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Stereoselective Rhodium-Catalyzed Amination of Alkenes

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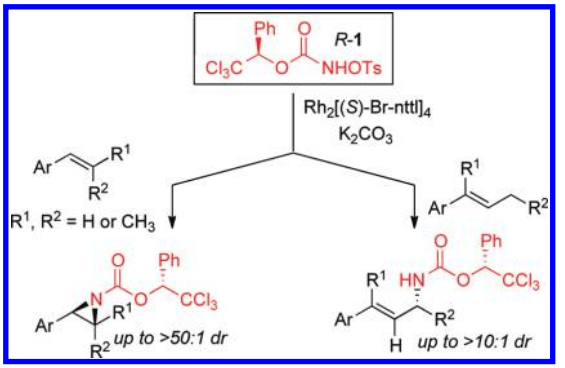
ABSTRACT



The first stereoselective rhodium-catalyzed intermolecular aziridination and C−H amination of alkenes to produce chiral carbamate-protected aziridines and allylic amines is described. Good yields and diastereoselectivities were achieved using a readily available chiral *N*-tosyloxycarbamate and stoichiometric amount of the alkene substrate. Furthermore the protecting group is easy to cleave under mild reaction conditions.

Nitrogen-containing molecules such as chiral amines are ubiquitous components of biologically active products.[1] As a result, numerous synthetic methods were developed to access these building blocks.[2] Aziridines are one of the smallest nitrogen-containing heterocycles which also display interesting biological activities.[3] Furthermore, they can undergo ring-opening reactions leading to a variety of amine products.[4] Typical methods to create C−N bonds involved functional group manipulations.[2] Novel methodologies to perform direct C−H amination or aziridination reactions of carbon frameworks have recently been described using metal-catalyzed nitrene transfer.[5] Metal nitrenes can be generated from azides,[6] haloamines,[5e,7] or, most frequently, iminoiodinanes.[8] Over the past decade,

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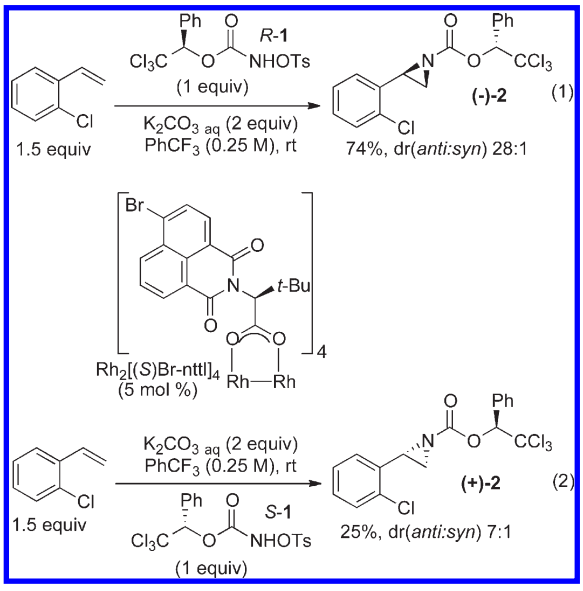
the use of iminoiodinanes has considerably progressed with the possibility of generating the active species *in situ* by oxidation of an amine reagent with a hypervalent iodine reagent.[9] Racemic aziridines were prepared using such a methodology with a broad scope of substrates in good to excellent yields.[10] Several asymmetric intermolecular aziridination reactions of alkenes with iminoiodinanes using chiral metal complexes have been reported, although the scope of substrates was rather limited.[11] Conversely, high stereoselectivities were achieved for a wide range of substrates, when azide reagents were used as metal nitrene precursors in the presence of chiral ruthenium[6b] and cobalt catalysts.[6e] A major drawback associated with these methodologies is the synthesis of the complex chiral ligand which required many steps. Furthermore, the existing methods produced *N*-sulfonyl aziridines that required harsh conditions to be cleaved, which are not compatible with sensitive products such as aryl aziridines.[12] The *N*-(trimethylsilylethylsulfonyl) group has been introduced to address this issue; however its cleavage required an excess of expensive TASF and proceeds only in 62−65% yield with arylaziridines.[13] As a result there is still a need for a general highly stereoselective method to produce protected aziridines that can be cleaved under mild reaction conditions. Herein, we report the use of a stable, readily available chiral *N*-tosyloxycarbamate as a metal nitrene precursor to perform stereoselective intermolecular amination of alkenes in the presence of a chiral rhodium catalyst.

