In summary, a novel and efficient method for the synthesis of bicyclo[4.2.1]nonane-2-ones was established. Application of the present methodology to the synthesis of the mediterraneols 1 is in progress in our laboratory.

(11) This is supported by the MM2 calculations[7] for the most stable conformers of 16 and 17 which lie within ca. 2 kcal/mol. Namely, the dihedral angle between the endo hydrogen-C(9) bond and the central cyclobutane bond is in the range of -160.5° to -70.7° for six conformers of 16, while the corresponding angle between the exo hydrogen-C(9) bond and the C(1)-C(6) bond is in the range of -33.2° to 58.2° for five conformers of 17.

Acknowledgment. Thanks are due to the Instrumental Analysis Center, Faculty of Engineering, Osaka University for assistance in obtaining NMR and mass spectra.

Supplementary Material Available: Experimental details of the acid-catalyzed reactions of **3a-g**, **12**, **13**, **16**, and **17**; spectroscopic and analytical data for **3a-f**, **8a-e**, **9-16**, and **18**; Table SI listing the results of the acid-catalyzed reactions of **3a-g** with various acids; 2D ^{13}C-INADEQUATE spectra of **8a**, **9**, **10**, and **18** (23 pages). Ordering information is given on any current masthead page.

Copper-Catalyzed Aziridination of Olefins by (*N*-(*p*-Toluenesulfonyl)imino)phenyliodinane

David A. Evans,* Margaret M. Faul, and Mark T. Bilodeau

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

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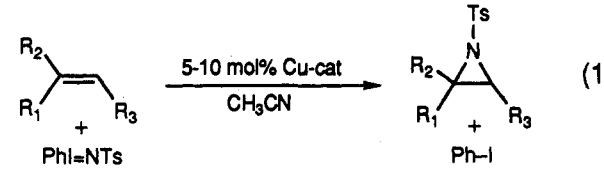
Summary: The Cu(I)- or Cu(II)-catalyzed aziridination of both electron-rich and electron-deficient olefins employing (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane, PhI=NTs, as the nitrene precursor, affords *N*-tosylaziridines in yields ranging between 55%-95%.

In a seminal 1967 publication, Kwart and Kahn[1] reported the copper-bronze-catalyzed aziridination and allylic insertion reactions of benzenesulfonylazide with cyclohexene. Subsequently, Mansuy disclosed that aziridination of a number of olefins can be achieved with (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTs)[2] using Fe(III)- and Mn(III)-porphyrins as catlysts.[3] Other evidence for catalytic imido group transfer has appeared in the literature;[4] however, the number of olefinic substrates, nitrene precursors, and catalysts that have been evaluated in these studies has been limited. In view of the demonstrated utility of suitably functionalized aziridines in organic synthesis,[5] it is noteworthy that the scope of this reaction has not been fully developed.

Based on the proven ability of Cu(I)-based catalysts to promote olefin cyclopropanation, we have explored the scope of soluble copper catalysts in the analogous aziridination processes. In our preliminary studies concerned with the development of chiral variants of the cyclopropanation process, we have found that Cu(I) is a highly effective catalyst.[6] The purpose of the present paper is to describe the scope and optimized reactions of the Cu(MeCN)$_4$ClO$_4$[7] and Cu(acac)$_2$-catalyzed olefin aziridination using PhI=NTs as the nitrene precursor (eq 1).



(1)

Our preliminary results suggest that copper is superior to other metal complexes such as Mn(TPP)Cl, Fe(TPP)Cl, Rh$_2$(OAc)$_4$, and Co(acac)$_2$. With regard to the catalytically active oxidation state of copper, it was surprising to find that both Cu(I) and Cu(II) salts (for example, halide, triflate, and nitrate) were catalytically competent and that either Cu(MeCN)$_4$ClO$_4$ or Cu(acac)$_2$ appeared to be the catalysts of choice based on yields of olefin aziridination.

