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Ir-Catalyzed Asymmetric and Regioselective Hydrogenation of Cyclic Allylsilanes and Generation of Quaternary Stereocenters via the Hosomi-Sakurai Allylation

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Dedication ((optional))

Abstract: A number of cyclic dienes containing the allylsilane moiety were prepared via Birch reduction and subjected to iridium-catalyzed regioselective and asymmetric hydrogenation, which provided chiral allylsilanes in high conversion and enantiomeric excess (up to 99 % ee). The compounds were successively used in the Hosomi-Sakurai allylation with various aldehydes employing TiCl_4 as Lewis acid, providing adducts with two additional stereogenic centers in excellent diastereoselectivity.

Introduction

Allylsilanes are very versatile reagents, which possess high thermal stability and rather low sensitivity to moisture and oxygen. They are relatively inert towards a range of synthetic methodologies such as oxidation, reduction and hydrogenation,^[1] yet they react smoothly with aldehydes and ketones in presence of Lewis acids. This transformation has been reported by Hosomi and Sakurai in 1976^[2] and has been thoroughly studied and applied in synthesis since, allowing stereoselective carbon-carbon bond formation. The method has been employed as a key step in the total synthesis of many complex natural products,^[3] such as (+)-Tetronomycin^[4] and Lycopodium alkaloids.^[5]

In the past few decades the focus has been oriented on enantio- and regioselective synthesis for many chemical transformations. This led to the development of various chiral Lewis^[6] and Brønsted acids^[7] as well as to the use of optically active allylsilanes^[8] to direct the stereochemical outcome when introducing two or more stereogenic centers in the target molecules.

Numerous reports on chiral acyclic allylsilanes appeared in the literature,^[8d] but few on cyclic allylsilanes.^[9] Organ and co-workers reported the example of Sakurai allylation with cyclic silanes bearing a stereogenic center, reacting with various electrophiles in presence of TiCl_4 (Scheme 1a).^[9a] High

diastereomeric ratios were achieved and in some cases only a single diastereoisomer was obtained. Later, Shea reported a bridgehead cyclic allylsilane that gave rise to single diastereomers when employed in analogous transformations (Scheme 1b).^[9b] Nonetheless, only the relative stereochemistry of the products was controlled in both cases since the starting materials were prepared in racemic form. In order to control absolute stereochemistry, it can be anticipated to install a stereochemically defined chiral center distal or proximal to the allylsilane moiety. Additionally, if the reagent bears double substitution on the γ -carbon, it would generate a chemically challenging stereodefined quaternary center in the adducts (Scheme 2).

Scheme 1. Work by Organ (a) and Shea (b) group.

Results and Discussion

Recently we have reported the Ir-catalyzed asymmetric and regioselective hydrogenation of carbocyclic olefins.^[10] Henceforth we envisioned that the introduction of a silyl group

Scheme 2. General procedure for the synthesis of compounds 4.

could afford chiral cyclic allylsilanes upon asymmetric monohydrogenation, which would be useful substrates for the stereoselective Hosomi-Sakurai reaction to obtain further functionalized cyclohexane structures.

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The prochiral allylsilanes turned out to be easily generated from the reduction of benzyl silanes (**1**, Scheme 2). The formed cyclohexadienes (**2**) are suitable substrates for the initial installation of a stereogenic center using the iridium catalyzed asymmetric monohydrogenation.

Figure 1. Catalysts used in this study.

Dimethyl substituted silane **2a** (Table 1) was chosen as model substrate for the hydrogenation catalyst screening. Iridium N,P-catalysts containing thiazole **i** and imidazole **ii** ligands (**Figure 1**) were evaluated, as they had been previously found to be the most efficient classes for the hydrogenation of cyclohexadienes.^[10b] The ligand was found to have great influence on the hydrogenation outcome, especially in presence of the acid-sensitive allylsilane group.^[11] The catalyst containing a thiazole ring had been reported to be more acidic compared to the imidazole,^[11b] and lead to lower conversion to the desired product (Table 1, entries 1 and 2). The imidazole catalyst **ii** was chosen and we studied the effect of basic additives (PVP and KHCO_3); they granted improvement of the reaction outcome with a slight increment in the enantioselectivity (70-71% ee, entries 3 and 4).

Scheme 3. Possible protodesilylation pathway generating undesired byproducts.

