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Silver-Catalyzed Asymmetric Allylation: Allyltrimethoxysilane as a Remarkable Reagent

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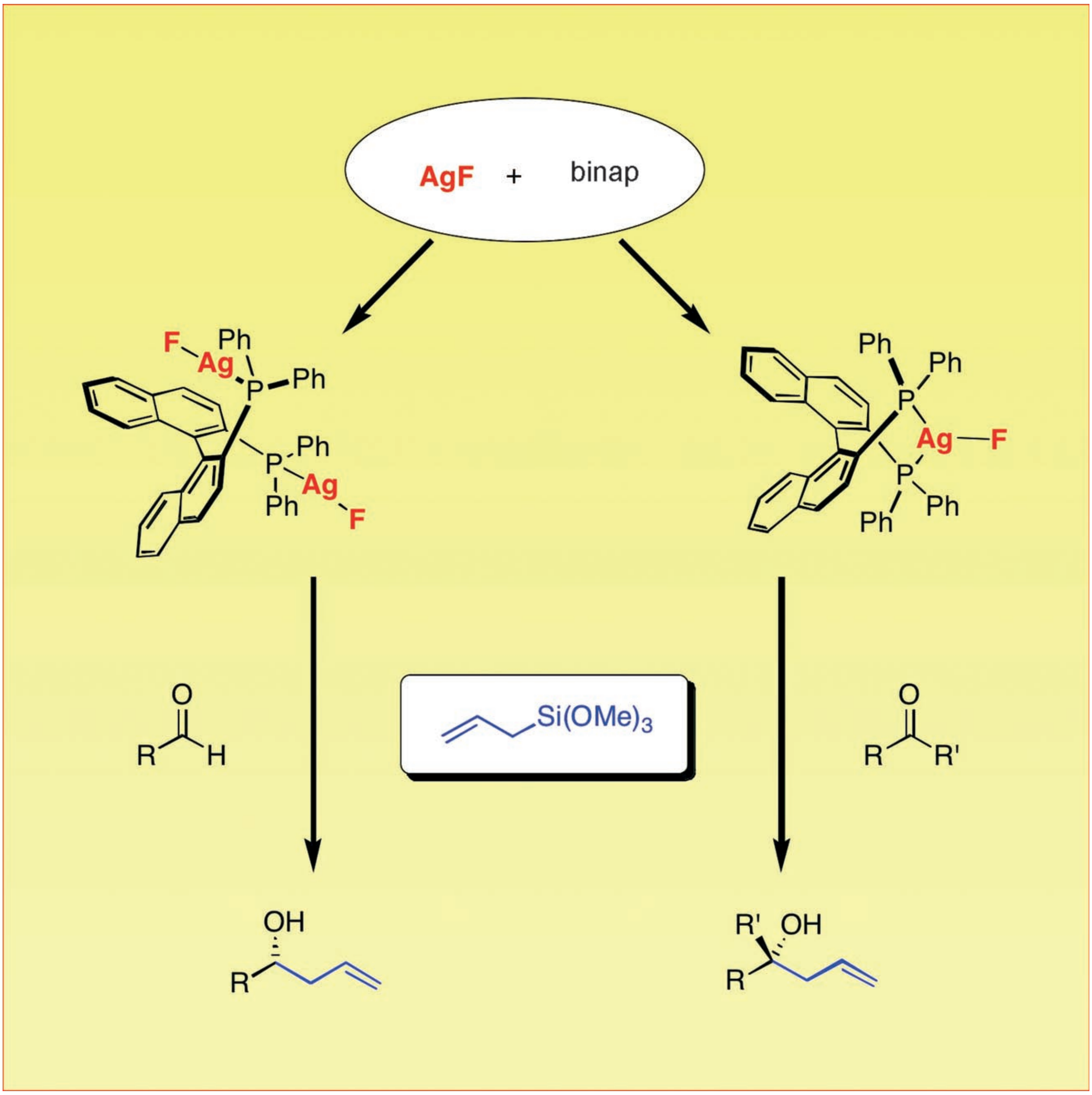


Abstract: Recently, there have been some reports on the use of allyltrimethoxysilane for enantioselective allylation with various metal fluorides or a combination of chiral complex and fluoride anion. These reactions can be applied not only to aldehydes but also to ketones and imines. In this Focus Review we discuss the development of asymmetric allylation with allyltrimethoxysilane catalyzed by chiral silver complexes.

