a chiral catalyst and MeOH as an achiral proton source, various optically active cyclic ketones were prepared with high enantioselectivity up to 99 % ee.

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