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Copper-catalyzed enantioselective aziridination of styrenes*

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Abstract: Studies regarding the copper-catalyzed enantioselective aziridination of styrenes with *N*-tosyloxycarbamates are presented. Catalyst, ligand, and reagent optimization will be discussed. Chiral aziridines were obtained in good yields and modest-to-good levels of stereochemical induction.

Keywords: aziridines; bisoxazoline; stereoselectivity; tosyloxycarbamates; Troc group.

Chiral aziridines are found in a variety of biologically active compounds [1]. They are also valuable chiral building blocks, as they undergo a variety of ring-opening reactions while keeping their stereochemical integrity [2]. Recently, aziridines were reported as masked 1,3-dipoles that react with alkenes, alkynes, nitriles, and carbonyl compounds to produce various [3 + 2] cycloadducts [3].

Synthetic strategies to access chiral aziridines [4] include ring-closing reactions of chiral precursors [5] and nucleophilic addition of metal carbenes or diazo compounds to imines [6]. Another attractive approach is the reaction of metal nitrenes with alkenes [7,8]. Iminoiodinanes are the most widely used metal nitrene precursors to perform stereoselective aziridination reactions. At the outset, the aziridination reactions were performed with preformed iminoiodinane such as TsN=IPh and NsN=IPh, but nowadays the more convenient procedure using iodosobenzene or iodobenzene diacetate to oxidize an amine reagent, generating in situ the corresponding iminoiodiane, is used [9]. Mansuy was the first to report the aziridination of alkenes with TsN=IPh and metallophorphyrin complexes to produce the corresponding aziridines [10]. These seminal publications were followed by development of asymmetric catalytic versions, using chiral metalloporphyrin [11]. Recently, Zhang showed that cobalt porphyrin complexes decomposed azide precursors into reactive metal nitrenes toward alkenes to give the corresponding aziridines with high enantioselectivity [12]. Evans and Jacobsen have concomitantly reported the first use of chiral copper complexes derived from bisoxazoline and salen ligand, respectively, as efficient catalysts for the aziridination of alkenes with TsN=IPh [13]. Improvement of the enantiomeric discrimation has been reported with novel copper complexes, in particular for cinnamate derivatives [14]. Finally, ruthenium [15] and rhodium [16] complexes have been also studied for the aziridination of alkenes with iminoiodinanes.

Despite the progress made in the last 30 years to perform enantioselective aziridination of alkenes, most systems are limited to the use of iminoiodinane precursors, which are strong oxidants and generate stoichiometric iodobenzene as a by-product. Moreover, most enantioselective aziridination reactions of alkenes produce aziridines protected with an *N*-tosyl group, which is notoriously difficult to remove. Only a few examples of sulfonyliminophenyl iodinane reagents have been reported as alternatives [17]. Novel precursors that produce aziridines with easily cleavable protecting groups appear thus highly desirable.

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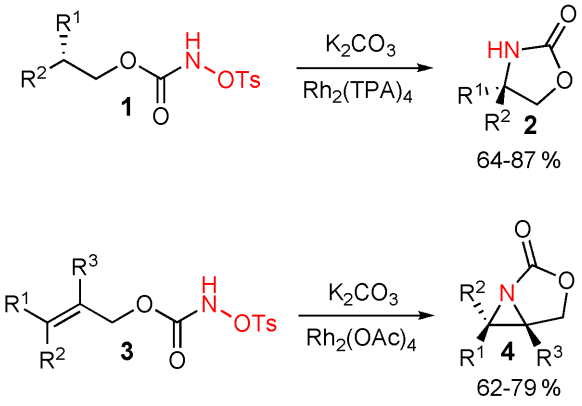
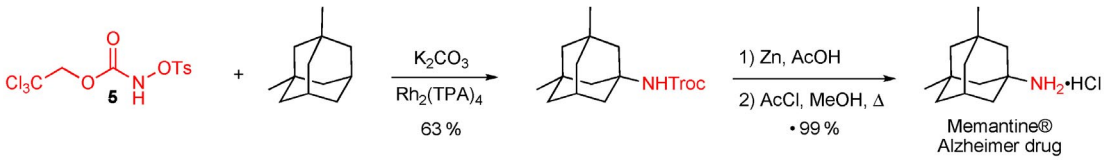
Our group has recently reported the use of *N*-tosyloxycarbamates as alternative precursors to produce metal nitrenes derived from rhodium and copper complexes which can undergo C–H insertion and aziridination reactions (Scheme 1) [18]. A variety of oxazolidinones **2** can be produced via rhodium-catalyzed intramolecular C–H insertion reactions from aliphatic *N*-tosyloxycarbamates **1** [19]. As *N*-tosyloxycarbamates are stable nitrogen precursors and are readily available, the reaction was easy to scale up and was run on a 50-mmol scale [20]. Intramolecular aziridinations were also achieved from allylic *N*-tosyloxycarbamates **3** [18].



