ORGANIC LETTERS

2003
Vol. 5, No. 24
4607−4610

A New, Mild Synthesis of *N*-Sulfonyl Ketimines via the Palladium-Catalyzed Isomerization of Aziridines

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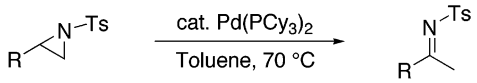
Received September 12, 2003

ABSTRACT



A new method for the synthesis of *N*-tosylketimines via the palladium-catalyzed isomerization of *N*-tosylaziridines is described. The mild reaction conditions tolerate the presence of a variety of functional groups including ketones, esters, and acetals. The reactions are believed to proceed via the oxidative addition of the aziridine to Pd(0) and represent the first examples of transformations involving Pd(0)-mediated oxidative additions of aziridines that do not proceed through allylpalladium intermediates.

Sulfonyl imines are versatile intermediates in organic synthesis.[1] For example, they are used as substrates in hetero Diels−Alder reactions[2] and trimethylenemethane cycloadditions,[3] which provide a useful route to nitrogen heterocycles. They are also employed as electrophiles in a wide variety of addition[4] and reduction[5] reactions.

As a result of the broad synthetic utility of sulfonylimines, a large number of methods have been developed for their preparation.[1] Although the formation of sulfonyl *aldimines* can be achieved through several methods, synthesis of sulfonyl *ketimines* remains a serious challenge.[1] For example, in contrast to *N*-alkyl imines, *N*-sulfonyl imines are difficult to prepare via condensation reactions.[1] Typically the condensation of primary sulfonamides with aldehydes and ketones requires harsh reaction conditions and is usually limited to the preparation of nonenolizable sulfonyl aldimines.[1,6,7]

Many other strategies have been developed for the conversion of aldehydes to *N*-sulfonyl imines,[8−10] including methods for the in situ generation of sulfonyl imines.[2a,4e,f] However, these protocols are usually limited to the synthesis of nonenolizable sulfonylimines derived from aldehydes; the use of these methods for sulfonyl ketimine synthesis is rare and is limited to preparation of diaryl ketimine derivatives.[9]

The most general methods for the synthesis of sulfonylketimines involve the condensation of oximes with sulfinyl chlorides[11] or sulfonyl cyanides.[12] However, sulfinyl chlo-

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(10) For synthesis of enolizable tosyl aldimines via photochemical rearrangement of naphtho[1,8-*de*]-dithiin-1-*N*-tosylsulfilimines, see: Fujii, T.; Kimura, T.; Furukawa, N. *Tetrahedron Lett.* **1995**, *36*, 1075−1078.

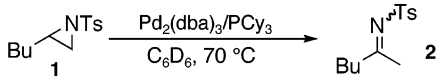
(11) (a) Artman, G. D.; Bartolozzi, A.; Franck, R. W.; Weinreb, S. M. *Synlett* **2001**, 232−233 and references therein. (b) Brown, C.; Hudson, R. F.; Record, K. A. F. *J. Chem. Soc., Perkin Trans. 2* **1978**, 822−828.

10.1021/ol0357651 CCC: $25.00
Published on Web 10/31/2003

rides are often unstable and highly reactive. The analogous sulfonyl cyanides are easier to manipulate but are quite expensive and generate toxic byproducts.

Because of the limitations of the above transformations, the development of a new method for the synthesis of sulfonyl ketimines under mild conditions would be desirable. An ideal method would be general, atom economical, catalytic, and tolerant of a wide range of functional groups and would not require toxic or otherwise hazardous reagents.

During the course of our studies on the reactivity of transition metal complexes toward aziridines[13] we found that treatment of 2-butyl-*N*-tosylaziridine (**1**) with a stoichiometric mixture of $Pd_2(dba)_3/PCy_3$ in C_6D_6 at 70 °C led to the clean formation of *N*-tosylketimine **2** (eq 1).[14,15] The transformation

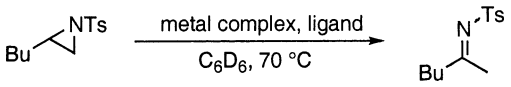


1 2 (1)

of **1** to **2** was found to proceed effectively with only a catalytic amount (5 mol %) of palladium. Given the mild nature of these reaction conditions and the essentially quantitative conversion of aziridine to imine, we reasoned that the palladium-catalyzed isomerization of aziridines could potentially be employed as a very mild synthesis of *N*-tosyl ketimines that would tolerate a wide variety of functional groups. Our preliminary studies on the efficacy of this transformation are described herein.

