A Simple Copper Catalyst for Both Aziridination of Alkenes and Amination of Activated Hydrocarbons with Chloramine-T Trihydrate

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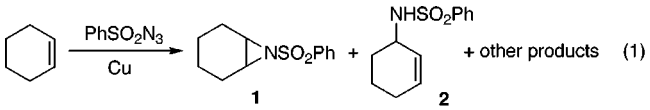
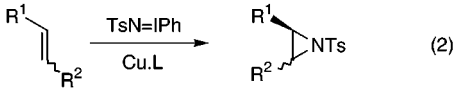
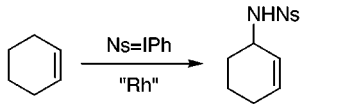
Introduction

In 1967 Kwart and Kahn reported the copper-catalyzed decomposition of benzenesulfonyl azide in the presence of cyclohexene to yield products consistent with a nitrene-transfer mechanism (eq 1).[1] Both the aziridine **1** and the allylic amination **2** products are synthetically very interesting, and throughout the 1980s the groups of Breslow and of Mansuy sought catalysts which led to higher yields and selectivities for each of these two classes of product.[2]

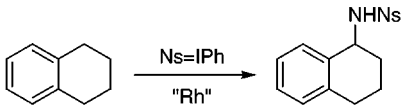




It was not until 1991 that an efficient and general nitrene-transfer aziridination procedure was developed by the group of Evans.[3] Simple copper(I) and copper(II) salts were found to give high yields of aziridines from a wide range of alkenes and TsN═IPh (eq 2), with only isolated examples of allylic insertions. In 1993 the groups of Jacobsen and of Evans simultaneously reported an asymmetric variant of this reaction, with very high ees being recorded for some classes of substrate.[4] A nitrene-transfer mechanism was formally proposed by Jacobsen in 1995.[5] The disadvantage of the Evans aziridination procedure is the necessity of using TsN═IPh as the nitrene-transfer agent, because its two-step synthesis is notoriously capricious and iodobenzene is liberated as a byproduct. Andersson recommends instead the nitro analogue NsN═IPh,[6] the synthesis of which is more straightforward, and this is the favored nitrene-transfer agent in the promising, but to date more limited, rhodium-catalyzed aziridination developed by the group of Müller.[7]



Ns = $NO_2C_6H_4SO_2$-



Very recently, Müller has published a study of the amination of hydrocarbons with the same rhodium-NsN═IPh systems. High yields of aminated products were observed with cycloalkenes (eq 3) and with benzylic substrates (eq 4), but, as with the rhodium-catalyzed aziridination, very large excesses of hydrocarbon are required.[8] Another very recent paper, from the Katsuki group, describes a copper-catalyzed benzylic and allylic amination procedure using *t*-BuOO(C═O)NHTs (one-step synthesis) as the nitrogen source.[9] Benzylic amination was efficient, but for allylic amination 1 equiv of catalyst was required for an acceptable yield. Although the products are consistent with a nitrene-transfer mechanism, this reaction is believed to be a radical process.[9]

Our interest in nitrene transfer sulfimidation[10] led us to investigate cheap, commercially available chloramine-T hydrate ($TsNClNa\cdot(H_2O)_3$) as a nitrene-transfer agent.[11] In fact, chloramine-T has very recently been shown by Komatsu's group to aziridinate alkenes with copper(I) triflate as catalyst,[12] but this process has the drawback of requiring prior dehydration of chloramine-T, a procedure with a *significant explosion hazard*.[13] To avoid this hazard Cenini's group exchanged sodium for tetraalkylammonium. Using iron and manganese catalysis (but surprisingly not copper or rhodium) and huge excesses of cycloalkene substrates, they obtained mixtures of products, including aziridines and allylic amination products.[14]

Herein we describe a mechanism-based approach to selection of an efficient catalyst for *nitrene-transfer from*