Keywords: allylation • allylic compounds • asymmetric catalysis • nucleophilic addition • synthetic methods

1. Introduction

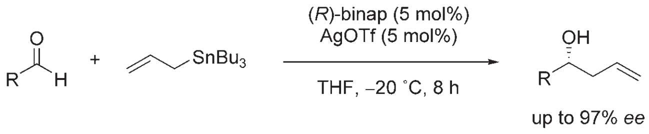
The allylation of carbonyl compounds is a powerful and important process based on nucleophilic addition to carbonyl derivatives to give homoallylic alcohols.[1] As such functional groups are often seen in natural products or biologically active molecules, there is a strong demand for efficient methods to construct such groups. In 1976, Hosomi and Sakurai discovered that titanium tetrachloride catalyzed the allylation of carbonyl compounds with allyltrimethylsilane.[2] Two years later, they also found that tributylammonium fluoride (TBAF) can promote the same reaction.[3] Now well-known as the Sakurai–Hosomi reaction, these methods are the best for transforming carbonyl compounds into homoallylic alcohols, which are a very important functional group for organic transformation; the Sakurai–Hosomi reaction is now complementary to allylation with classic allyl Grignard reagents.

Allylic trialkoxysilanes are known as reactive allylic silanes as they form pentacoordinated silicates by reaction with nucleophiles.[4] Our group reported the first example of catalytic asymmetric addition of allyltrimethoxysilane to aldehydes catalyzed by the p-Tol-binap–AgF complex (Tol-binap = 2,2′-bis(di-*p*-tolylphosphanyl)-l,l′-binaphthyl).[5] Recently, there have been some reports on the use of allyltrimethoxysilane for enantioselective allylation with various metal fluorides or a combination of chiral complex and fluoride anion. These reactions can be applied not only to aldehyde but also to ketone[6] and imine.[7] Herein we focus on the development of asymmetric allylation with allyltrimethoxysilane catalyzed by chiral silver complexes.

2. Silver-Catalyzed Asymmetric Addition of Allyltrimethoxysilane to Carbonyl Compounds

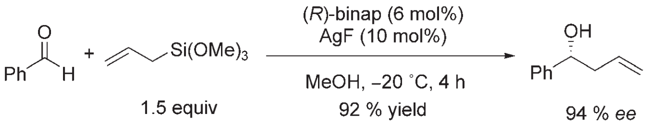
2.1. AgF·Binap-Catalyzed Asymmetric Allylation in MeOH

In 1996, we reported binap–silver-catalyzed (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) asymmetric allylation under mild reaction conditions with allyltributyltin as an allylating reagent.[8] We reported that binap·AgOTf (Tf = trifluoromethanesulfonyl) is an excellent catalyst for catalytic enantioselective allylation, methallylation, *anti*-selective crotylation, and pentadienylation with the corresponding allyltributyltin reagents (Scheme 1).[9] This system gave high reactivity and enantioselectivity compared with other previously reported Lewis acid catalyzed methods with allyltributyltin.[1]



Scheme 1. Enantioselective allylation with allyltin reagents.

Later, from an environmental point of view, we switched our focus on allylmetals from allyltin to allylsilane. We investigated the nucleophilic addition of allyltrimethoxysilane with silver salt·(*R*)-binap complexes, and found that the AgF·(*R*)-binap complex is an effective catalyst for this reaction (Scheme 2). In contrast, a cationic complex such as



Scheme 2. Chiral AgF complex catalyzed enantioselective allylation in MeOH.

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AgOTf·(*R*)-binap gave only 5 % yield. Among the solvents tested, alcohols proved to be effective for the reaction, and MeOH provided both high yield and enantioselectivity owing to the high solubility of AgF in methanol. Interestingly, excess amounts of silver fluoride with respect to binap gave higher enantioselectivity. In a later study by X-ray and ^{31}P NMR spectroscopy, the true structure of the silver catalyst in this reaction was found to be the bimetallic complex (Ag/binap = 2:1) as shown in Figure 1.[10]

These optimal conditions facilitated the allylation of various aromatic aldehydes and gave high yields and enantioselectivities (up to 94 % *ee*) with 6 mol % catalyst loading. However, the method still has some limitations: whereas various aromatic aldehydes gave excellent yields and enantioselectivities, aliphatic aldehydes did not react efficiently. By using this catalyst, remarkable *anti* selectivities were observed for the reaction with (*E*)- and (*Z*)-crotyltrimethoxysilane, irrespective of the configuration at the double bond (Scheme 3). Thus, the reaction seems to proceed through a closed cyclic transition state with the allylmetal species generated in situ.

