Nucleophilic Rh\textsuperscript{1} Catalyzed Selective Isomerization of Terminal Aziridines to Enamides

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The selective isomerization of various terminal N-8oc protected aziridines to enamides was realized using the highly reactive nucleophilic rhodium catalyst C with the Lewis acid LiNTf\textsubscript{2} as co-catalyst under moderate conditions. The reaction proceeds smoothly with only 1 mol\% catalyst loading and excellent yields were achieved. An intermediate containing an enamide with a non-conjugated terminal C=C double bond was detected during the course of the reaction, which isomerizes to form the thermodynamically favored 2-amido styrene. Mechanistic insight is gained based on these observations.

Catalytic isomerizations of small molecules are of great importance for synthetic chemistry due to the ready availability of the substrates and the ideal atom economy of the transformation. The isomerization of epoxides, known as the Meinwald rearrangement, is an efficient method for the conversion of epoxides to carbonyl compounds, such as aldehydes and methyl ketones, which is catalyzed by Lewis acids to obtain aldehydes\textsuperscript{[1]} and promoted by Lewis acids with nucleophilic catalysts to yield methyl ketones.\textsuperscript{[2]} Recently, our group has realized the chemo- and regioselective isomerization of a diverse range of epoxides including the challenging \( \alpha \)-aryl oxiranes, with the highly nucleophilic rhodium bis(NHC) pincer catalysts A-C to obtain almost exclusively methyl ketones in excellent yields under very mild conditions.\textsuperscript{[3b-d,e]} Aziridines, the analogue of epoxides, are quite useful building blocks in both organic and pharmaceutical chemistry.\textsuperscript{[3]} The most popular reaction for an aziridine transformation is the generation of \( \beta \)-lactams catalyzed by transition-metal complexes under the exposure of carbon monoxide.\textsuperscript{[4]} Most recently, the ring opening of aziridines was well-studied and it behaves as an effective pathway to gain \( \beta \)-functionalyzed amines which can easily be transformed further.\textsuperscript{[5]}

However, the isomerization of aziridines has been rarely investigated. In 2002, the Nakayama group reported a Lewis acid catalyzed aza-pinacol rearrangement of various N-tosyl aziridines to N-tosyl imines with BF\textsubscript{3}.\textsuperscript{[6]} One year later, the Wolfe group introduced the palladium-catalyzed isomerization of terminal N-tosyl aziridines to sulfonyl ketimines (Scheme 1, (a)).\textsuperscript{[7]} Recently, Lledós, Riera and co-workers described an iridium-catalyzed isomerization of geminal disubstituted N-sulfonyl aziridines to allyl amines (Scheme 1, (b)).\textsuperscript{[8]}

The potential products of the aziridine isomerization are manifold, such as the mentioned N-tosyl imines and allyl amines. Another kind of products expected are enamides which are valuable substrates for the asymmetric hydrogenation to gain access to optically pure amines.\textsuperscript{[9]} Common methods to generate enamides usually include reacting ketones with amines\textsuperscript{[10]} or applying its derivatives such as vinyl halides, triflates and tosylates with amines through transition-metal catalyzed cross-coupling reactions.\textsuperscript{[11]} Recently, the Beller group described the Pd-catalyzed carbylation reaction of imines to enamides.\textsuperscript{[12]}

Herein, we provide an alternative synthetic strategy for the preparation of various enamides via the selective isomerization of terminal aziridines catalyzed by highly nucleophilic rhodium catalysts (Scheme 1, (c)).

The synthesis of the aziridine candidates usually started from commercially available phenylalanine derivatives. They were reduced firstly with NaBH\textsubscript{4} as the reducing agent and I\textsubscript{2} as the catalyst to obtain the corresponding amino alcohols in

![Scheme 1. Isomerization of terminal aziridines with transition-metal complexes.](image-url)
almost quantitative yields.\textsuperscript{[13]} Afterward, the amino substituent of the amino alcohols was protected with the respective protecting group.\textsuperscript{[26]} The last step was a one pot reaction that consisted of converting the hydroxyl group into a better leaving group by tosylation and the ring closure with the strong base KOH in refluxing THF.\textsuperscript{[23]} All desired terminal aziridines were generated in moderate to good yields.

