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# Asymmetric, *anti*-Selective Scandium-Catalyzed Sakurai Additions to Glyoxyamide. Applications to the Syntheses of *N*-Boc D-Alloisoleucine and D-Isoleucine

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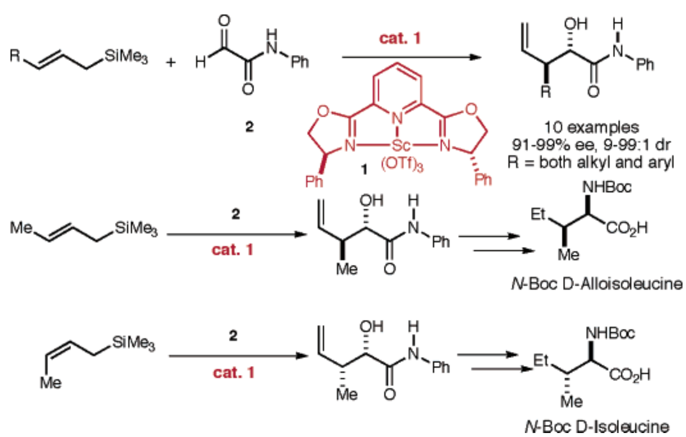
**ABSTRACT**




**An enantio- and diastereoselective Sakurai–Hosomi reaction, catalyzed by chiral scandium pyridyl-bis(oxazoline) (pybox) complexes, has been developed. Both alkyl- and aryl-substituted allylsilanes are effective coupling partners with *N*-phenylglyoxamide. Applications of this reaction to the asymmetric syntheses of *N*-Boc D-alloisoleucine and D-isoleucine are described.**

In this communication we report our results on the use of the chiral scandium complex **1** as an effective catalyst for the enantioselective Sakurai–Hosomi[1] addition of terminally substituted allylsilanes to *N*-phenylglyoxamide (**2**). This reaction furnishes "ene-type" products with *anti* diastereoselection and is therefore complementary to our recently reported *syn*-selective, scandium-catalyzed glyoxamide-ene reactions.[2] These crystalline enantiopure adducts are versatile chiral building blocks for *β*-substituted α-hydroxy and α-amino acids.

The synthesis of homoallylic alcohols through the nucleophilic allylation of aldehydes and ketones continues to be a powerful transformation.[3] The first catalytic enantioselective variant using a chiral (acyloxy)borane (CAB) complex was reported by Yamamoto.[4] Subsequently, Keck and others have reported the use of various Lewis acidic metals and BINOL/BINAP-based chiral ligands in promoting asymmetric allylations.[5] The corresponding Lewis base catalyzed reactions have also been reported by Denmark and others.[6]

(1) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295.
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(3) For general reviews on diastereoselective allylation/crotylation reactions, see: Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763 and references therein.
(4) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561.

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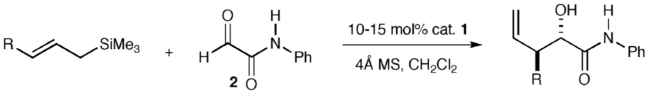
Optimization studies using (*E*)-crotyltrimethylsilane demonstrated that reactions carried out at −20 °C with 10 mol % catalyst afforded good enantioselection (95% ee) and *anti* diastereoselection (26:1) (Table 1, entry 1). Under these conditions, allylation of unbranched (*E*) alkyl-substituted silanes afforded the expected products in good yields and excellent enantio- and diastereoselectivities (entries 3 and 4). (*Z*)-Crotyltrimethylsilane was also evaluated under the same conditions, affording the *syn* product with excellent enantioselectivity (94%) and moderate *syn* diastereoselectivity (4:1) (entry 2). The complementary stereoselectivity of (*E*) and (*Z*) geometrical isomers displayed in entries 1 and 2 is noteworthy because the Lewis acid promoted Sakurai−Hosomi reaction, which proceeds via an open transition state, is known to be stereoconvergent with respect to olefin geometry.[3,6b] Our qualitative observations indicate that the pybox ligand architecture seems to impart significant levels of diastereocontrol to these addition reactions.