Thus, electronic properties of the aromatic substituent on the imidazole ligand were examined. When an electron-withdrawing group (Figure 1, catalyst **iii**) was installed, it led to low conversion and enantiomeric excess (34% ee, entry 5). The increase in electronic density from the 2,4-dimethyl group (Figure 1, catalyst **iv**) to the more electron-donating 2,4-dimethoxy group (Figure 1, catalyst **v**) contributed to improve the conversion (92 to 95%) and to reach excellent enantiomeric

excess (88-98% ee, Table 1, entries 6 and 7). Most ligand structures afforded mixtures of the hydrogenated product (**3a**) and volatile compounds, probably by causing the protodesilylation of the allylic substrate and its further hydrogenation (Scheme 3). Dimethoxy catalyst **v** was found to prevent this issue, most likely due to its decreased acidity and was then chosen to further study the solvent effect. A screening was carried out, showing that CH_2Cl_2 , benzene and toluene gave comparable results (97-98% ee, Table 1, entries 7-9). However, the use of α,α,α -trifluorotoluene enabled a cleaner reaction, with full conversion and 99% ee (entry 10).

Table 1. Optimization of the reaction conditions for the asymmetric hydrogenation of **2a**^[a]

Entry	cat.	solvent	additive	conv.(%) ^[b]	ee (%) ^[c]
1	i	CH_2Cl_2	-	70	80
2	ii	CH_2Cl_2	-	90	65
3	ii	CH_2Cl_2	PVP	99	70
4	ii	CH_2Cl_2	KHCO_3	99	71
5	iii	CH_2Cl_2	-	75	34
6	iv	CH_2Cl_2	-	92	88
7	v	CH_2Cl_2	-	95	98
8	v	Benzene	-	93	97
9	v	Toluene	-	97	97
10	v	α,α,α -trifluorotoluene	-	99	99

[a] Reaction conditions: 0.05 mmol substrate, 0.5 mol% catalyst, 0.5 mL of solvent, 10 bar of H_2 , 18 h, rt. [b] Conversion determined by ^1H NMR spectroscopy. [c] Enantiomeric excess determined by GC analysis using a chiral stationary phase.

With the best conditions defined, the hydrogenation was extended to analogous cyclic silanes. The substrate scope included the variation of the alkyl chain length and its position on the ring. The results from the asymmetric hydrogenation of these substrates are summarized in Table 2. Catalyst **v** performed excellently in the reduction regardless of the substitution pattern. Hydrogenations occurred with high conversion, allowing the isolation of the optically active allylsilanes in good to excellent yield (70-96%). Substrates having ethyl and *n*-butyl groups on the 4 or 5 position tended to give slightly lower enantioselectivity 92-94% ee (Table 2, entries 1, 2, 5 and 6). Having an isobutyl group on the 4 position didn't affect the enantioselectivity, giving 99% ee (Table 2, entry 3). Similarly, when the methyl substituent was replaced with ethyl and *n*-butyl on the 2 position of the tetrasubstituted allylsilane, excellent enantioselectivity 99% ee (Table 2, entries 7 and 8) was still obtained.

The obtained chiral β,γ -substituted allylsilanes could then be employed in the Hosomi-Sakurai reaction, generating a sterically

demanding quaternary center in the homoallylic alcohol adduct. The initial reactivity optimization studies employed the dimethyl allylsilane **3a** as model substrate and benzaldehyde as standard electrophile. Screening of different Lewis acids showed that TiCl_4 was the appropriate choice in order to have a selective reaction (Table 3). SnCl_4 promoted the allylation as well, although producing higher amounts of side-products and showing opposite diastereoselectivity (entry 2)^[12]. SiCl_4 resulted mainly in the desilylation (**6**) of the starting material. The use of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ did not afford the desired product and generated complex reaction mixtures.

Table 2. Substrate scope of the asymmetric hydrogenation of cyclic allylsilanes.^[a]

Entry	Substrate	Product ^[b]	Yield (%) ^[c]	ee (%) ^[d]
1			84	92
2			84	93
3			96	99
4			70	99
5			87	93
6			89	94
7			70	99
8			95	98

[a] Reaction conditions: 0.05 mmol substrate, 0.5 mol% catalyst, 0.5 mL of solvent, 10 bar of H_2 , 18 h, rt. [b] Predicted absolute configuration for the major product. [c] Isolated yield. [d] Enantiomeric excess determined by GC analysis using a chiral stationary phase.