Our group has reported the use of transition-metal-catalyzed decompositions of *N*-tosyloxycarbamates to perform C−H insertion and aziridination reactions.[14] A number of practical advantages are associated with these reagents: they are easy to prepare via tosylation of *N*-hydroxycarbamates; they can be stored at rt for up to 6 months, and thermogravimetric analysis showed decomposition only above 180 °C. The C−H insertion reaction is not sensitive to water or solvent purity, proceeds at room temperature, and is easily scaled up.[14e] An intermolecular version using trichloroethyl-*N*-tosyloxycarbamate was developed which allowed the amination of alkanes and the aziridination of styrenes in good yields, producing respectively Troc-protected amines and aziridines.[14b,c] We have recently reported an asymmetric copper-catalyzed aziridination of styrenes with a more hindered *N*-tosyloxycarbamate (1,1-dimethyl-2,2,2-trichloroethyl-*N*-tosyloxycarbamate) that proceeded with only moderate levels of enantioselectivities.[14f] A solution to this ongoing problem might reside in the use of a chiral *N*-tosyloxycarbamate, in which inherent chirality would allow for double stereodifferentiation.[15] We thus prepared both enantiomers of 1-phenyl-2,2,2-trichloroethyl-*N*-tosyloxycarbamate ((±)-**1**) from the corresponding readily available chiral alcohol.[16]



The aziridination of 2-chlorostyrene was then tested in the presence of various amino acid derived chiral rhodium dimers.[17,18] The best results were obtained with Rh_2[(*S*)-Br-nttl]$_4$,[19,20] which provided the corresponding aziridine (−)-**2** in 74% yield and 28:1 dr for the matched case (eq 1).

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(12) Desulfonylation by metal reduction was reported to produce 2-phenylaziridine, although this reaction was either contaminated with ring-opened product or proceeded in low yield (40%). For further details, see: Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455–9461.

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(15) Such a strategy has been previously reported by Dodd and Dauban using a chiral sulfonimidamide (prepared in 23% yield via fractional recrystallization of diastereomers) for rhodium-catalyzed benzylic and allylic C−H insertion reactions; see: Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343. The scope was however limited when similar chiral sulfonimidamides were used in aziridination reactions. If acrylate substrates produced the desired aziridine with 94% de, for styrene, only 65% de was obtained. See ref 11d and 11e for details.

(16) (*R*)-1-Phenyl-2,2,2-trichloroethanol was readily produced in 94% yield and 95% ee on 50 mmol scale via catalytic CBS-reduction, according to literature procedure: Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. See Supporting Information for details.

(17) See Supporting Information for details.

(18) When the reaction was performed with an achiral catalyst (for instance [Rh_2(Oct)$_4$]), less than 20% conversion of a 1:1 mixture of diastereomers was obtained.

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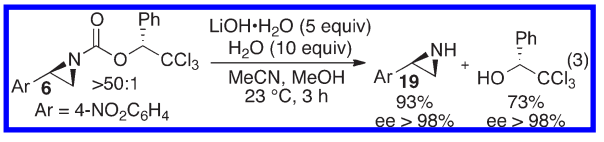
(20) The effect of the nitrogen protecting group was less important than the size of the R group, which is in sharp contrast with results recently obtained in cyclopropanation reactions with the same catalysts and diazo compounds. Our results suggested that the *C*2 or *D*2 symmetry would be the catalyst's reactive conformation. See: (a) Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383. (b) DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 7230. (c) Hansen, J.; Davies, H. M. L. *Coord. Chem. Rev.* **2008**, *252*, 545.

Lower yields and diastereoselectivities were obtained with the other enantiomer of the Ph-TrocNHOTs (**1**) (eq 2).[21]

After optimizing the reaction conditions, aziridine **2** was produced in 84% yield and 30:1 dr using 1 equiv of alkene and 1.2 equiv of Ph-TrocNHOTs (Table 1, entry 1). In contrast to existing procedures, the reaction is not sensitive to either water or air and is run at room temperature for only 90 min.[22] The potassium tosylate byproduct is removed by a simple filtration using Celite. Other 2-halostyrenes produced the corresponding aziridine in good yields and a high level of diastereoselectivity (entries 2–3). The functional group compatibility with the halide substituent is excellent, as no side reaction (such as a substitution reaction) was observed. As a result, further functionalization of the aziridine products would be possible using cross-coupling reactions. The aziridine products are highly crystalline materials, and an X-ray crystal structure was obtained for aziridine **4** to confirm the absolute stereochemistry.[17]

Only moderate dr was observed with an electron-donating group in the *ortho* position. For instance 5.5:1 diastereoselectivity was obtained for the aziridine derived from 2-methylstyrene (entry 4). Conversely, a good level of stereoinduction was observed with *para*-substituted styrenes (entries 5–9). It was possible to get a single diastereomer by simple trituration in hexanes (entry 6). Good to excellent diastereoselectivites were obtained with 2,4-disubstituted styrenes (entries 10–12) as well as with 2,5- and 2,3-disubstituted styrenes (entries 13–15). Whereas 3,4-disubstituted styrenes led to 7:1–9:1 dr (entries 16–17), quite surprisingly, a low level of stereoinduction was obtained with *meta*-substituted styrenes. For instance the 3-bromostyrene provided the desired aziridine in only a 2.8:1 dr (entry 18). Additional mechanistic studies are necessary to explain this latter substituent's effect with regards to dr.

