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STEREOSPECIFIC SYNTHESIS OF *N*-ACYL-(*E*)-VINYL-, DIENYL-, AND ENYNYLSULFOXIMINES

Robert S. Paley*[1] and Stephanie R. Snow

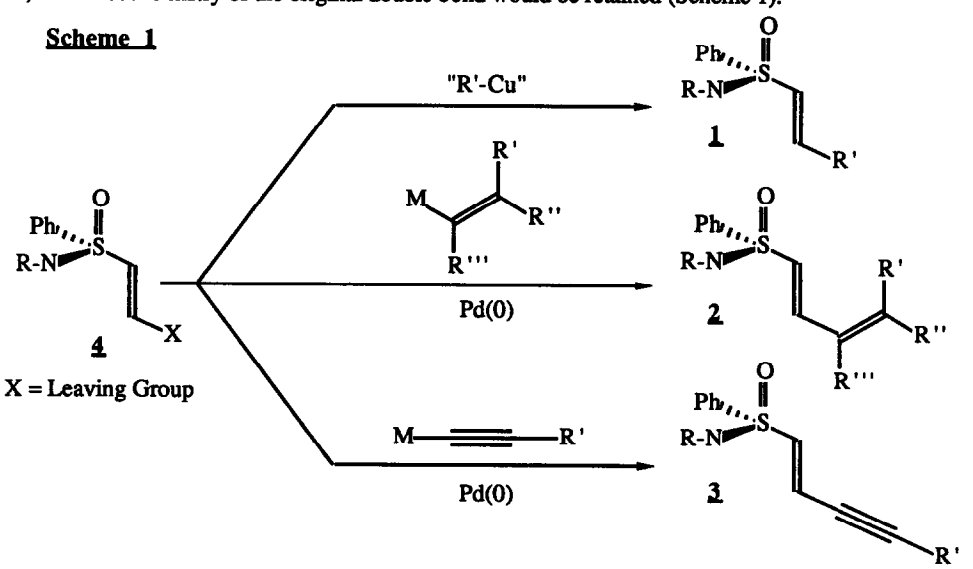
Swarthmore College, Dept. of Chemistry, Swarthmore, PA 19081

Summary: A β-tosylvinylsulfoximine, **5**, was used as the common starting point for the preparation of the title compounds. Treatment of **5** with "higher-order cuprates" or trialkylalanes (with a Pd(II) catalyst) afforded *N*-TBDMS-(*E*)-vinylsulfoximines, whereas dienylsulfoximines and enynylsulfoximines were obtained by treatment with divinylalanes and alkynylalanes in a Pd(0)-catalyzed process. The *N*-pivaloyl derivative of each sulfoximine was readily prepared.

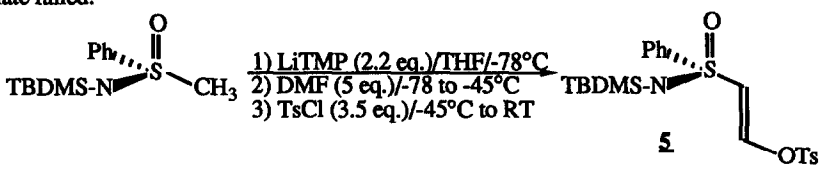
While utilization of vinylsulfoximines in a synthetic manner has been reported[2], if in a limited context, their *N*-acylated derivatives have yet to find any significant application. In light of our current interest in the development of the chemistry of optically pure *N*-acyl unsaturated sulfoximines in Lewis-acid catalyzed Diels-Alder processes and transition-metal mediated cycloaddition reactions, we required a general and flexible entry into systems of this type.

Though (*E*)-vinylsulfoximines (**1**) are available[3] via addition of α-lithiosulfoximines to aldehydes, followed by dehydration, the application of such methodology towards the preparation of dienyl- and enynylsulfoximines (**2**, **3**) seemed to be an unlikely prospect. To circumvent this potential difficulty, we decided to approach the synthetic problem in a different manner. It was our expectation to be able to effect carbon-carbon bond formation at the β-position of a vinylsulfoximine (**4**) by employing one or more of the recent advances in palladium(0)-catalyzed coupling reactions of alkenyl- and alkynylmetals.[4] Additionally, synthesis of (*E*)-vinylsulfoximines would be available, from the same starting material, by treatment with organocopper reagents[5]. In all cases, the stereochemistry of the original double bond would be retained (Scheme 1).