It is also known that TBAF can be used to initiate fluoride-promoted allylations, however we observed no such reactivity for the investigated cyclic silanes. TiCl_4 was then chosen to continue the selectivity optimization. The solvent of choice for the transformation is dichloromethane, and the reaction mixture

was kept at -78°C with a dry ice/acetone cooling bath for 1 h. The use of 3Å molecular sieves aided to increase the yield to 68% (Table 3, entry 6).

It was then necessary to investigate the diastereoselectivity of the reaction. The final allylation product bears three stereogenic centers, which can give rise to a maximum of four possible diastereoisomers. Stereoselectivity is dictated by the allylsilane preferred mode of attack, in which the incoming aldehyde is antiperiplanar to the allyl nucleophile and minimizing steric repulsion between the larger group on the aldehyde and the ring^[11] (Figure 2). This leads to two possible facial attacks either from top or bottom of the cyclohexyl ring. The attack on the top face gives rise to energetically more stable chair-like transition states TS1a and TS1b compared to the bottom attack, which forms a more energy demanding boat-like transition state TS2.

Table 3. Screening of Lewis acids for the Hosomi-Sakurai allylation.^[a]

Entry	Lewis acid	additive	dr ^[b]	Yield (%) ^[c]
1	TiCl_4	-	5:1	34
2	SnCl_4	-	1:6	20
3	SiCl_4	-	-	-
4	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	-	-	-
5	TBAF	-	-	-
6	TiCl_4	3Å MS	5:1	68

[a] Reaction conditions: 0.15 mmol substrate, 1.1 eq. Lewis acid, 1.1 eq. PhCHO , 1.5 mL of CH_2Cl_2 , 1 h, -78°C . [b] Diastereomeric ratio determined by ^1H NMR spectroscopy. [c] Isolated yield.

Thus, *trans* adducts are obtained as major product when substitution is present on the 4 position, which is in accordance with Organ's work, however *cis* adducts were obtained when it is on the 5 position. This was confirmed from single crystal X-ray crystallography of two individual compounds **8a** and **8e** (Figure 3). It was observed the formation of only two diastereoisomers, whose ratio was optimized by further varying the reaction conditions. It was in fact found that the diastereomeric ratio arising from the reaction of cyclic allylsilane **3a** with benzaldehyde is highly concentration-dependent (Table 4). This called for an investigation of the concentration effects of the individual reagents. The concentration of TiCl_4 and benzaldehyde was evaluated independently while keeping the allylsilane's concentration constant. A decrease in diastereoselectivity was observed in presence of excess benzaldehyde (Table 4, entry 5), while the use of excess TiCl_4 resulted in rather dramatic increase of the stereoselectivity

Figure 2. Proposed transition states for the formation of **8a** and **8e**.

Figure 3. Crystal structure of compounds **8a** and **8e**.

(Table 4, entry 6). Under optimized conditions, the Hosomi-Sakurai allylation was tested against a range of carbon electrophiles. A number of aliphatic aldehydes were reacted with

the dimethyl silane **3a**, and the results are shown in Table 5. The use of cyclohexanecarboxaldehyde afforded homoallylic alcohol **8aa** as

Table 4. Concentration dependence in the Hosomi-Sakurai allylation.

Reaction scheme: **3a** + PhCHO in CH_2Cl_2 at -78°C for 1h yields **8a** and **8a'** (relative stereochemistry).

Entry	Allylsilane (M)	Benzaldehyde (M)	TiCl_4 (M)	$dr^{[a]}$
1	0.03	0.03	0.03	3:1
2	0.10	0.10	0.10	5:1
3	0.22	0.26	0.26	12:1
4	0.60	0.73	0.73	30:1
5	0.30	0.60	0.30	2:1
6	0.30	0.30	0.60	45:1

[a] Diastereomeric ratio determined by ^1H NMR spectroscopy

a single diastereoisomer (Table 5, entry 1). The isobutyl- and ethyl-substituted compounds **8ab** and **8ac** were obtained with high ratios of 24:1 and 46:1, respectively (Table 5, entries 2 and 3). Using isobutyraldehyde **8ad** resulted in a less selective allylation, with a dr of 9:1 (Table 5, entry 4). When cyclopentanecarboxaldehyde was employed, the product **8ae** was again obtained in excellent diastereoselectivity (49:1, Table 5, entry 5). The substrate scope was then extended to differently substituted cyclic silanes. High stereoselectivity was reached in most cases (Table 5, entries 6-9). Changing substituent at the 4 position from methyl to isobutyl group (**8d**) didn't affect the dr (24:1, Table 5, entry 6).