Besides the mild reaction conditions and the simplicity of the purification procedure, another advantage associated with this method is to produce Ph-Troc-protected aziridines. Such a protecting group is easy to cleave under basic conditions.[14c] When aziridine **6** was submitted to lithium hydroxide in a biphasic media, free aziridine **19** was obtained in 93% yield without a ring-opening side reaction; the corresponding chiral alcohol can also be recovered in 73% yield without racemization (eq 3).

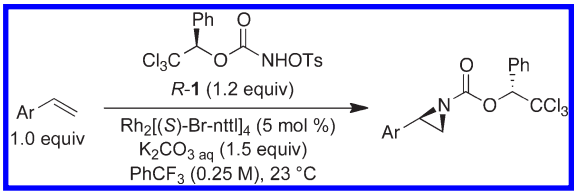


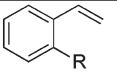
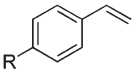
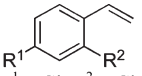
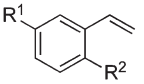
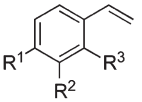
The aziridination of more substituted double bonds is quite challenging, as the allylic amination becomes a competitive pathway. We were pleased to find that the rhodium-catalyzed aziridination of *trans*-β-methylstyrene with *R*-**1** proceeded with an exquisite level of chemoselectivity and stereospecificity, producing exclusively the *trans*-aziridine **20** with a 17:1 dr (eq 4). The reaction of

(21) If 2 equiv of (±)-**1** and 1 equiv of alkene are used, the aziridine is isolated with 88% ee, indicating a kinetic resolution.

(22) Typical asymmetric aziridination reactions are run for more than 12 h, often at low temperature; see refs 6b, 6e, 11d, and 11e.

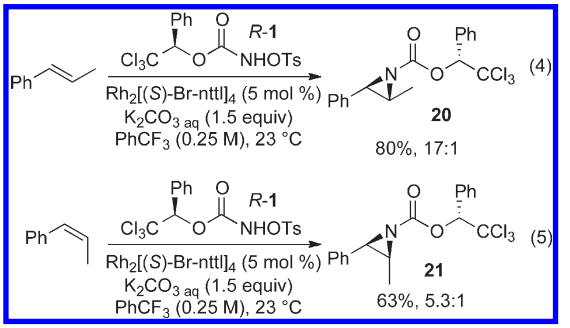
Table 1. Rhodium-Catalyzed Intermolecular Aziridination of Styrenes with *R*-**1**



entry	alkene	yield (%)[a]	dr[b]
			
1	R = Cl	(**2**) 84	30:1
2	R = Br	(**3**) 78	33:1
3	R = I	(**4**) 77	>50:1
4	R = Me	(**5**) 72	5.5:1
			
5	R = NO_2	(**6**) 75	8.5:1
6	R = NO_2	(**6**) 63[c]	>50:1[c]
7	R = Cl	(**7**) 76	8.0:1
8	R = Br	(**8**) 77	12:1
9	R = CF_3	(**9**) 74	8.0:1
			
10	R^1 = Cl, R^2 = Cl	(**10**) 85	25:1
11	R^1 = F, R^2 = Me	(**11**) 72	8.5:1
12	R^1 = Me, R^2 = Br	(**12**) 79	25:1
			
13	R^1 = Cl, R^2 = Cl	(**13**) 52	14:1
14	R^1 = Cl, R^2 = NO_2	(**14**) 51[d]	30:1[d]
			
15	R^1 = H, R^2 = Cl, R^3 = Cl	(**15**) 77	14:1
16	R^1 = Cl, R^2 = Cl, R^3 = H	(**16**) 82	7.0:1
17	R^1 = Br, R^2 = NO_2, R^3 = H	(**17**) 63[d]	9.0:1[d]
18	R^1 = H, R^2 = Br, R^3 = H	(**18**) 66[d]	2.8:1[e]

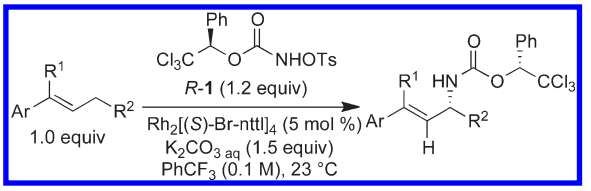
[a] Isolated yield by flash chromatography; aziridine products. [b] Determined by HPLC. [c] After trituration in hexanes using 1.5 equiv of alkene and 1.0 equiv of *R*-**1**. [d] 1.5 equiv of alkene and 1.0 equiv of *R*-**1**. [e] Determined by ^{1}H NMR.

