Iridium-Catalyzed Isomerization of *N*-Sulfonyl Aziridines to Allyl Amines.

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Supporting Information Placeholder

ABSTRACT: The iridium-catalyzed isomerization of *N*-sulfonyl 2,2-disubstituted aziridines to *N*-sulfonyl allyl amines is described. The selectivity of allyl amine vs imine is very high (up to 99/1). The isomerization is catalyzed by the readily available Crabtree's reagent and takes place in mild conditions without activation of the catalyst by hydrogen. The mechanism of this unprecedented transformation has been studied by theoretical calculations. The catalytic species is formed by a loss of the pyridine ligand. All intermediates and transition states of the catalytic cycle have been characterized.

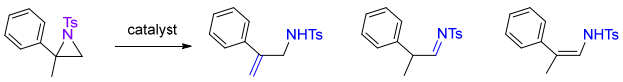
Isomerization processes such as thermal rearrangements and catalytic isomerizations are of great synthetic interest due to their perfect atom economy, being ideal transformations from the point of view of sustainability.[1] Terminal olefins,[2] allylic amines[3] and allylic alcohols[4] are the most common substrates for catalytic isomerization reactions using metal complexes.[5] Epoxides are also excellent substrates for isomerization. The rearrangement of epoxides to carbonyls, often referred to as the Meinwald rearrangement,[6] can be promoted by Lewis acids such as $BF_3{\cdot}Et_2O$, lithium salts or iridium chloride.[7] More recently, Mazet and co-workers uncovered the use of Pd and Ir hydride complexes as efficient catalysts for the isomerization of epoxides.[8,9] In spite of these precedents, the aza-version of the Meinwald rearrangement has received little attention.[10] In 2002, Nakayama et al. described the BF_3-promoted aza-pinacol rearrangement of various *N*-tosyl aziridines to give the corresponding *N*-tosyl imines.[11] Later on, in 2003, Ney and co-workers reported a palladium-catalyzed isomerization of monosubstituted *N*-tosyl aziridines to sulfonyl ketimines.[12]

The ring strain, the facility of preparation, and the utility of the potential products make aziridines the ideal substrates to study new catalytic isomerization reactions. Here we describe the isomerization of 2,2-disubstituted *N*-sulfonyl aziridines to allylic amines catalyzed by iridium catalysts. The process provides an efficient synthetic strategy for the preparation of many valuable compounds since allyl amines are versatile intermediates[13] in addition to being fragments of several biologically active compounds.[14,15]

We selected 2-methyl-2-phenyl-1-tosylaziridine **1a**, as model substrate since it can be easily prepared from acetophenone by simple Wittig olefination and subsequent aziridination. Aziridine **1a** can, in principle, isomerize to allyl amine **2a**, to imine **3a**, in a similar way to the Meinwald rearrangement of epoxides, or to enamine **4a** (Table 1)**.**

We started with the common catalysts used in the Meinwald rearrangement namely $BF_3{\cdot}Et_2O$ and $IrCl_3$. In both cases, a 1:1 mixture of allyl amine (**2a**) and imine (**3a**) was obtained in moderate yield (Table 1, entries 1, 2). In our efforts to promote the reaction selectively, our next attempt involved the use of Crabtree's catalyst **5a** (PF_6 salt).[16] This commercial Ir-P,N complex is a well-known hydrogenation catalyst.[17] The CH_2Cl_2 solution of the catalyst was activated by hydrogenation for few minutes as described for allylic alcohols.[4f,g] Allylic amine was obtained in good selectivity respect to the imine (6:1) after 3 h of reaction, using only 1 mol % of **5a** (Table 1, entry 3). The reaction was performed in a glove-box to avoid the formation of substantial amounts of *N*-tosyl-1-amino-2-phenylpropan-2-ol caused by aziridine ring-opening by moisture. Of note, enamine **4a** was not detected. We further improved the yield and selectivity using Pfaltz's version of Crabtree's catalyst (**5b,** BAr^F salt)[18] (entry 4) and toluene as a solvent (entry 5).

Table 1. Optimization of the isomerization of **1a**. The reactions were performed in a sealed vial, using 0.34 mmol of **1a** in CH_2Cl_2 [0.25 M], at room temperature



1a **2a** **3a** **4a**

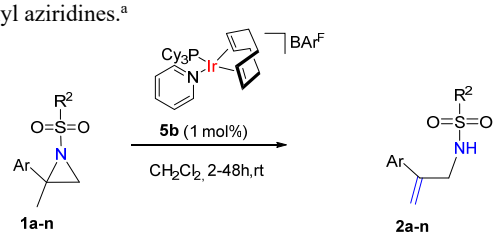
	Conditions	Yield (%)[b]	Isomer ratio 2a:3a:4a[a]
1	10 mol % $BF_3{\cdot}Et_2O$, 10 min	43	1:1:0
2	5 mol % $IrCl_3{\cdot}xH_2O$, 3 h	40	1:1:0
3[c]	1 mol % **5a**,[e] 3 h, H_2 activation	71	6:1:0
4[c]	1 mol % **5b,**[f] 3 h, H_2 activation	76	10:1:0
5[c,d]	1 mol %, **5b**,[f] 3 h, H_2 activation	81	95:5:0
6	1 mol % **5b**,[f] 3 h, no activation	85	99:1:0