Further switching the position of the methyl substituent (**8e**) did not alter the observed dr either, and a ratio of 31:1 was reached (table 5, entry 7). The ethyl-substituted product **8f** (Table 5, entry 8) could be isolated as a single diastereoisomer and the *n*-butyl-substituted counterpart **8g** (table 5, entry 9) was obtained with a dr of 34:1.

Table 5. Substrate scope for the Hosomi-Sakurai allylation.^[a]

$ \begin{array}{c} \text{R}^1\text{-Cyclohexane-CH=CH-Si(R}^2\text{)}_2 \\ \text{3a-g} \end{array} \xrightarrow[\text{-78 } ^\circ\text{C, 1 h}]{\text{TiCl}_4, \text{R}^3\text{CHO, CH}_2\text{Cl}_2, 3\text{ \AA MS}} \begin{array}{c} \text{R}^1\text{-Cyclohexane-CH=CH-CH(R}^3\text{)-OH} \\ \text{8a-g} \end{array} + \begin{array}{c} \text{R}^1\text{-Cyclohexane-CH=CH-CH(R}^3\text{)-OH} \\ \text{8a'-g'} \end{array} $			
Entry	Product	Yield (%) ^[b]	dr ^[c]
1		65	single stereoisomer observed
2		32	24:1
3		40	46:1
4		56	9:1
5		42	49:1
6		30	24:1
7		42	31:1
8		69	single stereoisomer observed
9		37	34:1

[a] Reaction conditions: 0.30 mmol substrate, 1.1 eq. TiCl_4 , 1.1 eq. aldehyde, 0.5 mL of CH_2Cl_2 , 1 h, -78°C . [b] Isolated yield. The lower yields are most likely due to protodesilylation and loss of volatile byproducts. [c] Diastereomeric ratio and relative stereochemistry determined by ^1H NMR spectroscopy.

Conclusions

In conclusion, the highly enantioselective preparation of chiral cyclic allylsilanes could be accomplished by means of N,P-iridium catalyzed asymmetric hydrogenation. The optically active allylsilanes were obtained in excellent *ee*'s (92–99%) with isolated yields of 70–96%, employing the recently developed

imidazole-based iridium catalyst **v**. The more electron donating ligand was found to be crucial for both reactivity and stereoselectivity. The chiral allylsilanes were successfully employed in Hosomi-Sakurai allylations giving rise to two new stereogenic centers in high diastereoselectivity. The developed methodology grants the generation of multiple stereocenters on the cyclohexane ring in few steps, starting from achiral materials and introducing additional functional groups for further synthetic transformations. Furthermore, this is to the best of our knowledge, the first example to be reported on the asymmetric synthesis of cyclic chiral allylsilanes by means of iridium catalysis.

Experimental Details

General procedure for asymmetric hydrogenations

A vial was charged with substrate (0.17 mmol) and Ir-complex (0.5 mol%). α,α,α -trifluorotoluene (1 mL) was added and the vial was placed in a high-pressure hydrogenation apparatus. The reactor was purged three times with Ar, then purged with H_2 filled to 10 bar with H_2 . The reaction was stirred at room temperature for 16 h before the H_2 pressure was released and the solvent was removed in vacuo. The crude product was purified through dry silica gel with pentane as eluent. Conversions were determined by ^1H NMR spectroscopy and *ee* values were determined using chiral GC or SFC. Racemates were prepared using the racemic version of the iridium catalyst.

General procedure for Hosomi-Sakurai reactions

The procedure for the Hosomi-Sakurai allylation was adapted from the literature.^[9a] To a mixture of allylsilane (0.35 mmol) and aldehyde (0.42 mmol) in anhydrous DCM (0.6 mL) 10 mg of activated molecular sieves (3Å) were added. The reaction vessel was sealed and the mixture degassed with argon for about 10 min, simultaneously cooling down to -78°C in a dry ice/acetone bath. After approximately 15 min of vigorous stirring, freshly distilled TiCl_4 (0.42 mmol) was added dropwise over 15 min. The reaction mixture was stirred for 1 h, then removed from the cooling bath and quenched immediately with saturated aqueous NaHCO_3 . The aqueous layer was extracted with Et_2O three times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using a gradient of 2% to 4% Et_2O in pentane as eluent.

The complete experimental section can be found in the supporting information, including compound characterization data, copies of NMR spectra and chromatogram.

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Keywords: Asymmetric monohydrogenation • Allylsilane • Regioselectivity • Allylation • Iridium-catalyzed

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