Scheme 1



To bring this strategy to fruition, racemic *N*-TBDMS-β-tosyl-(*E*)-vinylsulfoximine **5** was synthesized in a one-pot transformation from the corresponding *N*-silyl-*S*-methylsulfoximine[6,7] by deprotonation, addition of DMF, and trapping of the resulting enolate with tosyl chloride. The procedure afforded the β-tosylvinylsulfoximine as a white solid in 60 to 65% yield after column chromatography.[8,9] All efforts to prepare the enol triflate failed.[10]

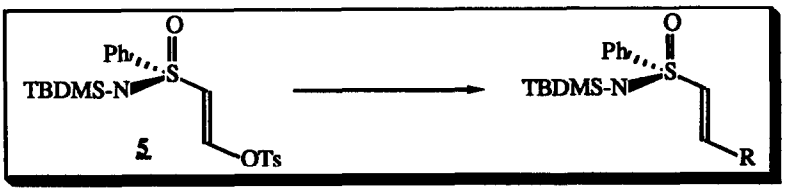


Initial attempts to cleanly transform β-tosylvinylsulfoximine **5** into vinylsulfoximines (**1**) were not successful. Treatment of **5** with the Gilman cuprate Bu_2CuLi furnished in low yield the desired product (**1c**, R=Bu) which was contaminated by an inseparable reduction product (R=H). However, treatment of **5** with the "higher-order" cuprate $Bu_2CuCNLi_2$ (1.2 eq.; -40°C; Et_2O/THF, 2:1) cleanly and rapidly afforded **1c** in high yield (74%) following chromatographic purification. Examination of the vinylic region of a 200 MHz ^1H NMR spectrum of the crude reaction material revealed that the product was stereochemically homogeneous; the (*E*)-vinylsulfoximine had been produced exclusively (J_{trans} = 14.7 Hz). This transformation, and its stereochemical outcome, was shown to be general for several other "higher-order" cuprates[11]; the results and reaction conditions are displayed below (See table).

An improved method for the preparation of the methyl analog (**1a**, R=Me), based on established Pd(0)-catalyzed cross-coupling reactions with alanes[12], was developed shortly thereafter. Treatment of **5** with $AlMe_3$ (1.1 eq.) and $Pd(PPh_3)_2Cl_2$ (5 mol %) in benzene produced (*E*)-vinylsulfoximine **1a** (R=Me) in excellent yield (87 %). The success of this reaction could not, however, be extended to the preparation of other alkyl analogs. For example, treatment of **5** with $AlEt_3$, under identical conditions, produced a *ca.* 1:1 inseparable mixture of the desired ethyl analog **1b** (R=Et) and the reduction product (R=H). Furthermore, the conversion was incomplete (as judged by TLC) after 48 hrs.

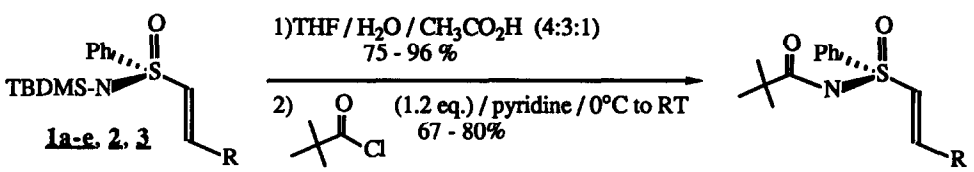
Encouraged by the successful application of this palladium-catalyzed alane coupling methodology to the synthesis of vinylsulfoximine **1a**, we sought to determine if alkenyl and alkynyl groups could also be transferred to β-tosylvinylsulfoximine **5**. It was gratifying to discover that when **5** was treated with divinylethylalane[13] (1.5 equiv.; benzene/toluene, 1:1; 50°C; 45 min.) and $Pd(PPh_3)_4$ (10 mol %), dienylsulfoximine **2** was produced in 85% yield. Once again, ^1H NMR of the crude reaction material had indicated that the product was stereochemically pure. This procedure was a significant improvement, in terms of isolated yield and ease of chromatographic purification, over the transformation which employed a "higher order" vinyl cuprate.[14] To demonstrate that alkynyl groups could be transferred, enynylsulfoximine **3** was prepared in an analogous manner by treatment of **5** with 1-hexynyldimethylalane.[15] Enynylsulfoximines of this type should be useful precursors to dienylsulfoximines via triple bond reduction.

To complete the synthesis of the target *N*-acyl unsaturated sulfoximines, each of the *N*-TBDMS-sulfoximines described (**1a-e**, **2**, **3**) were efficiently desilylated and subsequently acylated with pivaloyl chloride, as shown below.