[a] Measured by ^{1}H NMR. [b] Isolated yield of **2a**. [c]The reaction was carried out in a pressure tube and prepared in a glove-box, charged with 1 bar

of H_2 and then degassed (x3) with N_2. [d]Toluene was used as solvent. [e][Ir(cod)(PCy_3)(Py)]PF_6 (**5a**). [f][Ir(cod)(PCy_3)(Py)] BAr^F (**5b**).

Unexpectedly, during the optimization, control experiments revealed that the isomerization proceeded even without H_2-activation of the catalyst. Stirring the CH_2Cl_2 solution of aziridine **1a** with catalyst **5b** at room temperature allowed the isomerization to allyl amine **2a** with complete regioselectivity and excellent yield (entry 6). Moreover, the use of the glove-box was no longer necessary. To the best of our knowledge, this is the first example in which Crabtree's catalyst has been used without activation either by hydrogen or temperature. These conditions are much simpler in terms of practicality and scalability than the ones that involve activation of the catalyst.

Table 2. Scope of the iridium-catalyzed isomerization of *N*-sulfonyl aziridines.[a]

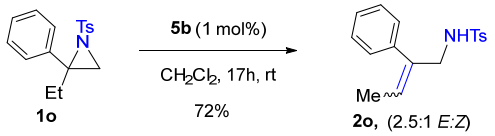


Entry		Ar	R^2	Conv. (**2**:**3**)[b]	Yield (%)[c]
1	1a	Ph	*p*-Tol	>99 (99:1)	87[g]
2[d]	1b	*p*-Cl-Ph	*p*-Tol	>99 (91:9)	82
3[e]	1c	*m*-Cl-Ph	*p*-Tol	>99 (98:2)	80
4[e]	1d	*o*-Cl-Ph	*p*-Tol	>99 (87:13)	68
5	1e	*p*-MePh	*p*-Tol	>99 (92:8)	76
6	1f	2-naphthyl	*p*-Tol	>99 (98:2)	79
7	1g	*o*-MeO-Ph	*p*-Tol	>99 (81:19)	72
8	1h	*p*-F-Ph	*p*-Tol	>99 (93:7)	79
9	1i	*m*-F-Ph	*p*-Tol	>99 (97:3)	82
10[e]	1j	*p*-CF_3-Ph	*p*-Tol	>99 (93:7)	67
11[e]	1k	*p*-NO_2-Ph	*p*-Tol	>99 (90:10)	69
12[e]	1l	*p*-I-Ph	^{i}Pr	>99 (96:4)	82
13[d]	1m	*p*-Br-Ph	^{i}Pr	>99 (98:2)	78
14[d]	1n	Ph	Me	>99 (99:1)	96

[a] The reaction was performed in a sealed vial, using 0.33 mmol of substrate. [b]Determined by ^{1}H NMR. [c]Isolated yield after column chromatography. [d] 3 mol % of **5b** was used. [e]The reaction was carried out using 3 mol% of **5b** and heating up to 40 ºC.[g]1 gram of **1a** and 0.5 mol% of **5b** were used.

To test the scope of the reaction a collection of 2-aryl-2-methyl *N*-sulfonyl aziridines were treated with catalyst **5b** under the optimal conditions. Without activation of the catalyst, aziridines **1a-n** transposed selectively to the allyl amines **2a-n** in good yields (Table 2). Electron-donating (EDG) and electron-withdrawing (EWG) groups in the aryl ring were well tolerated although the reactivity of aziridines with the EWGs was clearly lower. Harsher reaction conditions (3% catalyst loading) were required in some cases (Table 2, entries 2, 13 and 14). For stronger EWG (entries 3, and 10-12), in addition, the temperature was increased to 40ºC. The reaction took place in a similar manner when the p-toluenesulfonyl group was replaced by propanesulfonyl or methanesulfonyl (entries 12, 13 and 14, respectively).

To further expand the scope of this transformation the methyl substituent in the aziridine was also modified. When the methyl was replaced by ethyl the reaction took place affording a mixture of *E*- and *Z*-allyl amines **2o** (Scheme 1)**.** When the methyl was replaced by phenyl, the β-elimination could not be achieved so the corresponding enamine (**2p)** was obtained instead (see SI).