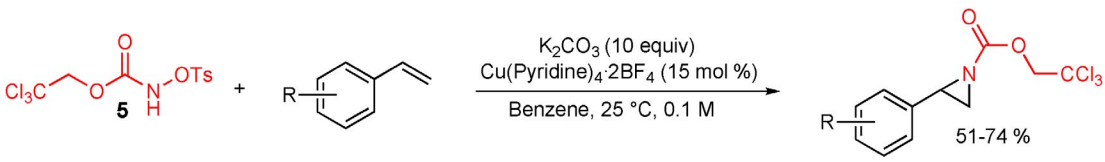
Scheme 1

2,2,2-Trichloroethyl-*N*-tosyloxycarbamate (**5**) was developed to perform *intermolecular* C–H insertion of alkanes [21]. This reagent leads to 2,2,2-trichloroethoxycarbonyl (Troc)-substituted amines, which are easy to deprotect to produce free amines in good yields [19]. Such a reaction was used for the synthesis of biologically active memantine (Scheme 2) [22].



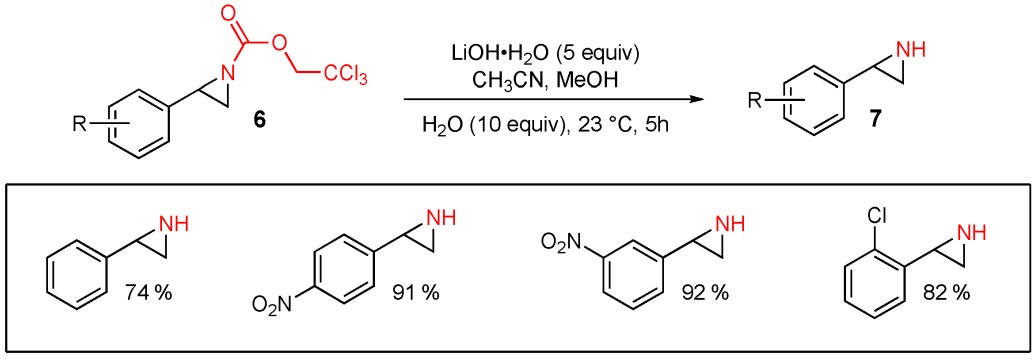
Scheme 2

We have also reported that copper(II) pyridine complexes catalyzed the aziridination of styrenes with 2,2,2-trichloroethyl-*N*-tosyloxycarbamate (**5**) to produce the corresponding Troc-protected aziridines in moderate yields (Scheme 3) [23].



Scheme 3

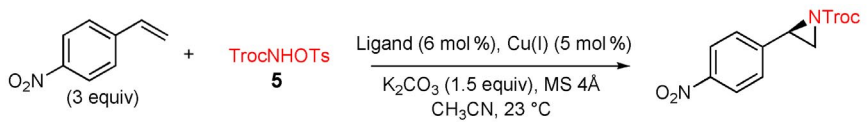
As mentioned above, one of the challenges for aziridination reactions is to produce aziridines containing a *N*-substituent easy to cleave. In contrast to what has been observed with *N*-tosyl aziridines, free aziridines **7** can be easily produced in good to excellent yields from *N*-Troc-aziridines **6** under mild basic reaction conditions without opening the aziridine moiety (Scheme 4) [23].

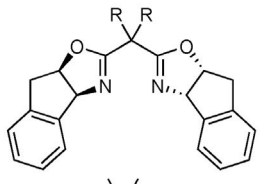
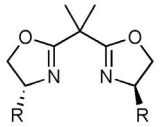
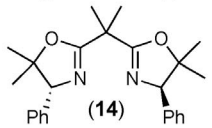


Scheme 4

We have recently studied chiral bisoxazoline copper(I) complexes [24] to catalyze enantioselective aziridination reactions with 2,2,2-trichloroethyl-*N*-tosyloxycarbamate **5** and styrenes (Table 1). Low levels of enantioselectivity were observed with indabox **8** and $CuSbF_6$ or Cu(OTf) (entries 1 and 2). Conversely, the use of $Cu(CH_3CN)_4PF_6$ produced the desired aziridine in 85 % yield with 46 % ee at 23 °C (entry 3). Lowering the temperature was detrimental for the yield and did not significantly improve the enantioselectivity (entry 4). The structure of the chiral ligand was then modified. Increasing the bite angle led to a decrease of enantioselectivity (entries 5 and 6).