Product	Reagents and Conditions	% Yield
R = Me **1a**	$Me_2CuCNLi_2$ (1.5 eq.) / Et_2O / 0°C / 10 min.	53
	$AlMe_3$ (1.1 eq.), $Pd(PPh_3)_2Cl_2$ (0.05 eq.) PhH / RT / 16 hrs.	87
Et **1b**	$Et_2CuCN(MgBr)_2$ (1.5 eq.) / Et_2O:THF (2:1) -40° to 0°C / 1hr.	60
n-Bu **1c**	*n*-$Bu_2CuCNLi_2$ (1.2 eq.) / Et_2O -40° to 0°C / 1 hr.	74
i-Pr **1d**	*i*-$Pr_2CuCN(MgCl)_2$ (1.5 eq.) / Et_2O:THF (2:1) -25° to -10°C / 20 min.	50
Ph **1e**	$Ph_2CuCNLi_2$ (2.5 eq.) / Et_2O:THF (5:1) -40° to -30°C / 15 min.	60
$CH{=}CH_2$ **2**	$(\text{vinyl})_2CuCN(MgBr)_2$ (1.2 eq.) / Et_2O -40° to -10°C / 1 hr.	35
	$(\text{vinyl})_2AlEt$ (1.5 eq.) / $Pd(PPh_3)_4$ (0.1 eq.) PhH:$PhCH_3$ (1:1) / 50°C / 45 min.	85
C≡C-Bu **3**	Me_2Al-C≡C-Bu (3.0 eq.) / $Pd(PPh_3)_4$ (0.1 eq.) pentane:PhH:$PhCH_3$ (1:1:1) / 50°C / 15 min.	52

To conclude, a number of stereochemically pure *N*-acyl unsaturated sulfoximines have been prepared from an *N*-silyl-(*E*)-β-tosylvinylsulfoximine by taking advantage of recently developed transition-metal mediated coupling reactions. We are presently examining other transformations in this vein in order to improve the overall efficiency while also exploring the application of these compounds in cycloaddition processes; results will be reported in due course.



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1 Address correspondence to this author at: Dept. of Chemistry, Univ. of New Hampshire, Durham, NH 03824.

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9 β-Tosylvinylsulfoximine **5** could be stored for several weeks under an argon atmosphere at -15°C.

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11 Lipshutz, B.H. *Synthesis*, **1987**, 325. A typical procedure is as follows: To a stirred suspension of flame-dried copper(I) cyanide (0.161 mmol) in Et_2O (1.0 ml) under argon was added ethyl magnesium bromide (0.322 mmol; 0.161 ml of a 2.0 M solution in THF), via syringe, at -78°C. The solution was stirred at 0°C for 15 min. and was then cooled to -40°C. A THF solution (0.5 ml) of **5** (0.107 mmol) was added to the cuprate via syringe. After warming to 0°C over 1 hr., the reaction was quenched with 9:1 saturated NH_4Cl / NH_4OH solution. The contents of the flask were diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to afford an oil. Column chromatography (19:1 pet. ether: ethyl acetate) gave **1b** as a clear oil (19.9 mg, 60%).

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13 Prepared, *in situ*, by treating a toluene solution of ethylaluminum dichloride with two equivalents of vinyl magnesium bromide at room temperature, as follows. (Use of dimethyl- or diethylvinylalane in this transformation was unsuccessful). To toluene (5.0 ml) at room temperature, under argon, was added ethylaluminum dichloride (0.67 mmol, 0.67 ml of a 1.0 M solution in hexanes) and vinyl magnesium bromide (1.34 mmol, 1.34 ml of a 1.0 M solution in THF). The suspension was stirred for 30 min., when a benzene solution (5.0 ml) of **5** (0.446 mmol, 201.5 mg) and $Pd(PPh_3)_4$ (0.045 mmol, 51.6 mg) was added via cannula. The flask was immediately immersed in a 50°C oil bath and stirred for 45 min. The workup consisted of dilution with CH_2Cl_2, followed by washing with saturated $NaHCO_3$ and brine. After drying ($MgSO_4$) and evaporation, column chromatography (19:1, pet. ether : ethyl acetate) afforded **2** as a clear oil (116.2 mg, 85%).

14 All efforts to use vinyl stannane / Pd(0) methodology to effect this transformation were unsuccessful.

15 Prepared, *in situ*, by treating a pentane solution of 1-hexyne with *n*-BuLi (1.6 M in hexanes) at -78°C, followed by addition of toluene and dimethylaluminum chloride (1.0 M in hexanes) at 0°C. The workup and purification was similar to that for dienylsulfoximine **2**; enynylsulfoximine **3** was obtained as a clear oil after column chromatography.

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