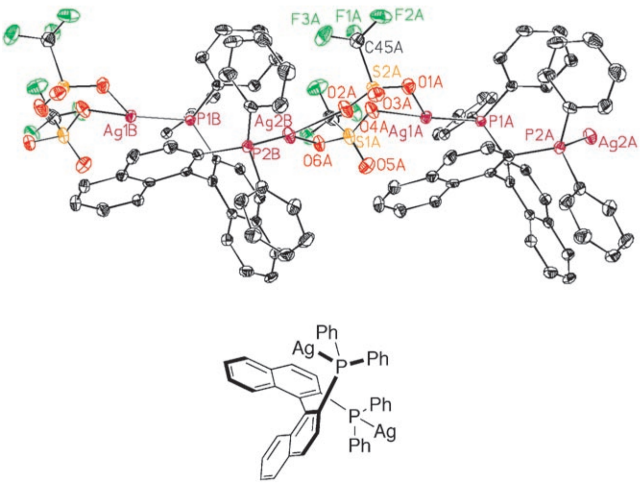

Figure 1. Binap·AgOTf (2:1) complex.[10d]

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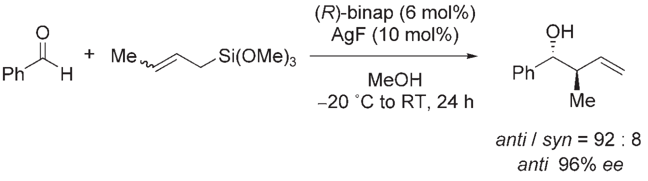
Manabu Wadamoto *received his BSc from Nagoya Univ. in 2000. He did his graduate studies at the Univ. of Chicago under the supervision of Professor Hisashi Yamamoto, during which he worked on silver-catalyzed asymmetric allylation. He received his PhD in 2006 and is carrying out postdoctoral research with Professor Karl A. Scheidt at Northwestern Univ.*



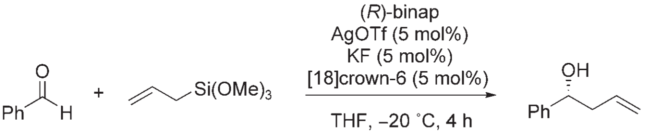
Scheme 3. Diastereoselective crotylation with chiral AgF complex.

2.2. AgOTf·Binap- and KF·18[Crown]-6-Catalyzed Asymmetric Allylation

Silver-catalyzed asymmetric allylation was studied to overcome some problems caused by the use of protic solvents. The (*R*)-binap·Ag^{I}-catalyzed reaction of allyltrimethoxysilane with benzaldehyde was tested to search for silver salts with sufficient catalytic activity.[11] No silver salts other than AgF (AgX; X = OTf, I, BF_4, SbF_6, ClO_4, NTf_2, NO_3, IO_4) gave any allylated product in THF or MeOH. Next, fluoride compounds were investigated as additives in combination with the (*R*)-binap·AgOTf catalyst. The addition of 1 equivalent of KF in MeOH gave the desired product in 5 % yield and with 59 % *ee*.

Owing to its insolubility in THF, KF cannot act as an activator of allylsilanes. A catalytic amount of TBAF showed good catalytic activity in THF with almost no enantioselectivity. [18]Crown-6 is known to improve the solubility of KF in THF or other aprotic polar organic solvents and to generate a reactive fluoride species. In fact, when a catalytic amount of KF and [18]crown-6 was added, the reaction proceeded smoothly in THF with 91 % *ee* (Table 1). In the absence of KF, however, the product was not obtained. Use of an increased amount of [18]crown-6 improved the chemical yield, but the enantioselectivity was lower.

Table 1. Effect of KF and [18]crown-6.



Binap [mol %]	Yield [%]	*ee* [%]
5	72	91
2	91	95

The reaction conditions of (*R*)-binap-, AgOTf-, KF-, and [18]crown-6-catalyzed asymmetric allylation with benzaldehyde were optimized. Three equivalents of allyltrimethoxysilane raised the yield but resulted in a decrease in enantioselectivity. We recently showed that the ratio of binap to silver salt is a very important factor in obtaining high yield and enantioselectivity;[10d,12] when (*R*)-binap was mixed with an equimolar amount of silver(I) salt at room temperature, a significant amount of a 2:1 complex of (*R*)-binap and silver(I) salt was formed in addition to the 1:1 complex. In fact, a mixture of 10 mol% of (*R*)-binap and 5 mol% of AgOTf gave only 21% yield of the product with 2% *ee*. When this reaction was carried out by changing the (*R*)-binap/AgOTf ratio, it was found that an excess amount of AgOTf raised the *ee* of the product, and a combination of 2 or 3 mol% of binap and 5 mol% of AgOTf gave the best results with 3 equivalents of allyltrimethoxysilane (Table 1).

To substantiate the effect of these ratios, the enantioselectivities of homoallyl alcohols obtained from the reaction of allyltrimethoxysilane and benzaldehyde were plotted against the *ee* of binap by using the two different binap/AgOTf ratios.[13] When the reaction was performed in the presence of a catalyst prepared from a 1:1 mixture of (*R*)-binap and AgOTf, a negative nonlinear effect was observed (Figure 2).