With the successfully prepared terminal aziridines, different protecting groups on the nitrogen atom were tested at the beginning (Scheme 2). The initial reaction conditions were 5 mol% \textit{in situ} generated B\textsuperscript{Lk} \textsuperscript{[24]} and aziridines in C\textsubscript{6}D\textsubscript{6} at 60 °C for 24 h. Non-protected aziridine 1a was not reactive under these conditions. N-Acetyl aziridine 1b was isomerized, but the desired product 2b was only formed in 40% yield along with 28% of dihydrooxazole. The latter is formed in a Lewis acid catalyzed side reaction with LiBr, as confirmed in a blank experiment. When the N-tosyl protected substrate 1c was applied, the reaction went quite fast even at room temperature and full conversion was achieved after 2 h. However, the desired enamides were not obtained due to polymerization as a side reaction. At 60 °C, 1d possessing the N-Cbz group was converted smoothly to obtain the desired 2d in 77% yield. To our delight, the N-Boc aziridine 1e can be rearranged at room temperature to yield the corresponding enamides in 75% yield. Therefore, the N-Boc protecting group was chosen for all further aziridines.

We tested the isomerization of N-Boc-2-benzylaziridine (1e) as the model substrate. A series of isolated rhodium catalysists efficient for epoxide rearrangement was applied. With the CO-containing catalyst A, only traces of the desired enamide were detected after 24 h (Table 1, entry 1). Under the identical conditions, a better yield (28%) was obtained with the more nucleophilic CO-free catalyst B and the best result was achieved using catalyst C to yield enamide 2e in 57% yield (Table 1, entries 2 and 3). This can be rationalized with the enhanced nucleophilicity of the 16 e\textsuperscript{-} complex C with a high-lying HOMO, while the 18 e\textsuperscript{-} catalyst B requires the dissociation of one olefin moiety to react as a nucleophile. A stronger Lewis acid, necessary for the pre-activation of the aziridine was beneficial for the catalytic reaction and the yield was increased to 66% when LiNTf\textsubscript{2} was used as the co-catalyst (Table 1, entry 4). Furthermore, the reaction proceeds considerably fast when it is carried out at elevated temperatures and the desired product 2e is obtained in 96% after 4 h at 80 °C (Table 1, entries 5, 6 and 7). To check the role of the additive, LiNTf\textsubscript{2} was omitted and no reaction was observed after 4 h at 80 °C, which shows that the Lewis acid is essential for the catalytic reaction (Table 1, entry 8). This also explains why the reaction almost stands still when the solvent C\textsubscript{6}D\textsubscript{6} is replaced by THF-d\textsubscript{3} or CD\textsubscript{3}CN, which indicates competitive binding between THF-d\textsubscript{3} or CD\textsubscript{3}CN and the substrate to the Lewis acid co-catalyst (Table 1, entries 9 and 10). Surprisingly, full conversions were also obtained with lower catalyst loadings and 1 mol% catalyst C proved sufficient for a fast and selective isomerization (Table 1, entries 11 and 12).

When extending the reaction time from 4 h to 24 h the Z:E ratio changes from 54:46 to 33:67, without influencing the overall yield. This indicates an isomerization of the kinetically