The influence of solvent polarity on the rate and efficiency of the reaction is striking. Although good yields of styrene aziridination may be achieved with a number of Cu- and Mn-based catalysts in either nonpolar or polar solvents, this substrate has proven not to be representative for either optimal solvent or metal catalyst extrapolations. A comprehensive screening of olefinic substrates and reaction solvents has led us to conclude that dipolar aprotic solvents such as MeCN and MeNO$_2$ are optimal for the reaction, and in the present study, the former solvent was shown to be the medium of choice.

The data for a representative selection of olefins with the catalyst Cu(MeCN)$_4$ClO$_4$ and Cu(acac)$_2$ is summarized in Table I along with the best results previously reported for either Mn(TPP)Cl or Fe(TPP)Cl. PhI=NTs, like its oxygen analogue PhI=O,[8] is insoluble in a variety of

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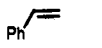
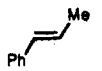
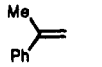
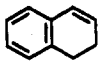
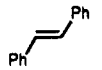
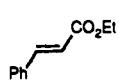
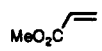
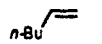
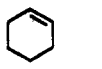
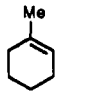
Table I. Copper-Catalyzed Aziridination of Representative Olefins (eq 1)

entry	olefin[a]	catalyst	yield,[b] %
1		$Cu(MeCN)_4ClO_4$	89
		$Cu(acac)_2$	95
		Mn(TPP)Cl[c]	80[d]
2		$Cu(MeCN)_4ClO_4$	81
		$Cu(acac)_2$	75
3		$Cu(MeCN)_4ClO_4$	89
		$Cu(acac)_2$	72
4		$Cu(MeCN)_4ClO_4$	23
		$Cu(acac)_2$	73
5		$Cu(MeCN)_4ClO_4$	81[e]
		$Cu(acac)_2$	50
		$Fe(TDCPP)ClO_4$	36[f]
6		$Cu(MeCN)_4ClO_4$	80[g,h]
		$Cu(acac)_2$	54[i]
		$Fe(TDCPP)ClO_4$	43[f,j]
7		$Cu(MeCN)_4ClO_4$	59
		$Cu(acac)_2$	51
8		$Cu(MeCN)_4ClO_4$	61
		$Cu(acac)_2$	32
9		$Cu(MeCN)_4ClO_4$	55[g]
		$Cu(acac)_2$	39
		$Mn(TDCPP)ClO_4$	23[k]
10		$Cu(MeCN)_4ClO_4$	90[l]
		$Cu(acac)_2$	95
11		$Cu(MeCN)_4ClO_4$	77[g]
		$Cu(acac)_2$	30
		$Mn(TDCPP)ClO_4$	0[k,m]
12		$Cu(MeCN)_4ClO_4$	66[n]
		$Cu(acac)_2$	32

[a] All reactions were performed in acetonitrile with 5–10 mol % catalyst and 5 equiv of olefin (0.4 M) at 25 °C unless otherwise noted. [b] Isolated yield of aziridine based on 1 equiv of PhI=NTs. [c] TPP = tetraphenylporphyrin, TDCPP = tetrakis-2,6-dichlorophenylporphyrin. [d] From ref 3a. [e] Reaction performed using CH_2Cl_2 as solvent. [f] From ref 3c. [g] Reaction performed at −20 °C. [h] Product isolated as a mixture of *cis*- and *trans*-1,2-diphenylaziridines in a rato of 9.0:1.0. [i] Products isolated as a mixture of *cis*- and *trans*-1,2-diphenylaziridines in a ratio of 1.5:1.0. [j] Product isolated as the *trans*-1,2-diphenylaziridine only. [k] From ref 3b. [l] 3 equiv of olefin was used. [m] Authors reported isolation of 70% allylic insertion product. [n] Reaction performed at 0 °C.

solvents, including MeCN, and the course of the reaction may be ascertained by the extent of dissolution of this reagent. Reaction rates are much faster in polar solvents (MeCN, $MeNO_2$) than in less polar media (PhMe, CH_2Cl_2). Under these latter conditions, the long reaction times necessary to complete the reaction lead to competition between olefin aziridination and decomposition of the nitrene precursor to *p*-toluenesulfonamide. Control experiments in the absence of an olefin trap indicate that PhI=NTs decomposes rapidly to *p*-toluenesulfonamide (<5 min, 25 °C) in MeCN using Cu(I) catalysis. It is assumed that the solvent is serving as the proton source.