In contrast to 2-vinyl-*N*-tosylaziridines, which readily undergo oxidative addition to Pd(0),[16] the oxidative addition of 2-alkyl or -aryl aziridines to Pd(0) has not been previously described.[13] Thus, to maximize the kinetic efficiency of this process, we examined the stoichiometric reaction of **1** with a number of palladium/phosphine complexes. Mixtures of $Pd_2(dba)_3$ and triarylphosphines such as PPh_3, P(*o*-tol)$_3$, BINAP, and dppf did not provide active catalysts for this reaction. In contrast, palladium complexes supported by electron-rich trialkylphosphines promoted the isomerization (Table 1). In general, preformed L_2Pd complexes were more reactive than catalysts generated in situ from $Pd_2(dba)_3$ or $Pd(OAc)_2$.[17] The steric properties of the ligand had a dramatic impact on reactivity. For example, both $Pd[PCy_3]_2$ (**3**) and

Table 1. Ligand Effects[a]



entry	metal complex	ligand	reaction time[b]
1	$Pd_2(dba)_3$	P(*o*-tol)$_3$	no reaction
2	$Pd_2(dba)_3$	Cy_2P(*o*-biphenyl)	no reaction
3	$Pd_2(dba)_3$	PCy_3	8 h
4	$Pd(OAc)_2$	PCy_3	no reaction
5	$Pd[P(t\text{-}Bu)_3]_2$		no reaction
6	$Pd[PCy)_3]_2$		1 h
7	$Pd[P(t\text{-}Bu)_2Me]_2$		25 min
8	$Pd[P(t\text{-}Bu)_2Cy]_2$		no reaction
9	$Pd[P(t\text{-}Bu)Cy_2]_2$		>72 h[c]

[a] Conditions: 1.0 equiv of substrate, 1.0 equiv of metal complex, C_6D_6 (0.015 M). All reactions provided a single product as judged by ^{1}H NMR analysis. [b] Time required for the complete conversion of substrate to product. [c] The reaction was stopped after 72 h and was found to have proceeded to 66% completion.

$Pd[P(t\text{-}Bu)_2Me]_2$ (**4**) were sufficiently reactive to promote the isomerization at room temperature, whereas $Pd[P(t\text{-}Bu)_3]_2$ did not catalyze the reaction even at 80 °C. Although **4** was more reactive than **3**, most reactions were conducted with commercially available **3**.

As shown in Table 2, a number of *N*-tosylaziridines are isomerized to *N*-tosylketimines in good yield in the presence of 2−4 mol % **3**. The reaction conditions are sufficiently mild to tolerate a variety of functional groups including esters (entry 3), olefins (entry 3), acetals (entry 4), and ketones (entry 5). The isomerization of these functionalized substrates is particularly noteworthy, as highly functionalized *N*-tosylketimines would be difficult to prepare using existing methods and have not been previously described. In contrast to the related isomerization of styrene oxide to 2-phenylacetaldehyde,[14b] 2-phenyl *N*-tosylaziridine **5** reacts at the less hindered carbon rather than the activated benzylic position, to afford sulfonyl ketimine **6** (entry 2). We also observed that *N*-acylaziridine **8** was converted to *N*-acylenamine **9** in 47% yield (entry 7).[18] At present, this method is limited to the isomerization of terminal aziridines; 1,2-disubstituted aziridines did not react under our standard conditions (entry 6). We are currently pursuing the development of other catalysts that may be capable of transforming more highly substituted substrates.