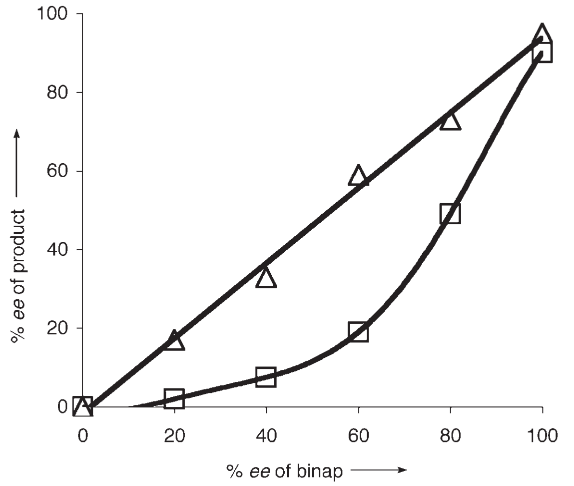
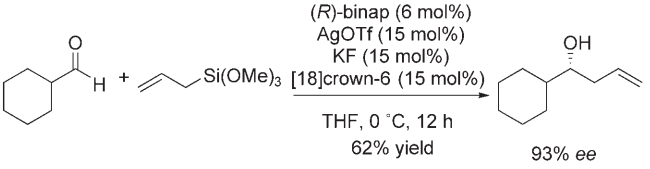


Figure 2. Plot of the nonlinear effect on the two different catalyst ratios. △ = 2 mol% binap, 5 mol% AgOTf; □ = 5 mol% binap, 5 mol% AgOTf.

In contrast, linear behavior was observed with a 1:0.4 mixture of (*R*)-binap and AgOTf. These findings support the hypothesis that at least two binap–silver complexes have certain catalytic activity and contribute to allylation when a 1:1 mixture of binap and AgOTf is used as catalyst, and a single binap–silver complex is formed with the 1:0.4 mixture.

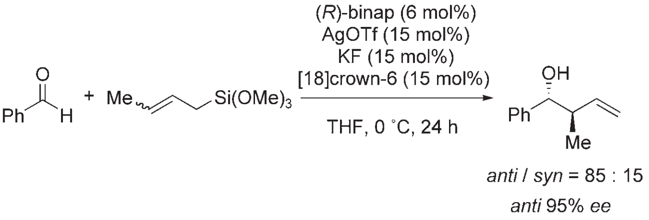
Optimized conditions were established for using THF as solvent at −20 °C, and we employed these conditions in the addition of allyltrimethoxysilane to various aldehydes. All reactions of aromatic and α,β-unsaturated aldehydes gave satisfactory yields and good *ee*s. With an α,β-unsaturated aldehyde, 1,2-addition took place exclusively.

Aliphatic aldehydes did not give any product in the presence of (*R*)-binap·AgF in MeOH.[5] Although these aldehydes gave relatively low chemical yields with 2 mol% of (*R*)-binap and 5 mol% of other catalysts, the treatment of cyclohexane carboxaldehyde with allyltrimethoxysilane with 6 mol% of (*R*)-binap and 15 mol% of AgOTf, [18]crown-6, and KF gave the allylated product in 62% yield with 93% *ee* (Scheme 4).



Scheme 4. Enantioselective allylation of aliphatic aldehydes.

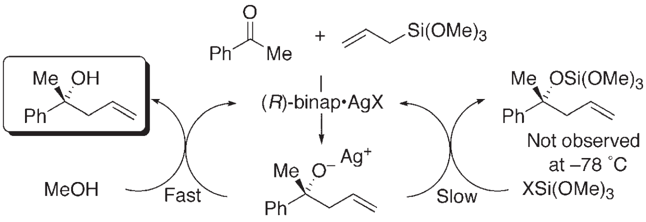
The reaction of (*Z*)-crotyltrimethoxysilane ($E/Z < 1{:}99$) in the presence of (*R*)-binap, AgOTf, KF, and [18]crown-6 ether in THF at 0 °C for 24 h gave the γ adduct almost exclusively with an *anti*/*syn* ratio of 85:15 (Scheme 5) The *anti* isomer had 95% *ee* and a 1*R*,2*R* configuration. *E*-enriched crotyltrimethoxysilane ($E/Z = 87{:}13$) gave the same selectivities and configuration. These results were quite similar to those given by the binap·AgOTf-catalyzed reaction with crotyltributyltin.



Scheme 5. Crotylation with AgOTf, (*R*)-binap, KF, and [18]crown-6.

