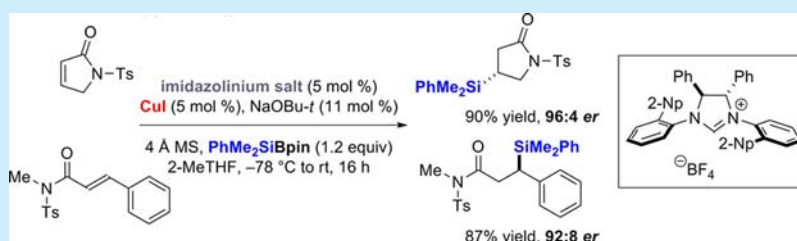


Cu(I)–NHC Catalyzed Asymmetric Silyl Transfer to Unsaturated Lactams and Amides

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Supporting Information

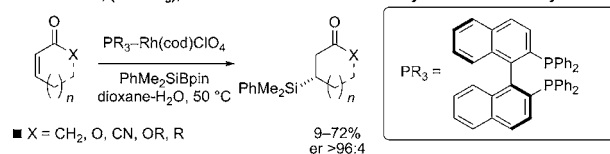


ABSTRACT: The first asymmetric silylation of unsaturated lactams and amides using Cu(I)–NHC catalysts and PhMe₂SiBpin has been accomplished. The method has been exploited in an expedient asymmetric synthesis of the (*R*)-enantiomer of the nootropic drug oxiracetam.

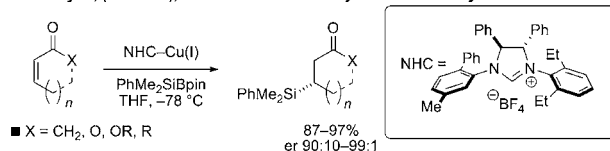
Silicon directly connected to an asymmetric carbon atom is a versatile functional group in organic synthesis.¹ Since the pioneering studies by Fleming and Tamao, the motif is widely used as a stereodefined placeholder for the hydroxyl group.² α -Chiral silanes are also valuable substrates in C–C bond-forming reactions.³ These applications have stimulated studies into the installation of the silicon group in an enantioselective fashion. Inspired by Fleming's conjugate addition of silylcuprates,^{2a–c,g,4} Hayashi's seminal Pd-catalyzed 1,4-disilylation of enones represented a breakthrough although the procedure has clear limitations in scope.⁵ A major development in the field was achieved by Oestreich who exploited the activation of the Si–B bond in Sugimoto's PhMe₂SiBpin reagent⁶ by Rh(I)-phosphine catalysts in efficient asymmetric silyl transfer to cyclic and acyclic α,β -unsaturated ketones, esters, imides, and lactones⁷ (Scheme 1A). In a further major advance, Hoveyda recently reported Cu(I)–NHC (*N*-heterocyclic carbene)⁸ catalyzed activation of the Si–B bond in PhMe₂SiBpin in asymmetric silyl transfer to cyclic and acyclic α,β -unsaturated ketones with single examples of additions to an acrylonitrile, acyclic ester, and lactone (Scheme 1B).⁹

Hoveyda found that NHC ligands derived from C₁-symmetric imidazolium salts gave the best results.^{9a} We have since studied the asymmetric silyl transfer to unsaturated lactones, which are challenging substrates for these transformations, using Hoveyda's protocol and a C₂-symmetric NHC ligand.^{10,11} Furthermore, we reported the kinetic resolution of racemic 5-substituted butenolides mediated by Cu(I)–NHC silyl transfer from PhMe₂SiBpin (Scheme 1C).^{11,12}

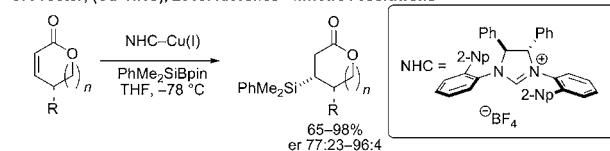
The importance of aza-heterocyclic motifs in natural products and biologically active compounds led us to consider whether an analogous Cu(I)–NHC-catalyzed asymmetric silyl transfer could be applied for the first time to α,β -unsaturated lactams. As highlighted recently by Alexakis, such substrates are