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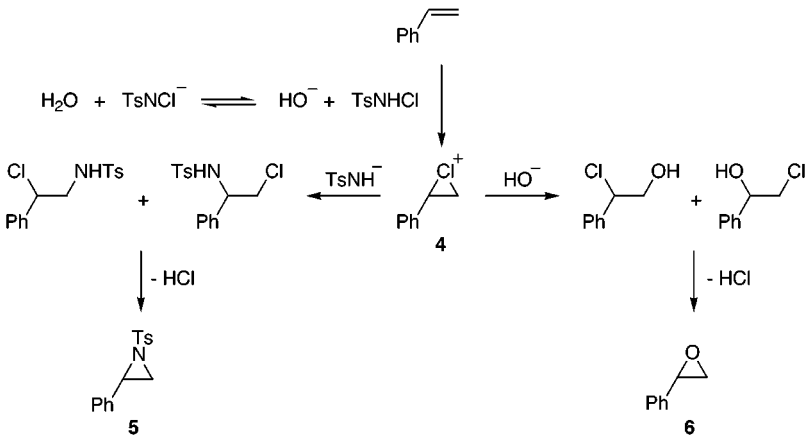
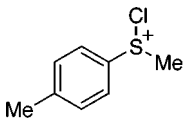
Scheme 1



chloramine-T trihydrate. Such a catalyst is desirable since (i) chloramine-T is a very cheap nitrene source, (ii) use of the trihydrate obviates the need for the hazardous dehydration, (iii) a large excess of alkene should not be necessary, and (iv) it offers potential for asymmetric modification.

Results and Discussion

In our earlier work on sulfimidation we noted that copper-catalyzed imidation of sulfides with chloramine-T appeared to have two alternative mechanisms, a Lewis acid mechanism and a nitrene-transfer mechanism.[11c] The proposed Lewis acid mechanism is similar to the traditional mechanism assumed for reaction of chloramine-T hydrate with sulfides, with the copper catalyst accelerating at least one of the steps. Importantly for the current study, in the absence of molecular sieves, the proposed sulfonium intermediates, e.g. **3**, are intercepted by water to produce sulfoxides. This was observed in reactions where no other nitrogen ligand was present. However, when ligands such as pyridine or bipy were added, *no* sulfoxide was observed even in the absence of sieves. This is consistent with the operation of a nitrene-transfer mechanism, which cannot lead to sulfoxide.



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We thus carried out a similar study with styrene as substrate. Interestingly, the copper (I) triflate−bipy catalyst appeared to act as a Lewis acid in this case, giving mixtures of aziridine **5** and *epoxide* **6**. We believe these two products arise from a common chloronium intermediate **4** (Scheme 1); indeed, chloramine-T has been used to prepare chlorohydrins.[15] In this work we aimed to promote the aziridine product, but we note that this reaction has the potential to be a useful epoxidation procedure. Inspired by other work at Warwick,[16] we reasoned that *n*-alkyl imines of pyridine-2-carboxaldehyde might favor aziridination, as they are known to be better ligands for iron(II) than bipy.[17] An initial screening led us to select catalyst **7** with which *no* epoxide was observed, even without added sieves, suggesting a nitrene-transfer mechanism (Scheme 2).

Scheme 2

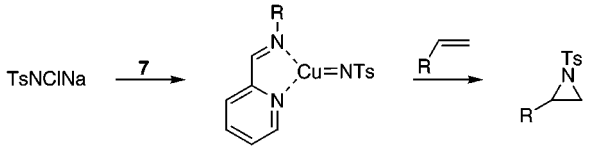
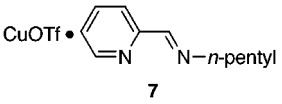


Table 1. Aziridination of Aryl Alkenes

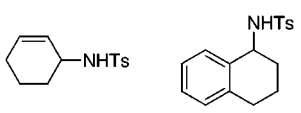
	alkene	equivs. alkene	aziridine yield (%)	$TsNH_2$ yield (%)	other yield (%)
1	Ph	1.1	25	50	25
2		5[a]	74	22	4
3[b]	Ph	1.1	32	44	24
4		5[a]	45	25	30
5		1.1	51	41	8
6		5[a]	76	12	12

[a] 5 equiv reactions were run at 5-fold dilution (see Experimental Section). [b] Reaction may not have gone to completion.



