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Stereochemical Studies of Ag-Catalyzed Hosomi–Sakurai Reaction Using Chiral Silanes

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Dedicated to Professor Alain Krief

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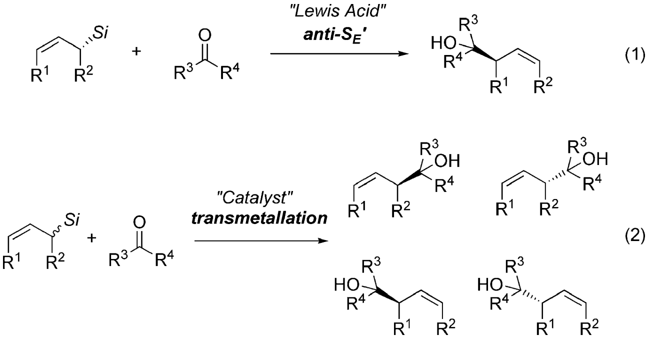
Stereochemical aspect of asymmetric Ag-catalyzed Hosomi–Sakurai reaction with ketones has been investigated. Several allyltrimethoxysilanes have been synthesized and used for the asymmetric reaction. Remarkably, among several possible diastereomers only two are generated with high levels of diastereo- and enantioselectivities. Based on the observations for different allyltrimethoxysilanes, we hypothesize formation of a single allylsilver species which undergoes addition to the ketone.

Introduction

Hosomi–Sakurai reaction of enantio-enriched allylsilanes[1] and carbonyls under Lewis acidic conditions generally proceeds through a S_E' mechanism.[2] One of the main characteristics of those reactions is stereospecific chirality transfer from the α-position of allylsilanes to the resulting homoallylalcohols [Scheme 1, equation (1)]. In contrast to those methodologies, protocols based on the transmetallation of allylsilane to a metal would generate a complex mixture of regio- and diastereomers due to the formation of highly reactive allylanion species [Scheme 1, equation (2)]. Distribution of these products can be controlled by the fine optimization of the catalyst. In that case, the process will be asymmetric transformation controlled by the chiral catalyst even when racemic allylsilanes are used.[3]



Scheme 1. Generation of four possible isomers from chiral allylsilane.

Our group has recently developed a method for highly diastereo- and enantioselective AgF-Difluorophos allyl- and crotylation reaction of ketones.[4,5] Main features of the reaction are (i) high level of enantioselectivity, (ii) excellent *syn*-selectivity regardless of the configuration of the starting crotylsilane and (iii) exclusive γ-regioselectivity (with respect to the starting crotylsilane). We discuss here the regio- and stereochemical aspects of the reaction and report the development of the robust asymmetric Hosomi–Sakurai reaction using chiral silver catalyst.

Results and Discussion

When the reaction was carried out using (but-3-en-2-yl)-trimethoxysilane, γ adduct was formed with remarkable *syn*-selectivity. The same product, with the same level of diastereoselectivity, was obtained when 2-butenyltrimethoxysilane was subjected to the standard reaction conditions (Scheme 2). We speculate that the reaction proceeds via a single allylsilver intermediate, generated through transmetallation process, and that the regio- and stereoselectivity of the reaction are determined by the stability and/or reactivity of that intermediate. Our hypothesis of a single reactive species is supported by the observation that the same regioisomer was formed from structurally isomeric allylsilanes (Scheme 2).

Considering the geometry of allylsilane, there are two possible stereo faces of the allylsilane that can approach the ketone, the face in which the silicon group resides (*syn*-addition) and the face opposite the silicon group (*anti*-addition). To clarify which of the two faces approaches the ketone, allylsilane **1** bearing phenyl group in 5-position was subjected to the standard reaction conditions (Table 1). Sur-

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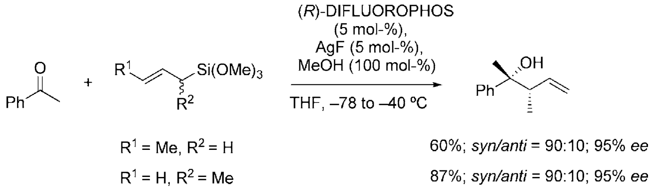
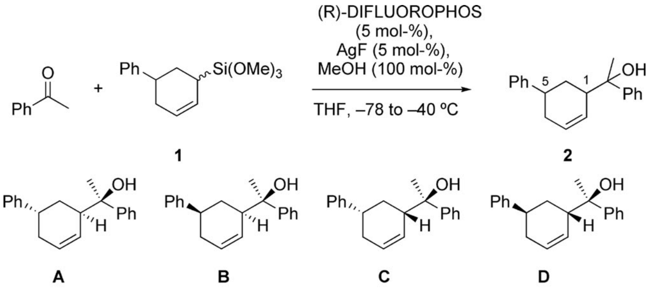