Scheme 1. Asymmetric Silyl Transfer from PhMe₂SiBpin to α,β -Unsaturated Carbonyls: (A) Rh-Catalyzed Transfer, (B) Cu-Catalyzed Transfer, (C) Cu-Catalyzed Transfer to Lactones, and (D) This WorkA. Oestreich, (Rh–PR₃), 2006: ketones • lactones • *Z*-acyclic imides • *Z*-acyclic esters

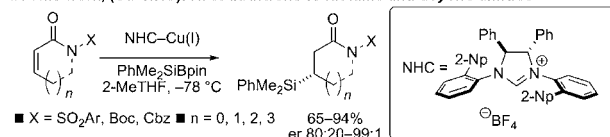
B. Hoveyda, (Cu–NHC), 2010: ketones • an acrylonitrile • an acyclic ester • a lactone



C. Procter, (Cu–NHC), 2013: lactones • kinetic resolutions



D. This work, (Cu–NHC): first additions to lactams and acyclic amides



problematic Michael acceptors and present a significant challenge for the development of new methods.¹³ In fact, the

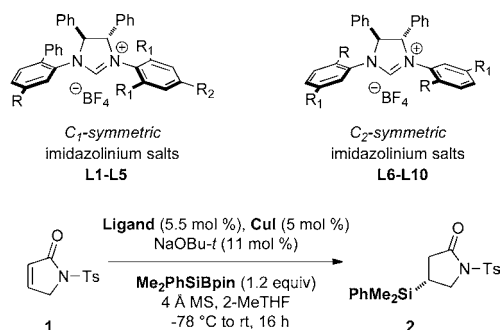
Received: November 20, 2013

Published: December 18, 2013

nonasymmetric silylcuprate addition to lactams remains essentially unexplored.¹⁴ Analogous additions of silicon nucleophiles to acyclic amides are known, but asymmetric variants rely on chiral auxiliary control^{15,16} and the development of a catalytic asymmetric variant represents a significant challenge. Here we report our investigations on the Cu(I)–NHC-catalyzed silyl asymmetric transfer to α,β -unsaturated lactams and amides (Scheme 1D). The method has been used in the catalytic asymmetric synthesis of the (*R*)-enantiomer of the nootropic drug oxiracetam.

We selected pyrrolidinone **1** bearing an electron-withdrawing protecting group on nitrogen as our model substrate. The use of *C*₁-symmetric imidazolium salt **L1**, a salt that has previously been employed successfully in conjugate silyl transfer to carbocyclic substrates (Table 1, entry 1),^{9a} gave low enantiocontrol.

Table 1. Screening of NHC–Cu(I) Complexes in Silyl Transfer to Lactam **1 (conv 89–99% by ¹H NMR)**



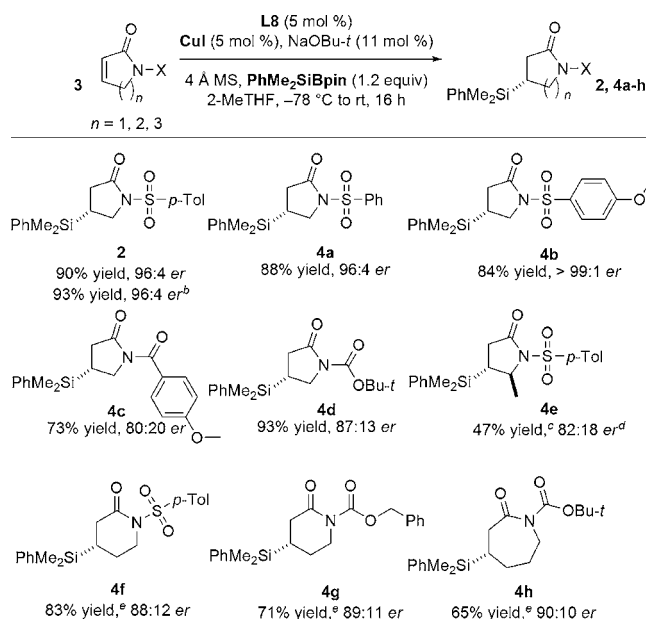
entry	ligand	type	R	R ₁	R ₂	er
1	L1	<i>C</i> ₁	Me	Et	H	62:38
2	L2	<i>C</i> ₁	H	Et	H	64:36
3	L3	<i>C</i> ₁	<i>i</i> -Pr	Et	H	54:46
4	L4	<i>C</i> ₁	H	Me	Me	69:31
5	L5	<i>C</i> ₁	Me	Me	Me	65:35
6	L6	<i>C</i> ₂	H	Ph	—	93:7
7	L7	<i>C</i> ₂	Me	Ph	—	83:17
8	L8	<i>C</i> ₂	2-naphthyl	H	—	96:4 ^a
9	L9	<i>C</i> ₂	2-naphthyl	<i>i</i> -Pr	—	58:42
10	L10	<i>C</i> ₂	2-anthryl	H	—	94:6
11	L8	<i>C</i> ₂	2-naphthyl	H	—	93:7 ^b