Scheme 1. Isomerization of *N*-tosyl 2-ethyl-2-phenyl aziridine (**1o**)

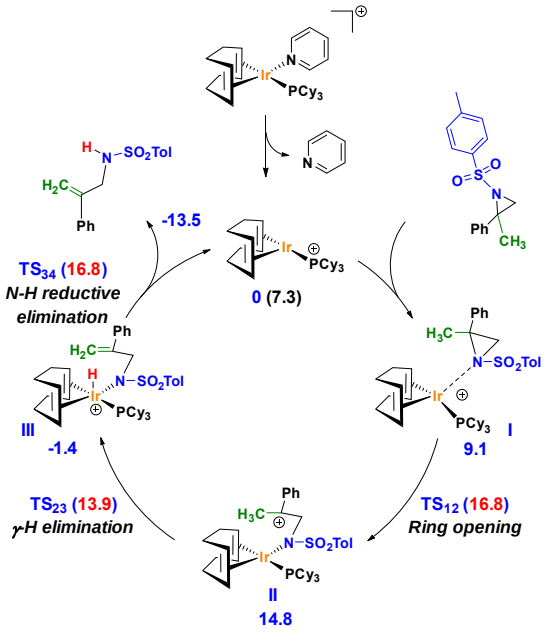
The synthetic applications of these allylic amines are numerous. Simple replacement of the tosyl group by a methyl in **2a** and **2o** afforded compounds that have been reported to be precursors of several potent herbicides[14] (see SI). Some propargyl derivatives of **2a** showed activity against monoamine oxidases, which are involved in the Parkinson's disease (PD).[15] Moreover, the rich chemistry of the allyl amines can be applied to the synthesis of azepanes, 3-pyrrolidin-2-ones and 2,5-dihydropirroles among others.[13]

The novelty of the transformation led us to perform a mechanistic study. First, given that the catalyst was used without activation by hydrogen, we sought to determine the real catalytic species involved. Of the three ligands of Crabtree's catalyst we hypothesized that pyridine would be the most labile. To test this notion, we added deuterated pyridine to a solution of **5b** in CD_2Cl_2. The signals of the free pyridine were easily detected by ^{1}H NMR (see SI). DFT calculations also confirmed that pyridine was the most labile ligand. In this regard, the calculated ΔG of dissociation in dichloromethane for the three ligands was 7.3 kcal mol^{-1} (py), 21.2 kcal mol^{-1} (PCy_3) and 34.5 kcal mol^{-1} (cod) (B3LYP-D3 calculations, see SI). In a second experiment, pyridine was added to a solution of **1a** and 5 mol % of **5b** in CD_2Cl_2 In this case, the reaction did not occur thereby indicating that the catalyst was fully inactivated by the excess of pyridine. Therefore, $[Ir(PCy3)(cod)]^+$, which is generated with a low energy cost, was identified as the catalytically active species.

The DFT study of the reaction mechanism indicated that it starts by approaching aziridine **1a** to this unsaturated species, leading to intermediate **I** (Scheme 2). In this initial species aziridine was not coordinated to the iridium center (Ir···N = 3.28 Å), thereby revealing the low donating capacity of the *N*-aziridine lone pair. Starting from intermediate **I,** aziridine ring opening followed by metal-assisted tautomerization was expected to yield the product. Ring–opening occurred from I with a low barrier of 9.5 kcal mol^{-1} (**TS$_{12}$,** 16.8 kcal mol^{-1}, Scheme 2) and gave rise to the carbocation intermediate **II**. In addition to the breaking of the N-C bond of the ring, this step also involved coordination of the *N*-aziridine to the Ir. We used a localized orbital approach to analyze the electronic rearrangements in the ring-opening step (see SI).[19] This analysis showed the movement of the N-C bonding pair toward the nitrogen, concomitant with the formation of a Ir-N bond from the N lone pair, with a positive charge remaining in C_α. It also showed that the phenyl substituent at C_β stabilizes the carbocation thus playing a key role in the ring-opening step, Accordingly, in **II** the C_β-C_{Ph} bond had a partial character of double bond (C_β-C_{Ph} = 1.43 Å). Indeed, for the 2,3-Me,Ph disubstituted aziridine intermediate **II** was found at 23.4 kcal mol^{-1}, largely above the 14.8 kcal mol^{-1} of the 2,2-disubstituted substrate.

The metal-mediated tautomerization that occurred after ring-opening could yield three different products (Table 1), depending

on the hydrogen that migrates. Migration from a C_γ-H (those in the Me substituent) to the nitrogen gave the allyl amine, while migration of C_α-H led to the imine or the enamine. In **II,** a C_γ-H bond, placed above the Ir, was involved in an agostic interaction with the metal (Ir···H-C_γ = 2.18 Å). This agostic C_γ-H bond was already activated (1.15 Å) for the γ-H elimination, which was practically barrierless (**TS_{23},** 13.9 kcal mol^{-1}, Figure 1).[20] The readiness of the C_γ-H bond **II** to participate in the H elimination step accounts for the selectivity toward the allyl amine product.