**Table 1.** Scope of Sc(III)-Catalyzed Sakurai−Hosomi Additions

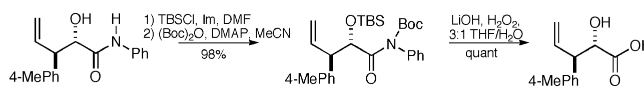



| entry[a] | R[b] | cat. loading | *T* (°C) | % ee[c] | *anti*/*syn* | % yield[g] | mp (°C) |
|---|---|---|---|---|---|---|---|
| 1 | Me | 10 mol % | −20 | 95 | 26:1[e] | 89 | 104 |
| 2 | (*Z*)-Me | 10 mol % | −20 | 94 | 1:4[f] | 76 | 90 |
| 3 | Et | 10 mol % | −20 | 91 | 32:1 | 76 | 50 |
| 4 | *n*-Pr | 10 mol % | −20 | 93[d] | 29:1 | 71 | 59 |
| 5 | Ph | 15 mol % | rt | 99[d] | 99:1[e] | 67 | 127 |
| 6 | 4-Me-Ph | 15 mol % | rt | 99 | 99:1 | 75 | 146 |
| 7 | 4-MeO−Ph | 15 mol % | rt | 97 | 99:1[e] | 64 | 135 |
| 8 | 4-F−Ph | 15 mol % | rt | 99 | 99:1 | 73 | 151 |
| 9 | 2-Me-Ph | 15 mol % | rt | 99 | 9:1[e] | 64 | 89 |
| 10 | *β*-Nap | 15 mol % | rt | 97 | 99:1 | 89 | 160 |

[a] All reactions were run overnight at the indicated temperatures. [b] 8.5 equiv of allylsilane was used; however, the unreacted portion could be recovered and reused without loss of selectivity. [c] Enantiomeric excesses were determined by HPLC using Chiracel OD-H, AD-H, or Whelk-(*S*) columns. [d] Absolute stereochemistry was determined by Mosher's ester analysis. Remaining product configurations were assigned by analogy. [e] *anti* stereochemistry confirmed by X-ray analysis. [f] *syn* stereochemistry confirmed by X-ray analysis. [g] Isolated yields.

The preliminary investigations into the reactivity of aryl-substituted allylsilanes revealed that higher temperatures (room temperature) and catalyst loadings are required. Under these conditions, aryl-substituted allylsilanes are generally observed to be more selective than their alkyl-substituted counterparts.[7] Importantly, substrates containing either electron-withdrawing or electron-donating substituents in the *para* position are effective coupling partners (entries 7 and 8). Nucleophiles with substituents in the *ortho* position as well as *β*-naphthylallylsilane are also tolerated (entries 9 and 10). An added benefit of using *N*-phenylglyoxamide (**2**) as an electrophile is that all of the desired products are routinely isolated as crystalline solids with well-defined melting points (Table 1). In addition, we were able to show that the *N*-phenylamide functionality can be conveniently converted into its carboxylic acid derivative in high yield. TBS protection of the alcohol followed by *N*-Boc activation of the amide and subsequent hydrolysis[8] afforded the expected carboxylic acid in 98% yield over three steps (Scheme 1).

**Scheme 1.** *N*-Phenylamide Hydrolysis




We anticipated that this enantioselective addition reaction could serve as a stereodivergent route to *β*-substituted α-amino acids. Because of its medicinal importance, D-alloisoleucine was identified as a relevant synthesis target. This amino acid is of interest due to its presence in biologically important depsipeptides.[9] and has been used as a chiral precursor for syntheses of isostatins,[10] oxytocin analogues,[11] and other natural cytotoxic depsipeptides.[9,12] As a consequence, a number of syntheses of this molecule have been reported.[13] In the following discussion, we report the Lewis acid mediated catalytic enantio- and diastereoselective route to D-alloisoleucine as well as its C(3)-epimer, the common amino acid D-isoleucine. The enantioselective step in each case involves the Sc-catalyzed allylation using (*E*)- and (*Z*)-crotyltrimethylsilanes, **3** and **9**, respectively (Schemes 2 and 3).

