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Enantioselective Ag-Catalyzed Allylation of Aldimines

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Abstract

A highly enantioselective synthesis of homoallylic amines, using allyltrimethoxysilane under Ag^I catalytic conditions, has been developed. Among the chiral ligands investigated, a remarkable difference in the resulting Ag^I complexes was observed. Under mild conditions and low catalyst loadings, homoallylamines were produced in high *ee* values (up to 80%) and good yields. The methodology can be further extended to a diastere- and enantioselective crotylation of aldimines.

Keywords

Aldimines; Silver; Allylsilane; Asymmetric synthesis

Introduction

Nitrogen functionalities represent a crucial architectural detail in many biologically active natural products and amino acids. The most efficient and convenient synthetic methods for preparation of these groups of compounds are based on the utility of imines as electrophilic reagents.[1] Many of these methods use various organometallic nucleophiles, some of which are highly toxic (such as organostannanes) or are nonselective (region- and/or stereoselective). [2] Even though several reports of asymmetric allylation of aldimines and ketimines are present in the literature, the examples of practical and efficient methods are scarce.

Allylic trialkoxysilanes have long been recognized as highly reactive species, upon formation of pentacoordinate intermediates in the presence of nucleophiles.[3] Beside their excellent reactivity, another advantage of allylic trialkoxysilanes is low toxicity, as opposed to allylic stannanes which are other commonly used allyl-transfer reagents. During our ongoing research program regarding Ag-catalyzed reactions, we have demonstrated that allyltrimethoxysilane acts as a highly reactive allyl-transfer reagent under Ag^I-phosphane catalytic conditions.[4] Herein we would like to report the development of enantioselective allylation reaction of aldimines using trimethoxyallylsilanes in the presence of Ag^I-phosphane ligand.

Results and Discussion

Our group reported the first example of asymmetric silver-catalyzed addition of allyltrimethoxysilanes to aldehydes.[5] Recently we have demonstrated that these conditions can be successfully applied to a highly diastereo- and enantioselective allylation of ketones. [6] Encouraged by the excellent reactivity of allyltrimethoxysilane-Ag^I-phosphane system for the asymmetric allylation reaction of aldehydes and ketones, we have focused our attention to

their aza-analogues. In contrast to carbonyl electrophiles, imines represent more challenging substrates since Lewis acid catalyzed reactions with imine electrophiles usually suffer from inhibition of the catalyst by the amine product. The development of an efficient protocol for asymmetric allylation of imines would therefore be highly a beneficial addition to the limited number of published methodologies.[2a]

For our initial studies we have adopted the reaction conditions described for the allylation reaction of ketones.[6] As in the case of carbonyls, the reaction with aldimines required the presence of a proton source to liberate the amine product. Imines derived from electron-rich amines were shown to be more desirable substrates for the reaction since electron-poor imines provided trace or no product. Solvent screening revealed THF to be the best choice of solvent providing the products in highest yields and enantio-selectivities. It should be noted that in the early stage of our studies crotylsilane was used, fearing that simple allyltrimethoxysilane would be insufficiently nucleophilic reagent. One of the remarkable observations made during the initial investigation of the reaction conditions was regarding the outstanding difference of the reactivity of monophosphane- and diphosphane-Ag^I catalysts (Scheme 1). Namely, when the reaction was carried out in the presence of monophosphane ligands, the products were obtained in quantitative yields. Diphosphane ligands, on the other hand, appear to form inactive complexes.

In our previous research, we have observed formation of three different diphosphane-Ag complexes which exhibit remarkably different reactivity and selectivity. Ratio of these complexes can be regulated by the nature of silver salt or varying the ratio of diphosphane ligand and silver salt.[7] We believe that using (*R*)-Difluorophos and AgF in 1:1 ratio generates predominantly inactive complex (Scheme 1).

Encouraged by the high reactivity of Ag^I-monophosphane catalyst, several monophosphane and MOP-type ligands were prepared and screened for the allylation reaction. Some of the results are shown in Table 1. Although many of the ligands exhibited high levels of reactivity, the enantioselectivities observed were unsatisfactory.

Contrary to our expectations of poor reactivity of simple allyltrimethoxysilane, we were pleased to find it is sufficiently reactive under the reaction conditions. Furthermore, the allylation reaction does proceed in the presence of diphosphane ligands, however the ligand/AgF ratio had to be increased to 1:2 [Scheme 1, (*R*)-Difluorophos:AgF ratio is 1:1].[7] Unfortunately, the yields of homoallylamines were generally low and in some cases indicated that the catalyst was inhibited by the amine product (Table 2). Despite the low reactivity generally observed in Table 2, difluorophos-AgF catalyst emerged as a promising lead for improvement (entry 5, Table 2).

