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Asymmetric Allylsilane Additions to Enantiopure *N*-Acylhydrazones with Dual Activation by Fluoride and $In(OTf)_3$**

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Chiral α-branched amines are common features of biologically active compounds. Direct asymmetric amine synthesis by addition to the C=N bond of carbonyl imino derivatives holds promise for improved access to these substructures by introducing a stereogenic center and a carbon–carbon bond in one step. However, the use of strongly basic organometallic reagents for this purpose[1] can result in competitive metalloenamine formation.[2] Development of alternative milder methods for the construction of C–C bonds is therefore of considerable importance.[3]

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[**] We thank the National Science Foundation (Vermont EPSCoR) and the University of Vermont for generous support.

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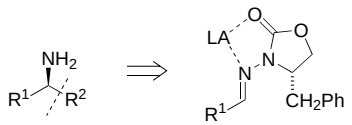
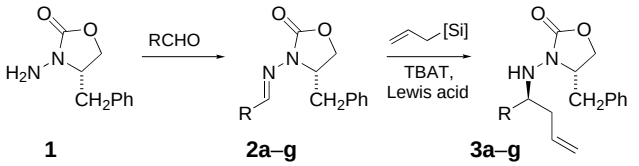
Previously we found that in the presence of Zn^{II} or In^{III} salts, chiral *N*-acylhydrazones (Scheme 1) underwent highly stereoselective radical additions[4] in which Lewis acid activation and restriction of rotamer populations were key design



Scheme 1. Retrosynthetic carbon–carbon bond disconnection of chiral α-branched amines to a Lewis acid activated chiral *N*-acylhydrazone precursor.

elements. We sought to exploit this design further with other reaction types that would broaden the variety of accessible chiral amines. An allyl group is particularly useful for subsequent synthetic manipulations, so extensive efforts have been directed toward the stereoselective allylation of chiral imines, iminium ions, and related C=N electrophiles.[5] We envisioned a novel dual activation protocol in which both the allyl donor and acceptor would be activated in a complementary fashion to promote C–C bond construction under relatively mild conditions. We hypothesized that the fluoride-promoted addition of an allylsilane to *N*-acylhydrazones in the presence of a Lewis acid would achieve this goal with excellent stereocontrol. There are surprisingly few examples of the Sakurai-like fluoride-promoted addition of allylsilanes to C=N bonds,[6] perhaps because of a prevailing perception that allylsilanes are rather unreactive toward imines without the use of strong Lewis acids.[7] We report herein convenient, highly stereoselective additions of allylsilanes to chiral *N*-acylhydrazones at room temperature with dual activation by fluoride and indium(III) trifluoromethanesulfonate.

Our initial studies examined the reaction of allyltrimethylsilane with chiral hydrazone **2a**[4] (Scheme 2). The use of a fluoride ion source required careful consideration of experimental protocols to avoid its potential incompatibility with



1 **2a–g** **3a–g**

Scheme 2. Addition of allylsilanes to enantiopure hydrazones with dual activation by Lewis acid and fluoride ion (**a**: R = Ph; **b**: R = *p*-tolyl; **c**: R = *m*-nitrophenyl; **d**: R = 2-naphthyl; **e**: R = 2-furyl; **f**: R = CH=CHPh; **g**: R = CH_2CH_3; for [Si] see Table 1).

Lewis acids. Eventually, we found that the soluble, air-stable, nonhygroscopic fluoride source tetrabutylammonium triphenyldifluorosilicate (TBAT)[8] could effectively promote allyltrimethylsilane addition to the complex formed by mixing **2a** with a Lewis acid, to provide **3a** [Scheme 2] with good stereoselectivity. The optimal protocol entailed mixing a slight excess of allylsilane with TBAT in CH_2Cl_2 while preparing a mixture of **2a** and a Lewis acid in CH_2Cl_2. After 4 h, these solutions were combined at room temperature, followed by a

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normal workup after completion of the reaction. Indium(III) trifluoromethanesulfonate ($In(OTf)_3$) was chosen from a broad range of Lewis acids screened ($ZnCl_2$, $InCl_3$, $In(OAc)_3$, $TiCl_4$, $SnCl_4$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, TMSOTf, $BF_3 \cdot OEt_2$).

Variations to the substituents on the silicon atom were examined next (Table 1). Although allyltrialkoxysilanes and various allylchlorosilanes were ineffective under these conditions, allyl(diisopropylamino)dimethylsilane led to a significant improvement and provided **3a** in high yield and stereoselectivity. Commercially available tetraallylsilane proved to be a superior allyl donor and gave **3a** in 78% yield with excellent stereocontrol (d.r. > 99:1).