In most cases the isolation of analytically pure *N*-tosylimines was achieved by rapid chromatography on silica gel. In some cases (Table 2, entries 4 and 5) the isolated products were contaminated with small amounts (ca. 5−15%) of byproducts resulting from partial hydrolysis of the imine by silica gel. However, we found the metal-catalyzed

(12) Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1992**, *57*, 4777−4780.

(13) (a) Hillhouse has recently reported the synthesis of an azanickelacyclobutane via oxidiative addition of 2-butyl-*N*-tosylaziridine to (bipy)$NiEt_2$ or (bipy)Ni(COD). See: Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890−2891. (b) The oxidative addition of ethyleneimine to Pt(II) under acidic conditions has been previously described. See: Mitchenko, S. A.; Slinkin, S. M.; Vdovichenko, A. N.; Zamashchikov, V. V. *Metallorg. Khim.* **1991**, *4*, 1031−1035.

(14) The palladium-catalyzed isomerization of epoxides to ketones has been previously reported. See: (a) Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 2095−2096. (b) Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1997**, *62*, 6547−6561 and references therein.

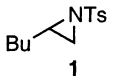
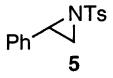
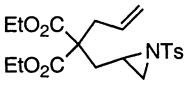
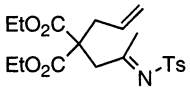
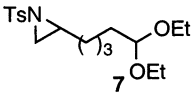
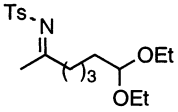
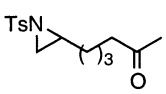
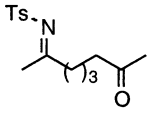
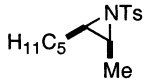
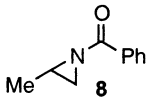
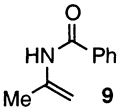
(15) Control experiments demonstrated that the aziridine did not isomerize when heated for 15 h at 70 °C in C_6D_6 with 1 equiv of tricyclohexylphosphine in the absence of Pd.

(16) For recent examples in catalytic reactions, see: (a) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887−5890. (b) Fugami, K.; Morizawa, Y.; Ishima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 857−860. (c) Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 5977−5980. (d) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836−11837.

(17) Mixtures of $Pd_2(dba)_3/PCy_3$ did effectively catalyze the isomerization of **1**. However, chromatographic separation of the imine product from dba was very difficult.

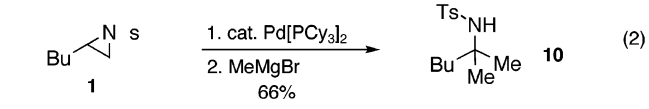
(18) Aziridines bearing *N*-benzyl or *N*-diphenylphosphoryl groups did not react under our standard conditions. The reaction of an *N*-boc aziridine proceeded very slowly, requiring 1 equiv **3** and >24 h at 80 °C to reach completion.

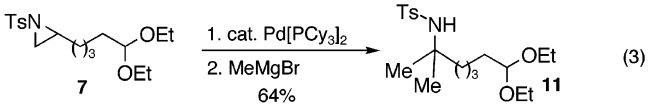
Table 2. Palladium-Catalyzed Isomerization of Aziridines[a]

entry	substrate	product	rxn time	yield[b]
1	 **1**	 **2**	4 h	74%
2	 **5**	 **6**	36 h	72%
3			34 h	73%
4	 **7**		4 h	86%[c]
5			12 h	70%[d]
6		—		0%
7	 **8**	 **9**	7 h	47%

[a] Conditions: 1.0 equiv of substrate, 2−4 mol % $Pd[PCy_3]_2$ (**3**), toluene (0.25 M), 70 °C. [b] The yields reported in this table are average isolated yields obtained from two or more runs. [c] This material contained ~15% of 7,7-diethoxy-heptan-2-one resulting from partial imine hydrolysis during chromatographic purification. [d] This material contained ~5% of *p*-toluenesulfonamide resulting from partial imine hydrolysis during chromatographic purification.