![Scheme 2. Isomerization of terminal aziridines with different protecting groups (PG). The yield of 2 was determined by \textsuperscript{'H} NMR calibrated to 1,3,5-trimethoxybenzene (internal standard). \textsuperscript{[30]} Along with 28% of dihydrooxazole. \textsuperscript{[31]} rt. \textsuperscript{[32]} 2 h.](image)

| Entry | Catalyst [mol%] | Additive [mol%] | T [°C] | Time [h] | Yield [%] \textsuperscript{[30]} | (Z:E) |
|-------|-----------------|-----------------|--------|---------|-----------------|-------|
| 1     | 5 (A)           | 10 (LiBr)       | rt     | 24 h    | <5              |       |
| 2     | 5 (B)           | 10 (LiBr)       | rt     | 24 h    | 78              | 50:50 |
| 3     | 5 (C)           | 10 (LiBr)       | rt     | 24 h    | 57              | 50:50 |
| 4     | 5 (C)           | 10 (LiNTf\textsubscript{2}) | rt | 24 h | 66 | 47:53 |
| 5     | 5 (C)           | 10 (LiNTf\textsubscript{2}) | 40 | 4 h | 87 | 47:53 |
| 6     | 5 (C)           | 10 (LiNTf\textsubscript{2}) | 60 | 4 h | 87 | 45:55 |
| 7     | 5 (C)           | 10 (LiNTf\textsubscript{2}) | 80 | 4 h | 96 | 41:59 |
| 8     | 5 (C)           | -               | 80 | 4 h | 0 | - |
| 9\textsuperscript{[30]} | 5 (C) | 10 (LiNTf\textsubscript{2}) | rt | 24 h | <5 | - |
| 10\textsuperscript{[30]} | 5 (C) | 10 (LiNTf\textsubscript{2}) | rt | 24 h | <5 | - |
| 11\textsuperscript{[30]} | 3 (C) | 10 (LiNTf\textsubscript{2}) | 80 | 4 h | 91 | 40:60 |
| 12\textsuperscript{[30]} | 1 (C) | 10 (LiNTf\textsubscript{2}) | 80 | 4 h | 90 | 54:46 |
| 13\textsuperscript{[30]} | 1 (C) | 20 (LiNTf\textsubscript{2}) | 80 | 4 h | 93 | 45:55 |
| 14\textsuperscript{[30]} | 1 (C) | 5 (LiNTf\textsubscript{2}) | 80 | 7 h | 86 | 28:72 |
| 15\textsuperscript{[30]} | 1 (C) | 70 (B(C\textsubscript{6}F\textsubscript{5})\textsubscript{2}) | rt | 2 h | 23\textsuperscript{[31]} | 57:43 |
| 16\textsuperscript{[30]} | 1 (C) | 10 (LiNTf\textsubscript{2}) | 80 | 4 h | 88 | 35:65 |
| 17\textsuperscript{[30]} | 1 (C) | 10 (LiNTf\textsubscript{2}) | 80 | 4 h | 88 | 36:64 |
| 18   | -               | 10 (LiNTf\textsubscript{2}) | 80 | 4 h | 0 | - |

[a] All reactions were carried out in J. Young NMR tubes and the additive was pre-activated with 10 μL THF-d\textsubscript{3}. [b] The yield (\textsuperscript{1}H NMR) of 2e was determined using 1,3,5-trimethoxybenzene as internal standard. [c] THF-d\textsubscript{3} as the solvent. [d] CD\textsubscript{3}CN as the solvent. [e] along with 40% N-Boc deprotected product; full conversion of 1e. [f] 0.2 M of 1e. [g] 0.4 M of 1e.
favored Z-(2e) isomer into the thermodynamically favored E-(2e) isomer. The loadings of the Lewis acid co-catalyst were examined as well. The yield of enamide 2e improved slightly with 20 mol% LiNTf₂ and a longer reaction time was needed when only 5 mol% Lewis acid was used (Table 1, entries 13 and 14). Usually strong Lewis acids are not compatible with carbamate protecting groups.\[16\] Nevertheless, we used 70 mol% of B(C₆F₅)₃ and found full conversion after 2 h room temperature, but besides 23% of the product, also 40% of the deprotected product was obtained (entry 15). Higher aziridine concentrations (0.2 mol/L and 0.4 mol/L, respectively) rarely influence the reaction rate and the desired enamide was obtained in comparable yields (Table 1, entries 16 and 17). The Z/E selectivity varies between 54:46 and 28:72. Finally, a blank test without rhodium catalyst C showed no conversion (Table 1, entry 18). Thus, the optimized reaction conditions (1 mol% Rh, 0.1 M aziridine, C₆D₆, 80 °C) were applied to explore the general- ity of this protocol.