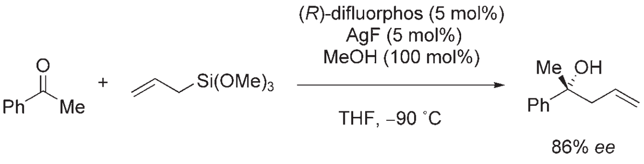
2.3. AgF·Difluorphos-Catalyzed Asymmetric Allylation of Simple Ketones

Initially, we tested the Sakurai–Hosomi allylation with acetophenone and allyltrimethoxysilane by using a catalytic amount of AgF and (*R*)-binap in MeOH. The desired product was not obtained at all even under reflux conditions. Athough AgF is not soluble in an aprotic solvent such as THF, the complex of AgF and (*R*)-binap prepared in MeOH is easily dissolved in THF. The desired tertiary alcohol with 63% *ee* was obtained with this complex.[6c] Notably, the silylated product was not obtained. The alcoholic proton of the product must have originated from the small amount of MeOH used for the preparation of the catalyst. This observation indicates that proton transfer from MeOH should be much faster than silyl transfer (Scheme 6).[6b,14] Therefore, an additional equivalent of MeOH improved the yield of the product significantly.



Scheme 6. Proposed catalytic cycle.

We recently documented that more than three complexes between silver and diphosphine exist (Figure 3).[10] According to these studies, each complex has a different reactivity and selectivity, and it is important to generate a single silver complex to achieve a highly stereoselective reaction. A survey of the ^{31}P NMR spectra of 1:1 mixtures of AgF and ligands revealed that (*R*)-difluorphos gave predominantly complex A, which is presumably due to the poor electron-donating ability of the phosphorus atoms. Significant improvement in enantioselectivity was observed with this solution. Finally, 86% *ee* was attained by conducting the reaction at −90 °C (Scheme 7).



Scheme 7. Optimal reaction conditions.

As summarized in Scheme 8, the catalytic enantioselective allylation of a variety of ketones was carried out under these conditions. Although the reaction proceeded smoothly with either electron-withdrawing or -donating groups attached to the aromatic ring, the electron-withdrawing group gave higher enantioselectivity. Remarkably, over 90% *ee* was attained from various aromatic cyclic ketones. Only 1,2-addition took place with both cyclic and acyclic conjugated enones. Notably, excellent *ee*s (up to 96%) were observed in the reactions with a series of α-halo unsaturated ketones.

The reactions between acetophenone and various allyltrimethoxysilanes were investigated with our new catalyst system. Crotyltrimethoxysilane gave branched *syn* products with high enantioselectivity from both *E* and *Z* isomers. Surprisingly, starting from racemic allylsilanes such as cyclohex-2-enyltrimethoxysilane, we observed the optically pure product almost exclusively (Scheme 9).

Thus, in sharp contrast with the previous study of S_E' allylation with a combination of chiral allylsilanes and Lewis acid,[1] the present catalyst provides high diastereo- and enantioselectivity regardless of the chirality of the starting allylsilane. We may therefore conclude that the allylsilver intermediate rapidly interconverts between two diastereomeric complexes (Scheme 10). The mechanism of this reaction thus involves differentiating the enantiotopic termini of a π-allylmetal intermediate. As this intermediate is derived from a chiral racemic precursor in which the chirality of the substrate is lost, this deracemization process constitutes a "dynamic kinetic asymmetric transformation", first proposed