^a90% Isolated yield. ^bTHF was used as the solvent.

Modification of the aryl substituents on nitrogen in a series of *C*₁-symmetric imidazolium salts did not increase the enantioinduction (Table 1, entries 2–5). A significant improvement was achieved upon switching from *C*₁-symmetric to *C*₂-symmetric ligands (entries 6–11). Pleasingly, the use of imidazolium salt **L8**, which provided the best results for 5-membered lactone substrates,^{10,11} proved to be optimal for asymmetric silyl transfer to pyrrolidinone **1**, and **2** was formed in 90% yield and with an *er* of 96:4. In the study, 2-MeTHF was used as an attractive alternative to THF,¹⁷ although the use of THF gave very similar yields and selectivity (Table 1, entry 8 vs 11). Attractively, the experimental protocol does not require the use of a glovebox.

With optimized conditions in hand, we next studied the scope of the reaction (Scheme 2). Five-membered lactam substrates bearing an arylsulfonyl substituent on nitrogen underwent efficient asymmetric silyl transfer to give β-silyl adducts **2**, **4a**, and **4b** in high yield and with an *er* up to >99:1. Importantly, the catalytic asymmetric silyl transfer could be scaled up and was

Scheme 2. Cu(I)–NHC Catalyzed Asymmetric Silyl Transfer to 5-, 6-, and 7-Membered Unsaturated Lactams^a



^aYields are for isolated products. ^bReaction run on a 5.0 mmol scale. ^c0.70 equiv of Me₂PhSiBpin used. ^dSelectivity factor, *s* = 9. ^e**L1** was used in place of **L8**.

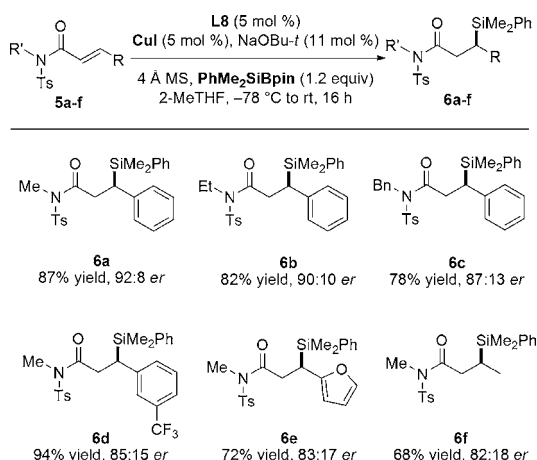
performed without loss of efficiency on a 5.0 mmol scale (formation of **2** from **1**). Increasing the steric demand of the arylsulfonyl substituent led to a decrease in yields and the level of enantiocontrol.¹⁸ Substrates bearing *p*-methoxybenzoyl and *tert*-butoxycarbonyl groups on nitrogen underwent high yielding silyl transfer although enantioselectivities were lower (<87:13 *er*) (**4c** and **4d**). In line with our observations on Cu–NHC catalyzed silyl transfer to racemic lactone substrates,¹¹ the kinetic resolution of racemic lactams was also possible: **4e** was obtained in 47% yield (maximum 50%) and 82:18 *er*. (The added steric congestion caused by the methyl substituent in the 5-position of the pyrrolidinone unit causes a drop in enantioselectivity.) When a substrate bearing a less activating phenyl substituent on nitrogen was investigated, a dramatic decrease in conversion and enantioselectivity was observed.¹⁹ Importantly, imidazolium salt **L8** gave the best yields and selectivities for all of the 5-membered lactam substrates studied (cf. Table 1).