The conversion of the C(2)-hydroxy group in **4** to the required C(2)-amino functionality was accomplished in a

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(7) During these studies, we developed efficient routes for the synthesis of *γ*-alkyl- and *γ*-aryl-substituted allylsilanes. See Supporting Information.

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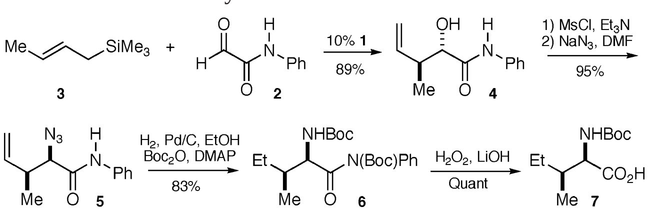
two-step procedure. Adduct **4** was subjected to 2.0 equiv of $MeSO_2Cl$ and $Et_3N$ ($CH_2Cl_2$, rt, 36 h) to afford the derived α-mesyloxyamide in high yield. The unpurified intermediate was treated with 1.1 equiv of $NaN_3$ in (DMF, 70 °C, 48 h), yielding the α-azido amide **5** without the need for flash chromatography in 95% yield over the two steps, with complete inversion of configuration at C(2). It is noteworthy that either raising the reaction temperature or increasing the amount of $NaN_3$ in an attempt to achieve a faster reaction rate led to product epimerization.

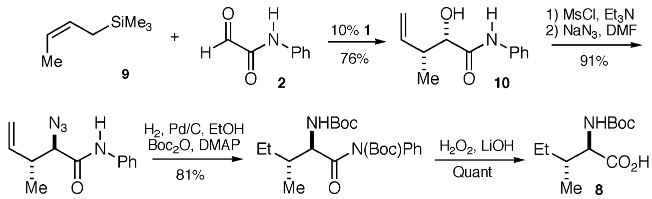
Catalytic hydrogenation of unpurified **5** ($H_2$ 1 atm, Pd/C, EtOH, rt, 5 h) effected hydrogenation of both the azide and the olefinic moieties, affording the corresponding saturated C(2)-primary amine, which was subsequently treated with 5 equiv of $Boc_2O$ and 2 equiv of DMAP[14] in an optimized solvent mixture of 1:9 $CH_2Cl_2$/MeCN (rt, 1 h) to furnish the product of mono-Boc protection of the primary amine, with consequential Boc protection of the *N*-phenylamide, bis-Boc-protected **6**. Peroxide-mediated hydrolysis[8] of **6** provided *N*-Boc D-alloisoleucine **7** in quantitative yield (Scheme 2) with an overall yield of 70%.

**Scheme 2.** Synthesis of *N*-Boc D-Alloisoleucine




Synthesis of C(3)-epimeric enantioenriched *N*-Boc D-isoleucine **8** was undertaken starting from the common precursor glyoxamide **2** using the alternative nucleophile (*Z*)-crotyltrimethylsilane **9**. Analogous transformations as previously described subsequently furnished enantio- and diastereopure *N*-Boc D-isoleucine **8** in 60% overall yield (Scheme 3).

**Scheme 3.** Synthesis of *N*-Boc D-Isoleucine




In summary, we have developed an asymmetric, *anti*-selective Sakurai−Hosomi reaction promoted by [Sc(S,S)-Phpybox]$(OTf)_3$ complex **1**. Good generality was demonstrated as both aliphatic and aromatic allylsilanes are effective nucleophiles in additions to the glyoxamide **2**. This reaction was applied to the straightforward enantioselective syntheses of *N*-Boc D-alloisoleucine **7** and D-isoleucine **8** from a common starting material, glyoxamide **2**. Within the syntheses delineated above, all except two of the intermediates are highly crystalline solids, making both routes applicable to large-scale preparations.

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**Supporting Information Available:** Experimental procedures, characterization data, and NMR spectra for all new compounds and for the syntheses of **7** and **8**. Crystallographic data and structures (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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