Table 1 Copper-catalyzed enantioselective aziridination of 4-nitrostyrene with 2,2,2-trichloroethyl-*N*-tosyloxycarbamate **5**.



Entry	Ligand		Cu(I)	ee[a,b]
1		R = Me (**8**)	$CuSbF_6$	13 %
2		Me (**8**)	Cu(OTf)	17 %
3		Me (**8**)	$Cu(CH_3CN)_4PF_6$	46 % (85 %)
4		Me (**8**)	$Cu(CH_3CN)_4PF_6$	51 % (56 %)[c]
5		CH_2CH_2 (**9**)	$Cu(CH_3CN)_4PF_6$	38 %[c]
6		H (**10**)	$Cu(CH_3CN)_4PF_6$	15 % (54 %)
7		R = *i*-Pr (**11**)	$Cu(CH_3CN)_4PF_6$	45 %
8		*t*-Bu (**12**)	$Cu(CH_3CN)_4PF_6$	44 % (62 %)
9		Ph (**13**)	$Cu(CH_3CN)_4PF_6$	50 % (65 %)
10			Cu(OTf)	68 % (70 %)
11		(**14**)	**$Cu(CH_3CN)_4PF_6$**	**71 % (82 %)**
12			$Cu(CH_3CN)_4PF_6$	70 % (60 %)[c]

[a] Determined by HPLC with chiralcel-OD column. [b] Isolated yields in parentheses. [c] Reaction was run at 0 °C.

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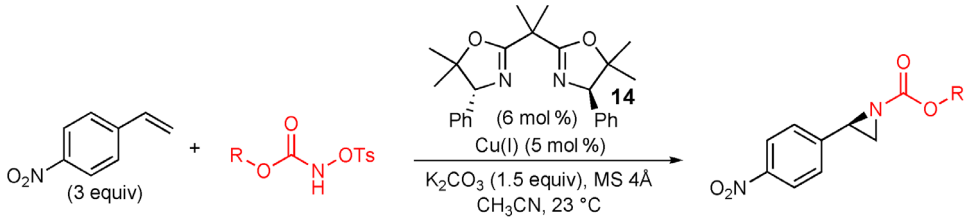
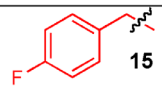
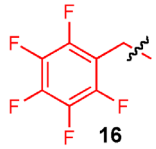
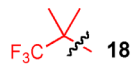
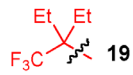
Bisoxazoline ligands derived from valine (**11**), *tert*-leucine (**12**), and phenylglycine (**13**) produced the desired aziridine with similar level of induction as achieved with indabox **8** (entries 7–9). However, *gem*-dimethyl-phenylglycine derived-bisoxazoline **14** produced a significant increase of the enantioselectivity, leading to the desired aziridine in 82 % yield and 71 % ee (entry 11). Again, there is no benefit in lowering the temperature of the reaction mixture.

The structure of the *N*-tosyloxycarbamate reagent was then studied (Table 2). We first postulated that the enantioselectivity could be improved by using a benzyl-substituted *N*-tosyloxycarbamate (**15**,**16**) through π-stacking interactions. However, derivatives **15** and **16** were less reactive and led to lower enantioselectivities (entries 1 and 2). The steric hindrance of the reagent was increased by adding substituents to the trichloroethyl moiety. Such a modification had a significant impact on the level of induction and 85 % ee was observed with *N*-tosyloxycarbamate **17**, but the reactivity was decreased (entry 3). The more reactive trifluoro derivative **18** was then prepared, but led to a lower level of induction even at 0 °C (entries 4 and 5). If the steric hindrance of the reagent is further increased, then the reagent becomes very unstable and decomposes before reacting, as shown with the *gem*-diethyl-trifluoroethyl reagent **19** (entry 6). The 1,1-dimethyl-2,2,2-trichloroethyl-*N*-tosyloxycarbamate **17** appears to be the best *N*-tosyloxycarbamate reagent so far to achieve a good level of stereochemical induction. A variety of additives were tested, but proved to be inefficient to significantly increase the enantiomeric excess or the yield.