Table 1. Variation of Silicon Substituents in TBAT/$In(OTf)_3$-Promoted Addition of Allylsilanes to Hydrazone **2a** (Scheme 2).

[Si] of allylsilane	Yield of **3a**[a]	d.r.[b]
$SiMe_3$	58%	94:6
$SiPh_3$	n.r.	–
$Si(OMe)_3$	n.r.	–
$SiCl_3$	n.r.	–
$SiMeCl_2$	n.r.	–
$SiMe_2Cl$	n.r.	–
$SiMe_2N(iPr)_2$	81%	95:5
$Si(allyl)_3$	78%	> 99:1

[a] Yields of isolated purified diastereomer mixtures (n.r.: no reaction). [b] Diastereomer ratio determined by means of HPLC (Microsorb-MV C8, 2-PrOH/hexane).

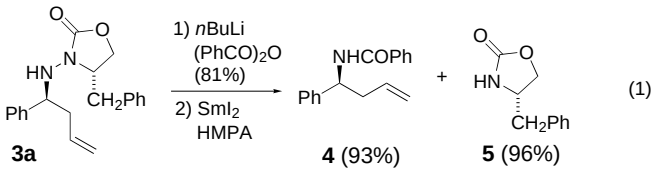
With effective reaction conditions in hand, a brief survey of the scope of the reaction was undertaken by using a series of hydrazones prepared from the corresponding aldehydes (Table 2). Aromatic aldehyde hydrazones **2b–e** generally gave homoallylic amines in good yield with excellent stereoselectivity, and α,β-unsaturated hydrazone (*E*)-**2f** underwent chemoselective addition to the C=N bond. Although propionaldehyde hydrazone **2g**[4] also participated in the reaction, the stereoselectivity was modest.

Table 2. Preparation of Various Aldehyde Hydrazones **2** and TBAT/$In(OTf)_3$-Promoted Addition of Tetraallylsilane (Scheme 2).

Hydrazone	Yield[a]	Allyl adduct	Yield[b]	d.r.[c]
2b	94%	**3b**	94%	98:2
2c	91%	**3c**	71%	> 99:1
2d	92%	**3d**	82%	98:2
2e	92%	**3e**	58%	96:4
(*E*)-**2f**	97%	**3f**	60%	95:5
2g	92%	**3g**	51%	82:18

[a] Yield of isolated hydrazone. [b] Yields of isolated purified diastereomer mixtures. [c] Diastereomer ratio determined by means of HPLC.

To determine the stereochemistry, the auxiliary was removed reductively from the *N*-benzoyl derivative of **3a** to give benzamide **4** [Eq. (1)], which was shown by means of optical rotation to have the *S* configuration.[9] Saturation of the allyl group of **3g** (H_2, Pd/C) gave a known derivative of (*R*)-3-aminohexane.[10] For insight into the mechanism, control experiments were conducted with **2a**:



3a **4** (93%) **5** (96%) (1)

1) Reaction in the absence of $In(OTf)_3$: 15% yield, d.r. 67:33.
2) Reaction without TBAT: 30% yield, d.r. 94:6.
3) Neither $In(OTf)_3$ nor TBAT: no reaction.
4) Additional $In(OTf)_3$ in the TBAT/allylsilane mixture prior to mixing with the $In(OTf)_3$–hydrazone complex: 66% yield, d.r. > 99:1.
5) However, after > 12 h, the mixture of $In(OTf)_3$, TBAT, and allylsilane behaves differently: 22% yield, dr 95:5.

Accordingly, ^1H NMR spectroscopy experiments (500 MHz, CD_2Cl_2, 27 °C) showed that tetraallylsilane is essentially unchanged after 4 h in the presence of TBAT, and when $In(OTf)_3$ is added, consumption of the tetraallylsilane requires at least a further 14 h. Transmetallation to an allylindium species therefore appears to be slow, and hence the reaction of a hypervalent silicate with the Lewis acid complexed hydrazone seems more likely.[11] Furthermore, the variation in the reactivity and selectivity upon changing the silicon ligands suggests the presence of silicon in the transition state of the addition. The improved yield and selectivity with tetraallylsilane over allyltrimethylsilane may be attributed to a more electrophilic silicon atom, which leads to greater fluoride ion affinity, increased hypervalent silicate population, and a later transition state.[12] Stereochemical results are consistent with the chelate structure in Scheme 1, in which restriction of rotamer populations facilitates steric blocking of the *Re* face.