Scheme 2. Catalyst controlled crotylation of ketones.

prisingly, only two isomers (**2A** and **2B**, Table 1) with high *ee* values were obtained. It was determined that those isomers were epimeric at 5-position. It is important to note that diastereo- and enantioselectivity do not depend on the *syn*/*anti* ratio of the starting silane **1** (Table 1). These results suggest that a single allylsilver intermediate, which undergoes addition to the ketone, is formed. Diastereoselectivity would therefore depend on the stability or reactivity of that intermediate.

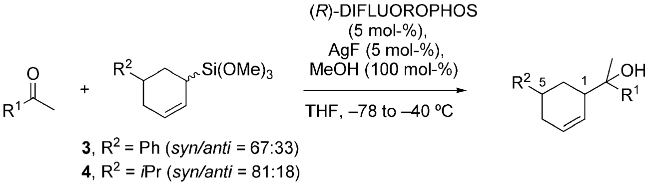
Table 1. Enantioselective allylation of acetophenone with (5-phenyl-1-cyclohexenyl)trimethoxysilane.[a]



Entry	**1**, *syn/anti*	Yield (%)[b]	**A/B/C/D**[c] (*ee* %)[d]
1	99 : <1	88	65 (86% *ee*):34 (98% *ee*):<1:<1
2	<1 : 99	>99	65 (88% *ee*):34 (>99% *ee*):<1:<1
3	67 : 33	>99	65 (90% *ee*):34 (>99% *ee*):<1:<1

[a] The reactions were carried out at –78 to –40 °C for 24 h. [b] Yields of the isolated products. [c] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess was determined by HPLC analysis (OD-H, Chiracel column).

Table 2. Enantioselective allylation of ketones with 5-substituted cyclohexenyltrimethoxysilanes.[a]



Entry	R^1	Allylsilane	Yield (%)[b]	**A/B/C/D**[c] (*ee* %)[d]
1	4-BrC$_6$H$_4$	**3**	90	65 (95% *ee*):34:<1:<1
2	Ph	**4**	80	85 (99% *ee*):14:<1:<1

[a] The reactions were carried out at –78 to –40 °C for 24 h. [b] Yields of the isolated products. [c] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess was determined by HPLC analysis (OD-H, Chiracel column).

An electron-withdrawing group in the 4-position of the acetophenone (Entry 1, Table 2) does not affect the diastereoselectivity of the reaction. However, introduction of the isopropyl group in the 5-position of the allylsilane (**4**, Table 2) provides an increased level of the diastereoselectivtity. Remarkably, asymmetric induction was observed at the C-5 atom despite the fact that the starting allylsilane was racemic.

Conclusions

In summary, a detailed stereochemical study of asymmetric Ag^I-catalyzed Hosomi–Sakurai reaction of ketones has been described. Plausible mechanistic scenario involves formation of a single reactive allylsilver species that reacts with ketones to furnish homoallyl alcohols in a highly regio-, diastereo- and enantioselective fashion. Our hypothesis is supported by the observation that stereochemical information in the allylsilane does not translate to the product. From this point of view, the main advantage of the method is that it does not necessitate tedious procedures for the preparation of enantio-pure allylsilanes.

Experimental Section

General Experimental Procedure for Allylation of Ketones: A flame-dried test tube was charged with AgF (1.6 mg, 0.012 mmol) and (*R*)-Difluorophos (8.4 mg, 0.012 mmol). To this mixture were added dry THF (2.5 mL) and MeOH (0.24 mmol) and the resulting mixture was stirred for 15 min. After 15 min, THF and MeOH were removed in vacuo. After all the volatiles were removed, the solid residue was dissolved in THF (2.5 mL) and cooled to –78 °C. After the reaction mixture was cooled, ketone (0.24 mmol) and allyltrimethoxysilane (0.24 mmol) were added. Upon reaction completion, as determined by TLC analysis, the reaction mixture was filtered through a short silica plug and concetrated in vacuo. The crude reaction mixture was purified by column chromatography (hexanes/Et$_2$O).

Acknowledgments

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