Under standard conditions (MeCN, 5–10 mol % catalyst, 1 equiv of PhI=NTs, 5 equiv of olefin, 0.4 M, 25 °C), the catalyzed aziridination reaction proceeds in good yields with both aromatic and aliphatic olefins. With phenyl-substituted olefins, both Cu(I) and Cu(II) afford high yields of aziridines (entries 1–6). In one noteworthy instance (entry 4), a significant difference between the two catalyst oxidation states was observed. With 1,2-dihydronaphthalene, Cu(II) proved to be the oxidation state of choice, affording a 73% yield of desired aziridine. In contrast, $Cu(MeCN)_4ClO_4$ afforded only a modest 23% of the aziridination product. All aliphatic olefins afforded good yields of aziridine with no accompanying allylic insertion (entries 9–12). The reaction of PhI=NTs with norbornene (entry 10) occurs from the less hindered exo face of the bicyclic nucleus to provide the exo adduct in high yield. Finally, the successful utilization of electron deficient olefins (entries 7, 8) in this reaction provides an important extension of the scope of the process. Although all of the reactions were initially carried out under a nitrogen atmosphere, this subsequently proved to be an unnecessary precaution for the $Cu(acac)_2$-catalyzed processes. For example, α-methylstyrene afforded a 66% yield of 1-methyl-1-phenylaziridine when the experiment was carried out open to the air with no precautions to ensure anhydrous conditions.

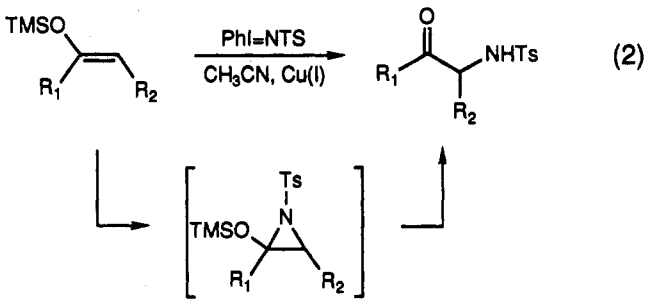
Table II. Cu-Catalyzed Aziridination of Enolsilanes (eq 2)

entry	olefin[a]	catalyst	yield,[b] %
1	R_1 = Ph, R_2 = H	$Cu(MeCN)_4ClO_4$	75
2	$R_1 = R_2 = -(CH_2)_4-$	$Cu(MeCN)_4ClO_4$	64

[a] All reactions were performed in acetonitrile at −20 °C with 5–10 mol % catalyst and 1.5 equiv of olefin (0.1 M). [b] Isolated yield of α-amino ketone based on 1 equiv of PhI=NTs.

Other attributes of the copper-catalyzed process are revealed in the comparative Fe(III)- or Mn(III)-porphyrin catalyzed aziridinations of *cis*-stilbene (entry 6). Aziridination of this substrate with these catalysts afforded the more stable *trans*-1,2-diphenylaziridine indicating that olefin isomerization is a concomitant process.[3] The analogous Cu(I)-catalyzed process at room temperature yielded 64% of a 1.0:1.5 ratio of *cis*- and *trans*-1,2-diphenylaziridines while repetition of the reaction at −20 °C afforded an 80% yield of a 9:1 ratio favoring the cis adduct.