7

We then screened catalyst **7** with a number of aryl alkenes (Table 1), using 5 mol % copper(I) triflate and 6 mol % ligand in acetonitrile. Pleasingly, even with only 1.1 equiv of alkene, respectable yields of aziridine resulted (entries 1, 3 and 5). With 5 equiv of alkene *and at higher dilution* (in entries 2, 4, and 6, the concentration of alkene was unchanged from the 1.1 equiv examples), the percentage of *p*-toluenesulfonamide ($TsNH_2$) byproduct decreased in all cases. However, with the two more electron-rich alkenes (entries 4 and 6), the percentage of other byproducts increased, presumably due to competing ionic additions. Nevertheless, for styrene and dihydronaphthalene (entries 2 and 6), good yields of aziridine were obtained.



8 **9**

When a representative alkyl alkene, cyclohexene, was used, very little aziridine was observed either with 1.1

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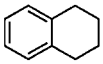
Table 2. Amination of Cyclohexene and Tetralin

	substrate		product	product distribution
				aziridine : **8** : $TsNH_2$: other
1		1.1	**8**	8 : 22 : 64 : 6
2		5[a]		8 : 6 : 86 : 0
				9 : $TsNH_2$
3		1.1	**9**	46 : 54
4		5[a]		<5 : >95

[a] 5 equiv reactions were run at 5-fold dilution (see Experimental Section).

or 5 equiv of alkene (Table 2), and the major product was *p*-toluenesulfonamide. However, we were excited to observe a significant amount of allylic amination product **8** (entry 1). This encouraged us to use a benzylic substrate; with tetralin (Table 2, entry 3) a reasonable yield of benzylic amination product **9** resulted. In the amination reactions, using more substrate (entries 2 and 4) favored production of even higher percentages of *p*-toluenesulfonamide and was thus detrimental. It should be noted that these reactions did not appear to have gone to completion within the standard three-day reaction time. Hence, ratios of products rather than yields are given.

The product distributions from reactions of chloramine-T catalyzed by **7** are markedly different to copper-catalyzed reactions of $ArSO_2N{=}IPh$ species,[3,6] in which competing amination is only very rarely observed, even with alkyl alkenes. In fact, the reactivity resembles much more closely that of Müller's rhodium-catalyzed reactions,[7,8] and we intend to pursue the mechanistic significance of this observation. Komatsu's group did not report results with simple alkyl alkenes,[12] so we are unable to make this comparison with their work.

In summary, the advantages of our new procedure for nitrene-transfer aziridination of aryl alkenes and amination of activated hydrocarbons are (i) that commercially available chloramine-T trihydrate can be used as the nitrene source *without prior dehydration or addition of molecular sieves* and (ii) that large excesses of hydrocarbon substrate are not required. Extension of this process to asymmetric aziridination and amination is underway.

Experimental Section

All reagents were from commercial sources. ^{1}H NMR spectra were recorded at 250 MHz in $CDCl_3$.

***N*-(2-Pyridinylmethylene)-1-pentanamine.**[17] *n*-Pentylamine (3.66 mL, 31.5 mmol) was added dropwise over 1 min to a stirred solution of pyridine-2-carboxaldehyde (3.0 mL, 31.5 mmol) in ether (10 mL) containing 4 Å molecular sieves (0.5 g) at 0 °C. The solution was left to stir overnight at ambient temperature before drying over anhydrous magnesium sulfate, filtration, and evaporation in vacuo to yield *N*-(2-pyridinylmethylene)-1-pentanamine (4.70 g, 83%). ^{1}H NMR δ 8.63 (m, 1H, Ar*H*), 8.35 (s, 1H, imine-*H*), 7.97 (m, 1H, Ar*H*), 7.72 (m, 1H, Ar*H*), 7.29 (m, 1H, Ar*H*), 3.65 (td, 2H, NCH_2), 1.71 (m, 2H, CH_2), 1.34 (m, 4H, 2 × CH_2), 0.90 (m, 3H, CH_3).