Scheme 2. DFT computed mechanism (B3LYP-D3 in CH_2Cl_2) for the isomerization of aziridine **1a** to allyl amine **2a**; the numbers are relative Gibbs energies in kcal mol^{-1}, taking as zero-energy the separated catalytically active species [Ir(PCy3)(cod)]+ and aziridine substrate **1a**. Relative energies of transition states are indicated in red.

The γ-H elimination step led to a notably stable amido hydride intermediate **III** (-1.4 kcal mol^{-1}, Scheme 2). In the final step of the isomerization N-H reductive elimination from **III** (**TS_{34},** 16.8 kcal mol^{-1}, Figure 1) formed the N-H bond and released the allyl amine product **3a**. The reductive elimination of the N-H bond entailed the highest barrier along the catalytic cycle (18.2 kcal mol^{-1}). Computational studies of homogenous reductive elimination of N-H bonds are much more scarce that those of C-H bonds.[21] Our transition state for this step has an interesting feature in that it can be described as an ion-pair, in which the aziridine nitrogen is completely dissociated (Ir···N = 3.12 Å) and ready to pick-up a proton from the cationic iridium moiety. Finally, the replacement of the allyl amine product by a reactant molecule closed the catalytic cycle.

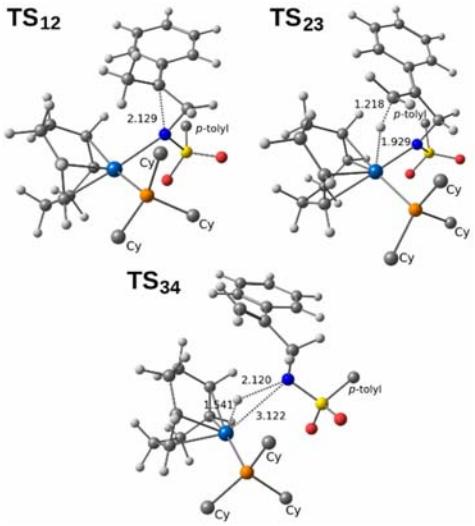


Figure 1. Optimized geometries for: ring opening, **TS_{12}**, γ-H elimination, **TS_{23}** and N-H reductive elimination, **TS_{34}**. The most important distances are also reported.

In summary, here we have described the selective isomerization of *N*-sulfonyl 2,2-disubstituted aziridines to *N*-sulfonyl allyl amines using the readily available Crabtree's catalyst. Of note, activation with hydrogen was not required and the reaction was performed in mild conditions and with low catalyst loading (usually 1 mol %). The catalytic species as well as a detailed reaction mechanism were studied by DFT-calculations. This novel transformation provides a new strategy for the synthesis of complex amines.

ASSOCIATED CONTENT

Supporting Information

Characterization of all new compounds. NMR experiments. Experimental and computational details. Energy profiles, cartesian coordinates and energies of all optimized structures.

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Author Contributions

A.C. did the experimental work. G.S. and G. U. perform the theoretical calculations. X.V. A.L. and A. R. directed the work and wrote the article.

Notes

The authors declare no competing financial interests.

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(20) **TS_{23}** is optimized as a transition state in the potential energy surface, but it is placed slightly above intermediate **II** when thermal and entropic corrections are added to build up the Gibbs energy profile.

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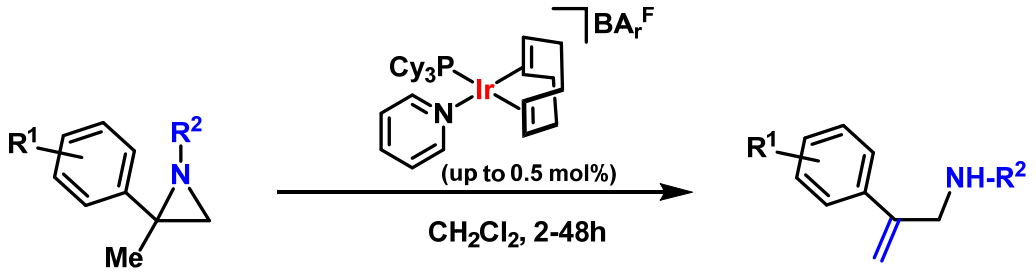
SYNOPSIS TOC



R^2=Ts,Ms,SO_2iPr

67-96% yield
(up to 99% selectivity)

- ✔ Novel catalytic application of Crabtree's catalyst.
- ✔ No activation needed; mild conditions
- ✔ Gram scale
- ✔ Air moisture-tolerant
- ✔ Theoretical mechanistic study

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