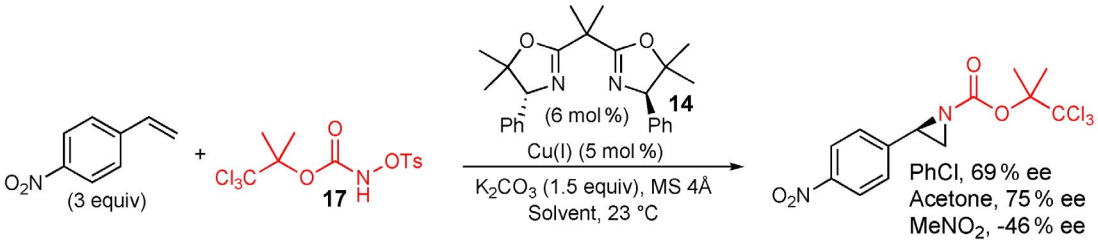
Table 2 Copper-catalyzed enantioselective aziridination of 4-nitrostyrene with various *N*-tosyloxycarbamates.



Entry	R	ee[a]	Yields[b]
1	 **15**	13 %	17 %
2	 **16**	20 %	46 %
3	 **17**	85 %	52 %
4	 **18**	71 %	82 %
5		82 %[c]	44 %[c]
6	 **19**	---	decomp

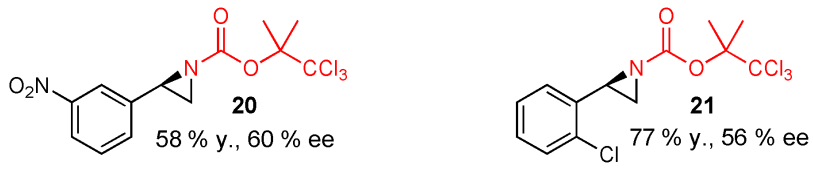
[a] Determined by HPLC with a chiral column. [b] Isolated yields. [c] Reaction was run at 0 °C.

Other solvents were also tested (Scheme 5). Chlorobenzene and acetone led to modest enantioselectivities, and only traces (<10 % conv.) of the desired product was observed. A reversal of the facial selectivity was observed using nitromethane, although the enantioselectivity remained modest. This effect is quite intriguing and will require further mechanistic investigation to be fully explained.



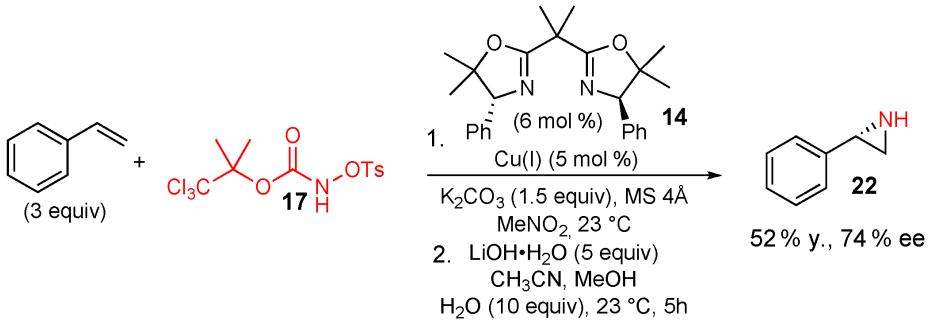
Scheme 5

Other styrene substrates were tested (Scheme 6). Although the yield was slightly improved, the corresponding aziridines **20** and **21** were obtained with a lower enantioselectivity.



Scheme 6

For styrene, the best result was obtained in nitromethane, which gives 74 % enantioselectivity for the production of the opposite enantiomer (Scheme 7). The *gem*-dimethyl-Troc group can be cleaved under the same reaction conditions as previously described and provided the unsubstituted aziridine **22** in 52 % yield over 2 steps.



Scheme 7

In conclusion, we have shown that 2,2,2-trichloroethyl-*N*-tosyloxycarbamate leads to Troc-protected aziridines, which can be easily deprotected. Moreover, a good level of stereochemical induction was observed for the aziridination of 4-nitrostyrene with a chiral bisoxazoline copper(I) complex and a

substituted *N*-tosyloxycarbamate. Work is in progress to further increase the yield and enantiomeric excess of such a process and to expand the scope of the reaction.

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