General Procedure for Aziridination and Amination. $(CuOTf)_2{\cdot}C_6H_6$ (46 mg, 0.09 mmol for 1.1 equiv of substrate, 10 mg, 0.02 mmol for 5 equiv of substrate) and *N*-(2-pyridinylmethylene)-1-pentanamine (19 mg, 0.1 mmol for 1.1 equiv of substrate, 4 mg, 0.02 mmol for 5 equiv of substrate) were added to acetonitrile (37 mL) in a Schlenk tube, using acetonitrile (2 × 1 mL) to aid transfer. The resulting yellow solution was stirred for 30 min under nitrogen. Chloramine-T trihydrate (510 mg, 1.8 mmol for 1.1 equiv of substrate, 113 mg, 0.4 mmol for 5 equiv of substrate) was added, aided with acetonitrile (1 mL). The resulting green solution was left stirring for a further 5 min before hydrocarbon substrate (2 mmol for 1.1 equiv of substrate, 2 mmol for 5 equiv of substrate) was added. The solution was stirred under nitrogen for 3 days. The resulting reaction mixture was quenched with 50% hexanes−ethyl acetate (25 mL) and filtered through a plug of silica gel (2.5 cm) and Celite 535 (0.5 cm). The silica gel was then washed with additional portions of 50% hexanes−ethyl acetate (3 × 25 mL), and the combined filtrates were concentrated in vacuo.

***N*-(*p*-Toluenesulfonyl)-2-phenylaziridine:**[3] ^{1}H NMR δ 7.86 (d, 2H, Ar*H*), 7.27 (m, 7H, Ar*H*), 3.77 (dd, 1H, C*H*Ph), 2.98 (d, 1H, *cis*-C*H*-aziridine), 2.43 (s, 3H, Ar-Me), 2.38 (d, 1H, *trans*-C*H*-aziridine).

***trans*-*N*-(*p*-Toluenesulfonyl)-2-methyl-3-phenylaziridine:**[3] ^{1}H NMR δ 7.82 (m, 2H, Ar*H*), 7.26−7.20 (m, 5H, Ar*H*), 7.13 (d, 2H, Ar*H*), 3.79 (d, 1H, C*H*Ph), 2.9 (dq, 1H, C*H*CH_3), 2.37 (s, 3H, ArCH_3), 1.83 (d, 3H, CH_3).

***N*-[(*p*-Toluenesulfonyl)amino]-1,2,3,4-tetrahydronaphthalen-1,2-imine:**[3] ^{1}H NMR δ 7.80 (m, 2H, Ar*H*), 7.28−7.01 (m, 6H, Ar*H*), 3.80 (d, 1H, C*H*-aziridine), 3.52 (d, 1H, C*H*-aziridine), 2.72 (dt, 1H, ArC*H*), 2.51 (dd, 1H, ArC*H*), 2.36 (s, 3H, ArCH_3), 2.21 (dd, 1H, CH_2CH), 1.62 (dt, 1H, CH_2CH).

***N*-(*p*-Toluenesulfonyl)-1-amino-2-cyclohexene:**[18] ^{1}H NMR δ 7.75 (m, 2H, Ar*H*), 7.30 (m, 2H, Ar*H*), 5.81 (m, 1H, C*H*=CH), 5.35 (m, 1H, CH=C*H*), 4.41 (m, 1H, N*H*), 3.80 (m, 1H, CH=CHC*H*NH), 2.43 (s, 3H, ArCH_3), 2.00 (m, 2H, CH_2CH), 1.85−1.40 (m, 4H, CH_2CH).

***N*-(*p*-Toluenesulfonyl)-1-amino-1,2,3,4-tetrahydronaphthalene:** ^{1}H NMR δ 7.81 (m, 2H, Ar*H*), 7.37−6.90 (m, 6H, Ar*H*), 5.30 (m, 1H, C*H*NH), 4.69 (d, 1H, N*H*, absent after D_2O shake), 3.10−1.45 (m, 6H, CH_2CH).

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