In contrast, for 6-membered lactam substrates, Hoveyda's *C*₁-symmetric imidazolium salt **L1**^{9a} gave the best results: asymmetric silyl transfer gave *N*-tosylpiperid-2-one **4f** and *N*-Cbz-piperid-2-one **4g** in good yields and with selectivities up to 89:11 *er*. A similar observation was made in the preparation of *N*-Boc-caprolactam **4h** (65% yield, 90:10 *er*) using imidazolium salt **L1**. These results clearly show that the ring size and the identity of the activating nitrogen substituent in lactam substrates are crucial when selecting the ligand for the asymmetric silyl transfer.

We next extended the protocol to linear *N*-tosyl α,β -unsaturated amides.²⁰ Pleasingly, employing imidazolium salt **L8** gave efficient silyl transfer, and good levels of enantioinduction were observed (up to 92:8 *er*) (Scheme 3). The process was found to be compatible with substrates bearing β -aryl, heteroaryl, and alkyl substituents on the electron-deficient alkene.²¹

The synthetic value of the protocol was showcased in an expedient asymmetric synthesis of the (*R*)-enantiomer of

Scheme 3. Cu(I)–NHC Catalyzed Asymmetric Silyl Transfer to *N*-Tosyl α,β -Unsaturated Amides^a

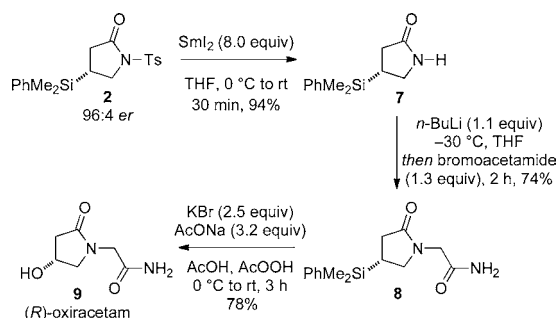


^aYields are for isolated products.

oxiracetam, a nootropic drug employed in the treatment of diseases related to Alzheimer's.²²

Thus, lactam **2**, the product of Cu(I)–NHC asymmetric silyl transfer, underwent efficient removal of the *N*-tosyl group upon treatment with SmI_2 (Scheme 4).²³ The resulting N-H lactam **7**

Scheme 4. Asymmetric Synthesis of (R)-Oxiracetam



underwent *N*-alkylation to give **8** in 74% yield. Subsequent oxidation under Fleming–Tamao conditions²⁴ gave (R)-oxiracetam ($\alpha_{\text{D}} = +34.2$ ($c = 1.0$, H_2O); lit. $+36.4$ ($c = 1.0$, H_2O))²² in 78% yield (Scheme 4).

In summary, the first Cu(I)–NHC catalyzed asymmetric silyl transfer from $\text{PhMe}_2\text{SiBpin}$ to unsaturated lactams and amides gives the corresponding β -silylated lactams and amides in good yields and enantioselectivities. While C_2 -symmetric NHC ligands give the best results for 5-membered lactams and acyclic amides, C_1 -symmetric NHC ligands work best for 6- and 7-membered lactam substrates. The protocol has been exploited in a short asymmetric synthesis of (R)-oxiracetam.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^1H and ^{13}C spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank The Leverhulme Trust (V.P.) and the EPSRC (J.P.R.) for funding and Robyn Bullough (University of Manchester) for assistance optimizing the conversion of **1**–**2**.

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