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STEREOSELECTIVE CONJUGATE ADDITIONS OF ALLYL SILANES AND ENOL SILYL ETHERS TO A CHIRAL 2-SUBSTITUTED-2-CYCLOHEXEN-1-ONE

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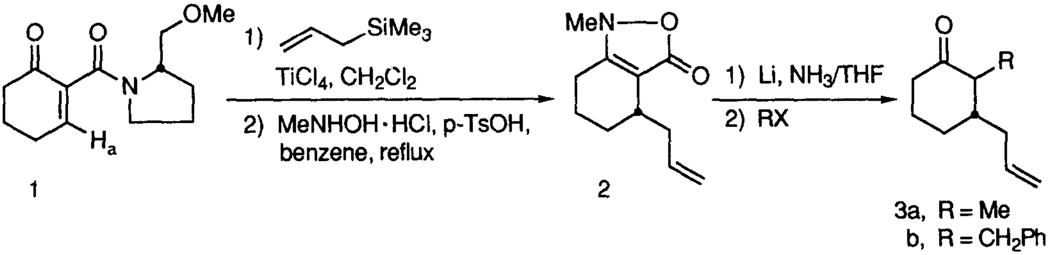
Abstract: Conjugate additions of allyl silanes (the Sakurai reaction) and enol silyl ethers (the Mukaiyama-Michael addition) to chiral 2-amidocyclohexenone **1** occur in excellent yields with high diastereoselectivities.

Grignard reagents undergo zinc or copper catalyzed conjugate additions to (2'S)-2-[[2'-(methoxymethyl)pyrrolidinyl]carbonyl]cyclohex-2-en-1-one (**1**) generally with good to excellent diastereoselectivities.[1] An exception is $CH_2=CHCH_2MgBr$ which gives competing carbonyl addition and deprotonation reactions. Herein, we report a solution to earlier problems associated with allyl ligand transfer and demonstrate that enol silyl ethers[2] undergo highly diastereoselective conjugate additions to **1**.



1

2

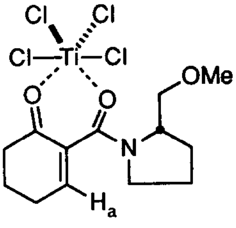
3a, R = Me
b, R = CH_2Ph

Treatment of a solution of **1** and 1 equiv of $TiCl_4$ in CH_2Cl_2 at -78°C with allyltrimethylsilane for 0.5 h followed by warming to room temperature and stirring for an additional 8 h gave the product of conjugate addition as a mixture of diastereoisomers in nearly quantitative yield. Subsequent reaction with N-methylhydroxylamine hydrochloride and p-toluenesulfonic acid in benzene at reflux gave the 1-methyltetrahydrobenzisoxazolin-3-one **2** in 92% overall yield from **1**. Chiral HPLC analysis indicated that **2** had been generated with 80% ee.[3] The absolute configuration of **2** was determined by olefin hydrogenation (5% Pd/c, ethyl acetate, 1 atm) to give a product identical to that prepared by the addition of $CH_3CH_2CH_2MgCl$ to **1**.[1]

Variation of initial reaction temperature from -78° to 25°C had little effect on the yield and diastereoselectivity of conjugate addition; however, variation of the molar equivalence of $TiCl_4$ had dramatic effects. With 2 equiv of $TiCl_4$, the overall yield of **2** remained high, but the enantiomeric excess was only 20%. The best stereoselectivity (94-96%) was obtained with 0.8 to 0.95 equiv of $TiCl_4$. With only 0.5 equiv, the yield of **2** dropped to 19%.

Table I. Effect of $TiCl_4$ on Conjugate Addition to **1**

entry	equiv of TiCl4	isolated 2	
		% yield	% ee
1	0.5	19	94
2	0.8	70	96
3	0.95	88	94
4	1	92	80
5	2	89	20



4

An analogous dependence of diastereoselectivity on the molar equivalence of $TiCl_4$ was found by Helmchen and co-workers in their pioneering studies of the Lewis acid catalyzed Diels-Alder addition of dienes to chiral acrylates derived from ethyl lactate.[4] An X-ray structure determination for a seven-membered chelate complex of the dienophile with $TiCl_4$ provided Helmchen with a rationale for stereocontrol.[5] An analogous six-membered ring chelate complex **4** is proposed to be the reactive intermediate in the observed conjugate additions to **1**.[6]

^1H NMR studies have provided support for a complex of **1** with $TiCl_4$. In CD_2Cl_2, **1** is an 80:20 mixture of amide rotational isomers with H_a appearing as triplets (200 MHz) at 7.04 for the major and 7.02 ppm for the minor isomers. In the presence of 1 equiv of $TiCl_4$ the triplets (80:20) for H_a shift downfield to 8.10 for the minor and 8.30 ppm for the major isomers; another minor broadened resonance appears at 7.9 ppm. There is little shift in the resonances for the methoxy group on the chiral auxiliary indicating that the coordinated $TiCl_4$ is not in close proximity to this part of the molecule. It is noteworthy that with 1 equiv of $TiCl_4$, key resonances are sharp and clearly resolved, but with less than or more than 1 equiv of $TiCl_4$, resonances are broadened and poorly defined. These effects most likely are a result of exchange processes before and after the equivalence point. Perhaps with >1 equiv of $TiCl_4$ a bis-$TiCl_4$ complex is formed,[7] which reacts with a diastereoselectivity different from that of **4**.