In summary, highly stereoselective allylsilane addition to enantiopure *N*-acylhydrazones occurs in the presence of easily handled, air-stable TBAT and $In(OTf)_3$, which appear to induce complementary dual activation of both reactants. To our knowledge, these are the first examples of useful auxiliary acyclic stereocontrol in allylsilane addition to stable, isolable imino derivatives. Considering the ubiquity of chiral amines and the synthetic versatility of the allyl group, applications to complex targets may be envisioned.

Experimental Section

Allyl addition: A solution of allylsilane (3 equiv) and TBAT (3 equiv) in CH_2Cl_2 (0.75 M), and a solution of $In(OTf)_3$ (1.3 equiv) and hydrazone **2a** in CH_2Cl_2 (0.1 M) were prepared separately. After 4 h at approximately 25 °C, the allylsilane/TBAT mixture was transferred by syringe to the hydrazone/$In(OTf)_3$ mixture. After 2 d at approximately 25 °C, the reaction mixture was washed with water, dried ($MgSO_4$), concentrated, and purified by flash chromatography.

Hydrazone formation: Aldehyde (0.4 mmol), **1** (0.25 mmol), $MgSO_4$ (200 mg), *p*-toluenesulfonic acid (catalytic amount) were heated in toluene (10 mL) at reflux for 10 min.

Received: August 1, 2001 [Z17653]

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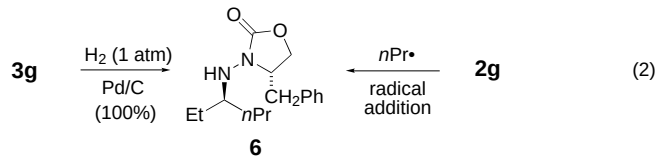

(2)

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Molecular Insight Into Surface Organometallic Chemistry Through the Combined Use of 2D HETCOR Solid-State NMR Spectroscopy and Silsesquioxane Analogues**

Mathieu Chabanas, Elsje Alessandra Quadrelli, Bernard Fenet, Christophe Copéret,* Jean Thivolle-Cazat, Jean-Marie Basset,* Anne Lesage, and Lyndon Emsley*

The structural characterization of heterogeneous catalysts remains difficult. In the late eighties, Feher and later others showed that polyhedral oligomeric silsesquioxanes (POSS) can be used to model the surface structure of partially dehydroxylated silica and therefore infer information about the coordination sphere of metal complexes directly supported on oxides such as silica.[1] This approach can also provide mechanistic insights on surface chemistry processes. However, no direct comparison between these models and their related surface complexes has been reported.

We have recently shown that the reaction of tris(neopentyl)neopentylidene tantalum, $[Ta(=CH\textit{t}Bu)(CH_2\textit{t}Bu)_3]$ (**1**) with $SiO_{2\text{-}(500)}$ gives a mixture of mono-$[\equiv SiO\text{-}Ta(=CH\textit{t}Bu)(CH_2\textit{t}Bu)_2]$ and bisgrafted surface complexes $[(\equiv SiO)_2Ta(=CH\textit{t}Bu)(CH_2\textit{t}Bu)]$,[2a] while its reaction with a $SiO_{2\text{-}(700)}$ provides the monografted species $[\equiv SiO\text{-}Ta(=CH\textit{t}Bu)(CH_2\textit{t}Bu)_2]$ ($\mathbf{2_s}$) as the sole surface species. The characterization was based on elemental analysis, the evolution of neopentane during grafting of **1**, and solvolysis of $\mathbf{2_s}$ as well as infrared (IR) spectroscopy.[2b]

We report here the use of high-resolution solid-state one-dimensional (1D) and two-dimensional (2D) NMR spectroscopy to study $\mathbf{2_s}$ and the use of high-resolution solution-state 1D and 2D NMR spectroscopy of its molecular analogue $[(c\text{-}C_5H_9)_7Si_7O_{12}Si{-}O{-}Ta(=CH\textit{t}Bu)(CH_2\textit{t}Bu)_2]$ ($\mathbf{2_m}$) to define the structure of $\mathbf{2_s}$ at a molecular level and to investigate the reaction pathway leading to the grafted species.

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[**] We are also indebted to the CNRS, ENS Lyon, and ESCPE Lyon for financial support. M.C. is grateful to the French ministry of education, research, and technology (MENRT) for a pre-doctoral fellowship. E.A.Q. gratefully acknowledges Università di Pisa and S.N.A.M. for financial support. 2D HETCOR = two-dimensional heteronuclear correlation.

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