With the optimized conditions in hand, various N-Boc terminal aziridines were converted successfully into the desired enamides (Scheme 3). The terminal aziridines 1f and 1g, possessing weak electron-withdrawing chloro and bromo substituents on the phenyl ring, were isomerized smoothly to yield the corresponding enamides in excellent yield (94% and 93%, respectively). Interestingly, aziridine 1h bearing a moderate electron-withdrawing fluoro group was rearranged much slower and full conversion was obtained after 24 h in 95% yield. To confirm this tendency, substrate 1i bearing a strong electron-withdrawing nitro group was tested. Harsher reaction conditions were required and the reaction can only be completed with 5 mol% catalyst C in 24 h (86% yield for 1i). Notably, the Intermediate bearing a terminal C=C double bond was observed, which is fully rearranged to the desired product after 24 h (see SI for details). In comparison, aziridine 1j with a strongly electron-donating methoxy substituent was converted considerably fast, finished within 3 h and no intermediate was detected. The corresponding enamides 2j were obtained in 95% yield. A closer look at the ¹H NMR spectra monitoring the reaction of the other substrates 1e and 1h revealed the formation of the respective intermediates as well. While the isomerization is fast for the substrate with an electron donating substituent (1j), it becomes even rate limiting in the case of 1h (14% left after 18 h) and 1i bearing electron-withdrawing substituents. To check the feasibility of this novel method for synthetic chemistry, a scaled-up reaction using 1e (1.3 mmol) and 1 mol% catalyst C was carried out and the desired enamide 2e was isolated by column chromatography in 72% yield with a Z/E ratio of 54:46.

A nucleophilic mechanism for the aziridine isomerization by a palladium(0) catalyst was suggested by the Wolfe group.\[7\] Together with the nucleophilic dual-activation mechanism (substrate pre-activation by a Lewis acid) we have reported for the epoxide isomerization, an analogous mechanism for the aziridines was proposed.\[28,4] The fact that the Lewis acid additive and non-coordinating solvents are required indicates a pre-activation of the terminal aziridines (Scheme 4, step (i)). This is followed by a nucleophilic attack of the 16 e⁻²⁺Rh²⁺ catalyst C at the most electrophilic side of the aziridine, which is also the least hindered position in this case (ii) and formation of intermediate i-1 which is likely stabilized by the Lewis acid as well. Subsequent β-hydride elimination (iii) could lead to the Rh⁺⁻ hydrido complex i-2 which releases the Intermediate by reductive elimination (iv) under regeneration of complex C. In case of aziridines containing electron donating substituents, i-2 could also isomerize directly to intermediate i-3 (v) from which
the thermodynamically favored product is released by reductive elimination under recovery of catalyst C (vi). As the isomerization rate of the Intermediate to the product 2 (step vii) is substrate depending and slows down in case of more electron-withdrawing substituents, we assume that this step is Lewis-acid catalyzed. A concerted [1,3]-H shift can not occur and a resting state that requires the oxidative addition of the Intermediate to the nucleophilic catalyst C under re-formation of the RhII hydrido complex i-2 would require the breaking of a strong NH bond and thus seems less likely.

In conclusion, we have presented the selective isomerization of a series of terminal aziridines to yield the desired enamides using the highly reactive nucleophilic rhodium catalyst C under moderate conditions. Most of the tested aziridines were converted smoothly with only 1 mol% catalyst loading and excellent yields were obtained. Intermediates containing the terminal C=C double bond were detected during the course of the reaction with substrates containing an electron poor group. The double bond migrates to the internal C=C double bond to complete the reaction. Based on these observations, a dual-activation mechanism including the activation of the substrate by the Lewis acid and the nucleophilic opening by the Rh catalyst is proposed. This novel transformation provides an alternative strategy for the synthesis of enamides.

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Conflict of Interest

The authors declare no conflict of interest.

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