The direct amination of silyl enol ethers[9] and silyl ketene acetals[10] by the thermolysis of azidoformates to produce N-substituted α-amino ketones and esters has been recently reported. Chiral silyl ketene acetals have also been employed and show useful levels of diastereoselectivity.[11] In a complementary reaction (Table II) we report the first Cu(I)-catalyzed amination of trimethylsilyl enol ethers using PhI=NTs (eq 2). The reaction produces the corresponding *N*-(*p*-toluenesulfonyl)-α-amino ketones in good yields, presumably by ring opening of the corresponding [(trimethylsilyl)oxy]aziridines, in analogy with the Rubottom oxidation.[12]



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The aziridination experiments with olefins (Table I) and enolsilanes (Table II) were carried out with 5.0 and 1.5 equiv of substrates, respectively. For those cases where the olefin might be considered as the valuable reaction component, 1.0 equiv of substrate may be employed with negligible loss in yield if the substrate concentration is increased to 1.0 M (checked for those experiments described in Table I, entry 11; Table II, entries 1, 2).

Ongoing studies are being directed toward extending the scope and developing enantioselective variants of this reaction.[6] It is our intention to develop a new catalytic, asymmetric enolate amination procedure to complement methods previously reported from these laboratories for the asymmetric synthesis of amino acids.[13]

Acknowledgment. Support has been provided by the NIH, the NSF, and Merck. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities.

Supplementary Material Available: Experimental procedures and spectral data for all compounds (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Synthesis of a Conformationally Restricted DNA Hairpin

Gary D. Glick

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1055

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Summary: A synthetic method based on disulfide bond crosslinking between modified thymidine bases has been developed to stabilize the conformation of DNA hairpin structures.

Physical studies of oligodeoxynucleotides provide a rich source of information regarding DNA structure.[1] Yet, such investigations can be hampered by the dynamic properties of these molecules.[2] This problem is often encountered in studies of hairpin stem-loop structures. At the DNA or salt concentrations required for crystallographic or NMR work, self (or partially self) complementary sequences can dimerize or oligomerize.[3] Indeed, only one X-ray[4] and several NMR[5] structures of DNA hairpins have been determined. Here, we describe a general method to stabilize the molecular architecture of DNA hairpins and apply it to prepare a conformationally restricted stem-loop structure whose sequence comes from the ColE1 cruciform.[6] Unlike many other procedures to crosslink oligodeoxynucleotides, this chemistry does not perturb native DNA structure.[7]

On a B-DNA duplex the pyrimidine N-3 position faces toward the center of the helix so that at the site of a T-T mismatch, the two N-3 atoms converge (to within 4.5 Å).[1] Molecular modeling studies suggest that if this mismatch is located at the terminus of a duplex, a six-atom linker can crosslink these N-3 positions without disrupting the native geometry of the helix. To bridge this distance, we have alkylated the 2'-deoxythymidine N-3 nitrogen with a mercaptoethyl linker so synthesis of an oligodeoxynucleotide with this base at the 3' and 5' termini permits formation of an intramolecular disulfide bridge across the helix.[8] In this scheme, the mercaptoethyl bridge comes

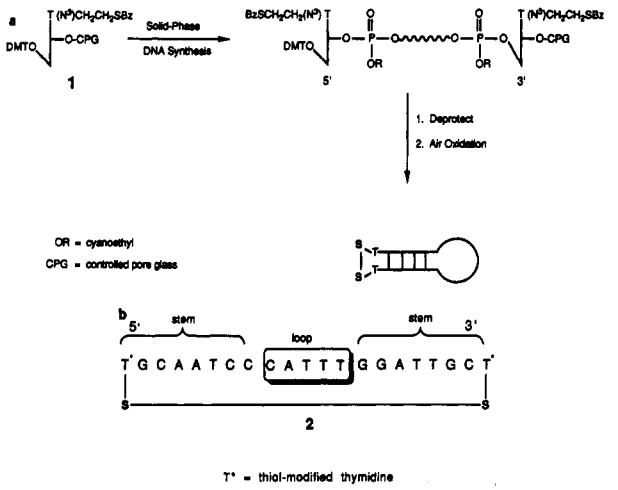

Figure 1. (a) General synthetic route to crosslinked hairpins. As depicted schematically, the lowest energy conformation of the crosslink places the disulfide bond and alkyl chains below the base of the stem. In this the geometry there are no eclipsing interactions in the linker and the C-S-S-C dihedral angle is 81°. (b) Sequence of the crosslinked hairpin.

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