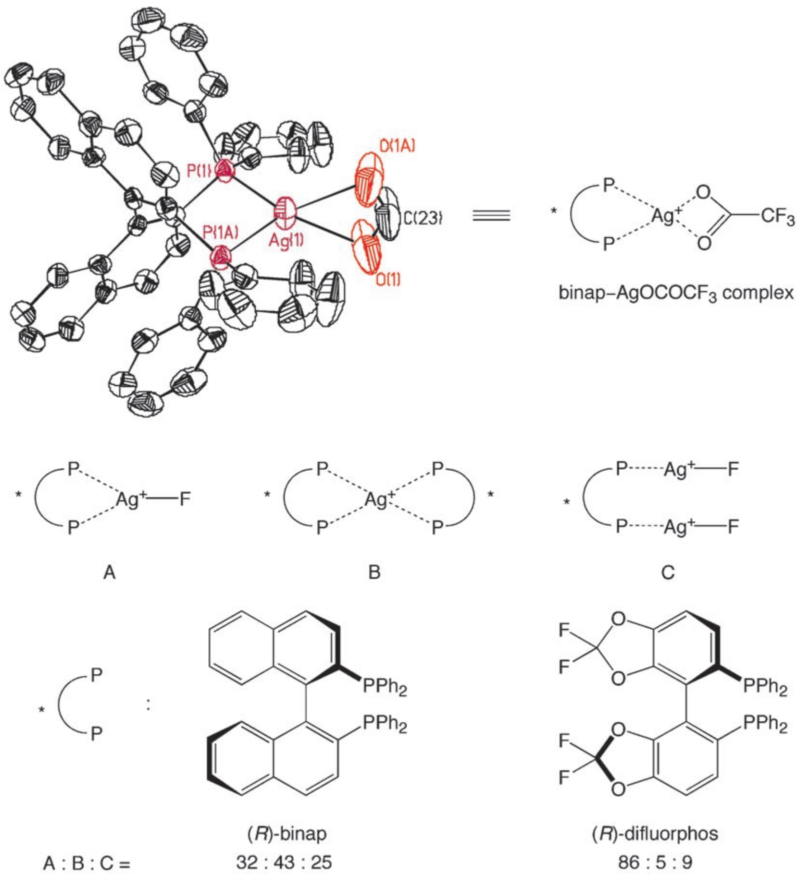
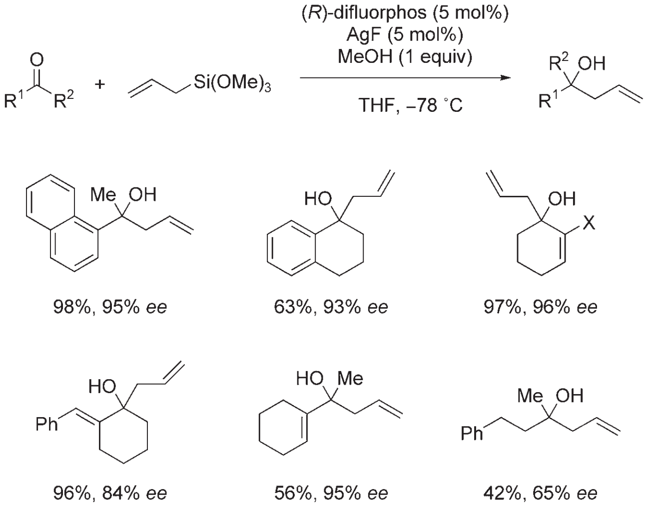
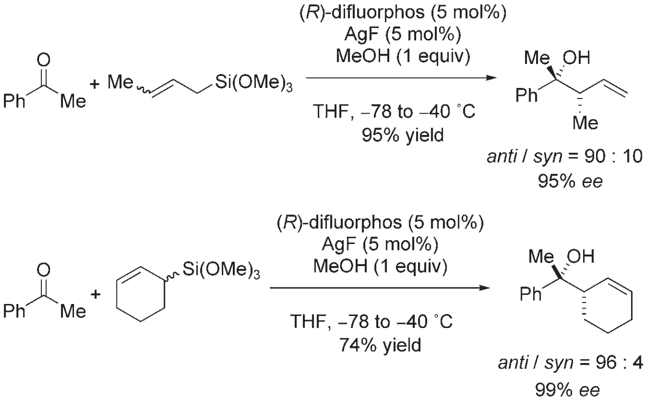


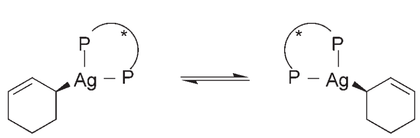
Figure 3. Ratio of the three silver–ligand complexes.[a,b] A 1:1 mixture of AgF and ligand was used. The A/B/C ratio was determined by ^{31}P NMR spectroscopy at −78 °C.



Scheme 8. Substrate scope.



Scheme 9. Catalytic diastereo- and enantioselective allylation.

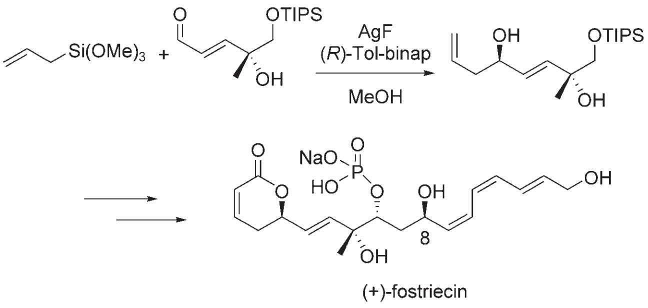


Scheme 10. Proposed interconversion of the intermediate.

by Trost and Crawley for their palladium-catalyzed asymmetric allylation–alkylation (AAA) process.[15a] The significant difference between our reaction and the AAA process of Trost and Crawley is that our π-allylmetal intermediate behaves as a nucleophile,[15b] whereas their AAA intermediate behaves as an electrophile for the palladium reaction.