With these new results, modifications of the reaction conditions were performed to affect the reactivity of the Ag-diphosphane catalyst. Various additives (alcohols and amines) used instead of MeOH, and different solvents or Ag^I-salts provided no improvement in the reactivity and caused a decrease of the enantioselectivity and/or reactivity. On the other hand, modification of the aldimine substrates had a more drastic effect on the performance of the catalytic system. The imine substrate bearing 2-PhOC₆H₄ group yielded a homoallylamine in synthetically useful yield and selectivity. With these optimized conditions in hand, enantioselective synthesis of homoallylamines using a wide range of imine substrates can be carried out (Table 3).

Conclusions

In summary, new method for the enantioselective synthesis of homoallylamines has been developed. Using simple allyltrimethoxysilane in combination with commercially available ligands and AgF, products can be obtained in synthetically useful yields and high

enantioselectivity. We have also shown that the methodology can be efficiently expanded to crotylsilane substrate to afford products in a highly diastereoselective fashion. Another advantageous feature of this protocol is the excellent level of regioselectivity observed.

Experimental Section

General Experimental Procedure for Allylation of Aldimines

A flame-dried test tube was charged with AgF (3.1 mg, 0.024 mmol) and (*R*)-Difluorophos (8.2 mg, 0.012 mmol). To this mixture was 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, aldimine (0.24 mmol) and allyltrimethoxysilane (0.48 mmol) were added. Upon reaction completion, as determined by TLC analysis, the reaction mixture was filtered through a short silica plug and concentrated in vacuo. The crude reaction mixture was purified by column chromatography (hexanes/EtOAc).

Acknowledgments

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7. We have recently reported that depending on the ligand/AgX ratio, complexes with remarkably different reactivity can be formed. Distribution of reactive and unreactive complexes can be affected by the ration and the nature of the counteranion. See: Momiyama N, Yamamoto H. *J. Am. Chem. Soc* 2004;126:5360. [PubMed: 15113198]

Ligand	Yield (%)	de (ee%)
(R)-MOP (10 mol-%)	> 99	93 (66) : 7 (40)
(R)-DIFLUOROPHOS (5 mol-%)	NR	NR
PPh ₃ (10 mol-%)	>99	87 : 13

Scheme 1.

Crotylation of aldimines using different Ag-phosphane catalysts.

Table 1Asymmetric crotylation of aldimines using Ag-monophosphane catalysts.^[a]

Entry

Ligand

1

(R)-MOP

2

Entry	Ligand
3	
4	
5	(S)-QUINAP
6	(S)-NMDPP

[a] The reactions were carried out using 1.0 equiv. of **4** and 2.0 equiv. of **2** at $-78\text{ }^{\circ}\text{C}$ for 18 h.

[b] Isolated products yield.

[c] Diastereomeric ratio determined by ^1H NMR spectroscopy.

[d] Enantiomeric excess determined by HPLC analysis (OD-H Chiracel column).

Table 2Enantioselective allylation of aldimine using AgF-diphosphane catalysts.^[a]

Entry	Ligand	Yield(%) ^[b]	ee(%) ^[c]
1	(<i>R</i>)-BINAP	37	76
2	(<i>R</i>)-TolBINAP	28	69
3	(<i>R</i>)-SYNPHOS	34	58
4	(<i>R</i>)-TUNEPHOS	12	82
5	(<i>R</i>)-DIFLUOROPHOS	25	88
6 ^[d]	(<i>S</i>)-PHANEPHOS	65	/
7 ^[d]	(<i>R,R</i>)-NORPHOS	58	/

^[a] Reactions were carried out using 1.0 equiv. of aldimine, 2.0 equiv. of allyltrimethoxysilane and 2.5 mol-% of (*R*)-Difluorophos or 5 mol-% of (*R*)-Mop at −78 °C to −20 °C for 24 h.

^[b] Isolated products yields.

^[c] Enantiomeric excess was determined by HPLC analysis (OD-H, Chiralec column).

Table 3Enantioselective allylation of aldimines using AgF-phosphane catalysts.^[a]

Entry	Ligand	Aldimine (R)	Yield(%) ^[b]	ee(%) ^[c]
1	(R)-MOP	1-naphthyl	>99	77
2	(R)-MOP	2-naphthyl	>99	70
3	(R)-DIFLOUROPHOS	2-naphthyl	74	62
4	(R)-MOP	<i>p</i> -PhOC ₆ H ₄	>99	60
5	(R)-DIFLUOROPHOS	<i>p</i> -PhOC ₆ H ₄	40	37
6	(S)-MOP	<i>o</i> -PhOC ₆ H ₄	>99	30
7	(R)-DIFLUOROPHOS	<i>o</i> -PhOC ₆ H ₄	70	82

^[a] Reactions were carried out using 1.0 equiv. of aldimine, 2.0 equiv. of allyltrimethoxysilane and 2.5 mol-% of (R)-Difluorophos or 5 mol-% of (R)-Mop at −78 °C to −20 °C for 24 h.

^[b] Isolated products yields.

^[c] Enantiomeric excess was determined by HPLC analysis (OD-H, Chiralec column).