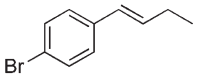
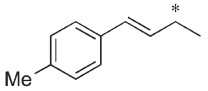
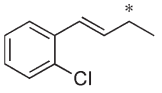
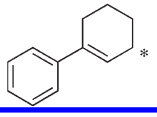
cis-β-methylstyrene also exclusively provided aziridine **21**, albeit in moderate dr (eq 5). It should be however noted that no isomerization from *cis* to *trans* product was observed suggesting that the aziridination reaction is concerted, presumably involving a singlet rhodium nitrene species.



Other substituted *Z*-alkenes, such as indene, 1,2-dihydronaphthalene, and *Z*-β-ethylstyrene also provided exclusively the desired aziridines in 30−52% yields but as a 1:1 mixture of diastereomers. In sharp contrast, more substituted *E*-alkenes lead to the corresponding C−H amination reaction (Table 2). Allylic amination products were obtained from *E*-β-ethylstyrenes in moderate yields and good diastereoselectivities (entries 1−3).

Table 2. Rhodium-Catalyzed Intermolecular Allylic Amination of Aromatic *E*-Alkenes with *R*-**1**

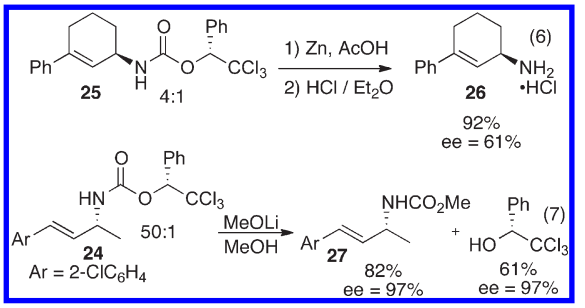


entry	alkene	yield (%)[a]	dr[b]
1		(**22**) 56	9.0:1
2		(**23**) 58	11:1
3		(**24**) 66	8.0:1
4		(**24**) 43[c]	>50:1[c]
5		(**25**) 69	4.0:1

[a] Isolated yield by flash chromatography; amination products. [b] Determined by HPLC. [c] Separation of diastereomers by flash chromatography.

The absolute stereochemistry was also established for product **22** via an X-ray crystal structure. The diastereomeric ratio could be enhanced by simple purification on silica gel leading to **24** in 43% yield with >50:1 dr (entry 4). 2-Phenylcyclohexene, a trisubstituted alkene was also reacted chemoselectively to produce the less hindered amine in good yields with a moderate diastereoselectivity (entry 5). To our knowledge this is the first time that such a switch of reactivity was observed for *Z*-alkenes vs *E*-alkenes in aziridination reactions.[23]

It is possible to easily cleave the Ph-Troc protecting group under standard reaction conditions using zinc in acetic acid.[14d] The corresponding allylic amine•HCl **26** was isolated in 92% yield without racemization (eq 6). If the recovery of the chiral alcohol is necessary, this is possible via carbamate exchange. Treating the Ph-Troc allylic amine **24** with lithium methoxide in methanol produced the methylcarbamate **27**[24] and the chiral alcohol in 82% and 61% yield respectively and 97% ee (eq 7).



In conclusion, a high level of stereoselection was obtained for rhodium-catalyzed amination and aziridination of alkenes using *R*-1-phenyl-2,2,2-trichloroethyl-*N*-tosyloxycarbamate (*R*-**1**) as a chiral reagent. Such a reagent is readily available on gram scale via a catalytic asymmetric reduction and is bench stable for up to 6 months. Carbamate-protected aziridines and amines were produced in good yields. No excess of starting material is required, and no extra oxidant needs to be added. Furthermore, it is possible to easily cleave the Ph-Troc protecting group to recover the free aziridine or amine in high yields without degradation.

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

(23) In electrophilic reactions, *E*-alkenes are known to be more hindered, thus less reactive than *Z*-alkenes. It might explain why the allylic C−H bond become more reactive with *E*-alkenes. Further studies will need to be pursued to fully explain these results.

(24) A few methods have previously reported to cleave allylic methylcarbamates without racemization; see: (a) Kresze, G.; Muensterer, H. *J. Org. Chem.* **1983**, *48*, 3561. (b) Wei, Z. Y.; Knaus, E. E. *J. Org. Chem.* **1993**, *58*, 1586.