2.4 Application of Allyltrimethoxysilane for Asymmetric Natural-Product Synthesis

These reagents were studied not only for the reaction with simple substrates but also in the asymmetric synthesis of complex natural products. Shibasaki and co-workers demonstrated the utility of this reaction in their catalyst-controlled asymmetric synthesis of fostriecin and 8-epi-fostriecin (Scheme 11).[16] It is a remarkable example of true enantioselective transformation that proceeds regardless of the chirality of the starting material. Itoh et al. demonstrated the synthesis of (−)-emetine by using asymmetric allylation with allyltrimethoxysilane.[7c]

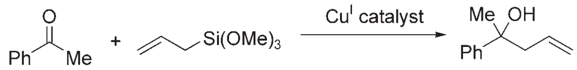


Scheme 11. The structure and the key step in the formation of (+)-fostriecin. TIPS = triisopropylsilyl.

3. Other Metal Fluoride Catalyzed Asymmetric Allylations with Allyltrimethoxysilane

In 2002, Shibasaki and co-workers developed the general catalytic allylation of ketones with allyltrimethoxysilane catalyzed by CuCl–TBAT.[6a] This is the first catalytic enantioselective Sakurai–Hosomi allylation of acetophenone. Although the observed enantioselectivity was relatively low, it was improved to 81% *ee* by choosing the ligand duphos under proper reaction conditions (Table 2).[6b]

Table 2. Chiral CuF-catalyzed asymmetric allylation of acetophenone.

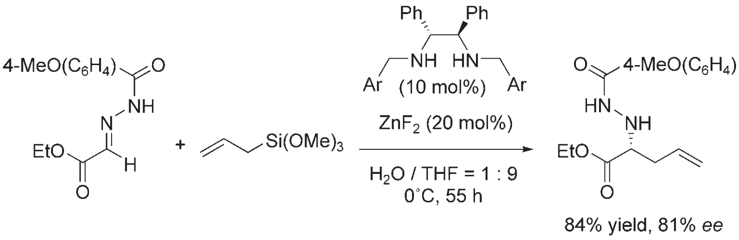


Conditions[a]	Yield [%]	*ee* [%]
CuCl–(*R*)-Tol-binap (15 mol%), TBAT (15 mol%), THF, 4°C	65	61 (*R*)
$CuF_2 \cdot 2H_2O$ (15 mol%), (*R*,*R*)-*i*Pr-duphos (30 mol%), DMF, −40°C	83	81 (*S*)

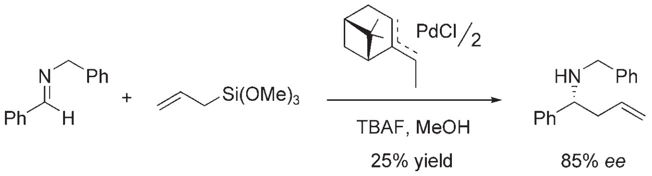
[a] DMF = *N*,*N*-dimethylformamide, duphos = 1,2-bis(phospholano)benzene, TBAT = *tert*-butylammonium triphenyldifluorosilicate.

The asymmetric allylation of acylhydrazono esters in aqueous media was achieved by using a catalytic amount of ZnF_2 and a chiral diamine ligand (Scheme 12).[7a] This reaction is the first example of catalytic asymmetric allylation of hydrazones. In this reaction, water plays a key role in giving the product, because the reaction does not proceed in THF without water.

Recently, Fernandes and Yamamoto reported the asymmetric allylation of simple imines with allyltrimethoxysilane.[7b] The reaction is triggered by dual activation/promotion by TBAF and the palladium complex (Scheme 13). Al-



Scheme 12. Chiral zinc fluoride catalyzed asymmetric allylation of an acylhydrazono ester.

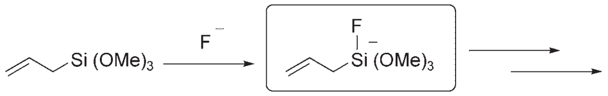


Scheme 13. Enantioselective allylation of imines with a combination of Pd and TBAF.

lylsilanes such as allyltrimethylsilane, allyltrimethoxysilane, and tetraallylsilane were screened for the asymmetric allylation of imines, and tetraallylsilane was found to be the best reagent (up to 94 % *ee*) for this reaction.

4. Conclusion

Both allyltrimethylsilane and allyltrimethoxysilane are readily available. However, the reactivity of allyltrimethoxysilane is significantly superior to that of allyltrimethylsilane, especially in the presence of fluoride anion. The difference in reactivity originates from the general ability of methoxysilanes to produce a stable silyl anion. Thus, in the presence of metal fluoride, the reaction proceeds smoothly to produce the very reactive silyl anion shown in Scheme 14.[5–7,11,17] Such a reactive species can behave as an excellent nucleophile towards various electrophiles. Once this species is generated, metal exchange from silicon to other metals, including silver, should be accomplished smoothly.