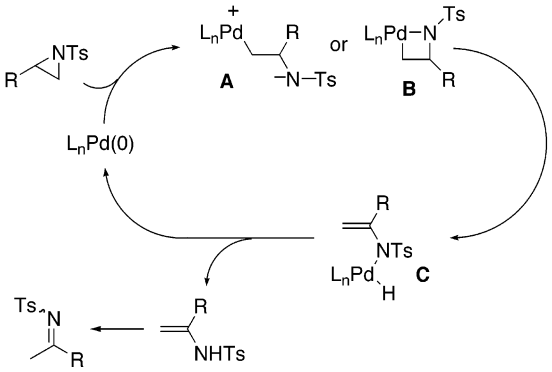
isomerization of aziridines is amenable to use in "one-pot" addition processes. For example, aziridine **1** was treated with a catalytic amount of **3** for 7 h at 70 °C until all of the starting material had been consumed as judged by ^{1}H NMR analysis. At this point the reaction mixture was cooled to room temperature, and methylmagnesium bromide was added. The resulting amine product **10** was isolated in 66% yield (eq 2). Substrate **7** was converted into **11** in an analogous manner (eq 3). These processes provide a three-step (two-pot) procedure for the conversion of a terminal olefin into a substituted *tert*-butylamine derivative.





On the basis of our observations and Hillhouse's elegant mechanistic studies on the oxidative addition of *N*-tosylaziridines to Ni(0)[13] we propose the following mechanism for the isomerization reactions (Scheme 1). Oxidative addition of the *N*-tosylaziridine to $Pd[PCy_3]_2$ presumably occurs in an S_N2 fashion[19] to afford either zwitterion **A** or azametallacyclobutane **B**. Intermediate **A** or **B** could then undergo β-hydride elimination to afford hydrido-palladium amido species **C**. Reductive elimination of **C** would provide an *N*-tosylenamine, which could tautomerize to afford the observed products. The fact that the tosylaziridine substrates, including 2-phenylaziridine, react at the less hindered carbon is supportive of a nucleophilic (S_N2) mechanism of oxidative addition rather than a mechanism involving Lewis acid mediated activation of the aziridine, which would most likely result in ring opening at the benzylic position.[20] It is not clear if azametallacyclobutane **B** is formed under our reaction conditions; however, it seems likely that β-hydride elimination occurs from an acyclic species such as **A**. Examination of models suggests that β-hydride elimination from **B** would be stereoelectronically unfavorable.[21]

Scheme 1. Proposed Catalytic Cycle



In conclusion, we have developed a new method for the synthesis of *N*-tosylketimines via a palladium-catalyzed isomerization of *N*-tosylaziridines. These reactions represent the first examples of transformations involving oxidative addition of aziridines to Pd(0) that do not proceed through allylpalladium intermediates. The reactions exhibit excellent functional group tolerance and are amenable to use in one-pot sequential reactions. Further studies to expand the scope of this reaction and to ascertain the nature of the intermediates in the catalytic cycle are currently underway.

Acknowledgment. The authors thank the University of Michigan for financial support of this work. J.P.W. thanks the Camille and Henry Dreyfus Foundation for a new faculty

(19) Hillhouse has shown that oxidative addition of Ni(0) to *N*-tosylaziridines proceeds with inversion of configuration, which suggests that oxidative addition occurs via an S_N2 mechanism. See ref 13a.

(20) Lewis acid mediated nucleophilic ring-opening reactions of *N*-tosyl-2-phenylaziridine typically afford products resulting from substitution at the benzylic position or mixtures of regioisomers. For recent examples, see: (a) Ungureanu, I.; Bologa, C.; Chayer, S.; Mann, A. *Tetrahedron Lett.* **1999**, *40*, 5315−5318. (b) Schneider, M. −R.; Klotz, P.; Ungureanu, I.; Mann, A.; Wermuth, C. -G. *Tetrahedron Lett.* **1999**, *40*, 3873−3876. (c) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2001**, *42*, 3955−3958.

(21) Zhang, L.; Zetterberg, K. *Organometallics* **1991**, *10*, 3806−3813.

award, and Research Corporation for an innovation award. J.E.N. acknowledges the University of Michigan for a Regents Fellowship. Additional unrestricted support was provided by Eli Lilly and 3M. The authors also thank Professors E. Vedejs and M. S. Sanford for their helpful comments on this manuscript.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0357651