It is proposed that the reactive form of complex **4** has the conformation shown in the computer-generated molecular structure (Figure 1). Axial additions at C(3) would occur from the least hindered α-face away from the methylene group of the chiral auxiliary.[8]

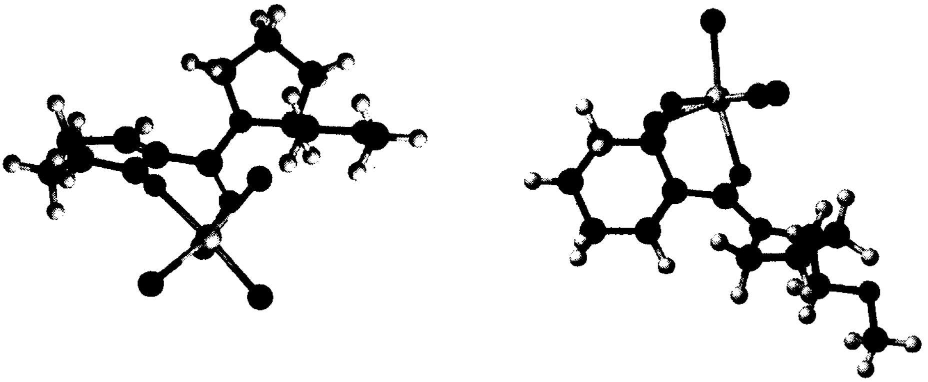
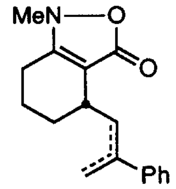


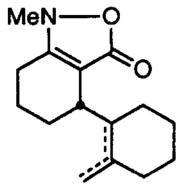
Figure 1. Two views of a computer-generated model of **4**

The sense of stereoselection found for the conversion of **1** to **2** also was observed for additions of 2-phenylallyltrimethylsilane and 1-trimethylsilylmethylcyclohexene to **1**. Tetrahydrobenzisoxazolin-3-one **5** was obtained as a 20:1 mixture of olefin isomers. Flash chromatography of the mixture on silica gel gave the *exo*-olefin (major isomer; 96% ee) and the *endo*-olefin (minor isomer; 96% ee). The 1:2 mixture of olefin isomers corresponding to **6** has not been separated.

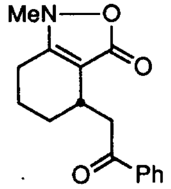
The enol trimethyl silyl ethers of acetophenone and cyclohexanone gave the corresponding ketones **7** and **8**. Absolute configuration of **7** was correlated with that of **5** (the *exo*-olefin isomer) by Wittig reaction of **7** with methylene triphenylphosphorane.[9]



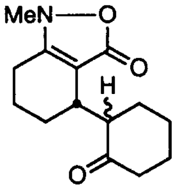
5, 77%; 96% ee



6, 86%



7, 83%; 94% ee



8, 84%; 94% ee

This preliminary characterization of **1** in reactions with allyl silanes and enol silyl ethers suggests that **1** and related chiral 2-substituted-2-cycloalken-1-ones should have substantial utility in asymmetric synthesis. Of particular importance for the asymmetric synthesis of 2,3-disubstituted cyclohexanones is the conversion of **2** to **3a** (66% isolated yield) by lithium in ammonia reduction at -78°C followed by alkylation with methyl iodide (-78°C to -33°C). Reduction-benzylation (benzyl bromide) of **2** gives **3b**.

Acknowledgment. This work was supported by the National Institute of General Medical Science (GM 33061). We thank Dr. Fook S. Tham for the X-ray structure determination (ref. 9), Richard Taylor for molecular modeling experiments, and Professor Günter Helmchen for X-ray coordinates for the structure reported in ref. 4.

References and Notes

1. Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc.* **1991**, *113*, 4926. It should be noted that **1** can be obtained from (2'S)-2-methoxy-1-[[2'-(methoxymethyl)pyrrolidinyl]carbonyl]benzene in 85% yield on a 10-20 g scale by a minor modification of the original experimental procedure: after Birch reduction, enol ether hydrolysis and olefin migration is accomplished with p-toluenesulfonic acid in refluxing benzene solution.
2. For examples of the conjugate additions of O-silylated ketene acetals to a 2-carbomethoxy-2-cyclohexen-1-one derivative, see: Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991**, *32*, 4665.
3. Chiral HPLC analysis was carried out on a Chiracel OD column (isopropyl alcohol and hexane; 1:10) with racemic **3** serving as a reference.
4. Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 112.
5. The geometry of the seven-membered ring chelate structure described in ref. 4 demonstrates that the ester carbonyl groups are partially π-coordinated to the Ti atom.
6. For a related application of an (S)-proline derived chiral auxiliary in Lewis acid catalyzed asymmetric Diels-Alder reactions, see: Waldmann, H. *J. Org. Chem.* **1988**, *53*, 6133.
7. An analogous bis-$TiCl_4$ complex was proposed in ref. 4 to account for decreased diastereoselectivities in the Diels-Alder reaction. X-ray determined atomic coordinates for the dicarbonyl·$TiCl_4$ portion of the published structure (ref. 4) were incorporated into the computer-generated model shown in Figure 1.
8. This argument is in accord with the conformational analysis of the analogous additions of Grignard reagents to **1**, but is now extended to include the role of Lewis acid catalyst (ref. 1). A more extensive discussion is reserved for the full account of this work.
9. The absolute configuration of **8** was deduced by an X-ray diffraction analysis of the major product obtained from conjugate addition to **1**.

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