Scheme 14. Activation of allyltrimethoxysilane.

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[1] a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207; b) G. Helmchen, R. Hoffmann, J. Mulzer, E. Schaumann, *Stereoselective Synthesis Methods of Organic Chemistry (Houben-Weyl)*, *Vol. 3*, *21st ed.*, Thieme, Stuttgart, **1996**, pp. 1357–1602; c) S. R. Chemler, W. R. Roush in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, chap. 11; d) S. E. Denmark, N. G. Almstead in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, chap. 10.

[2] a) A. Hosomi, H. Sakurai, *Tetrahedron Lett.* **1976**, *17*, 1295; b) A. Hosomi, H. Sakurai, *J. Am. Chem. Soc.* **1977**, *99*, 1673.

[3] A. Hosomi, A. Shirahata, H. Sakurai, *Tetrahedron Lett.* **1978**, *19*, 3043.

[4] a) K. Sato, M. Kira, H. Sakurai, *J. Am. Chem. Soc.* **1989**, *111*, 6429; see also: b) G. Cerveau, C. Chuit, R. J. P. Corriu, C. Reye, *J. Organomet. Chem.* **1987**, *328*, C17; c) A. Hosomi, S. Kohra, Y. Tominaga, *J. Chem. Soc. Chem. Commun.* **1987**, 1517.

[5] A. Yanagisawa, H. Kageyama, Y. Nakatsuka, K. Asakawa, Y. Matsumoto, H. Yamamoto, *Angew. Chem.* **1999**, *111*, 3916; *Angew. Chem. Int. Ed.* **1999**, *38*, 3701.

[6] a) S. Yamasaki, K. Fujii, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2002**, *124*, 6536; b) R. Wada, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8910; c) M. Wadamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 14556.

[7] a) T. Gastner, H. Ishitani, R. Akiyama, S. Kobayashi, *Angew. Chem.* **2001**, *113*, 1949; *Angew. Chem. Int. Ed.* **2001**, *40*, 1896; b) R. A. Fernandes, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 735; c) T. Itoh, M. Miyazaki, H. Fukuoka, K. Nagata, A. Ohsawa, *Org. Lett.* **2006**, *8*, 1295.

[8] A. Yanagisawa, H. Nakashima, A. Ishiba, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 4723.

[9] a) A. Yanagisawa, A. Ishiba, H. Nakashima, H. Yamamoto, *Synlett* **1997**, 88; b) A. Yanagisawa, H. Nakatsuka, H. Nakashima, H. Yamamoto, *Synlett* **1997**, 933.

[10] a) M. Ohkouchi, M. Yamaguchi, T. Yamagishi, *Enantiomer* **2000**, *5*, 71; b) M. Ohkouchi, D. Masui, M. Yamaguchi, T. Yamagishi, *J. Mol. Catal. A: Chem.* **2001**, *170*, 1; c) M. Ohkouchi, D. Masui, M. Yamaguchi, T. Yamagishi, *Nippon Kagaku Kaishi* **2002**, 223; d) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5360.

[11] M. Wadamoto, N. Ozasa, A. Yanagisawa, H. Yamamoto, *J. Org. Chem.* **2003**, *68*, 5593.

[12] a) A. Yanagisawa, Y. Nakatsuka, K. Asakawa, H. Kageyama, H. Yamamoto, *Synlett* **2001**, 69; b) A. Yanagisawa, Y. Nakatsuka, K. Asakawa, M. Wadamoto, H. Kageyama, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1477.

[13] H. B. Kagan, T. O. Luukas in *Comprehensive Asymmetric Catalysis*, *Vol. 1* (Ed.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 102.

[14] a) P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445; b) S. Kobayashi, H. Kiyohara, Y. Nakamura, R. Matsubara, *J. Am. Chem. Soc.* **2004**, *126*, 6558.

[15] a) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2944; b) G. Zanoni, S. Gladiali, A. Marchetti, P. Piccinini, I. Tredici, G. Viadari, *Angew. Chem.* **2004**, *116*, 864–867; *Angew. Chem. Int. Ed.* **2004**, *43*, 846–849.

[16] a) K. Fujii, K Maki, M. Kanai, M. Shibasaki, *Org. Lett.* **2003**, *5*, 733; b) K. Maki, R. Motoki, K. Fujii, M. Kanai, T. Kobayashi, S. Tamura, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 17111.

[17] N. Aoyama, T. Hamada, K. Manabe, S. Kobayashi, *J. Org. Chem.* **2003**, *68*, 7329.

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