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1,5-Rhodium Shift in Rearrangement of *N*-Arenesulfonylazetidin-3-ols into Benzosultams

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Supporting Information

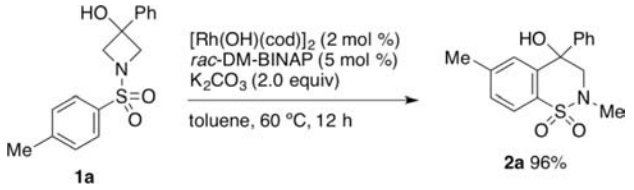
ABSTRACT: Benzosultams are synthesized in an enantiopure form starting from α-amino acids through a rhodium-catalyzed rearrangement reaction of *N*-arenesulfonylazetidin-3-ols. Mechanistically, this reaction involves C−C bond cleavage by β-carbon elimination and C−H bond cleavage by a 1,5-rhodium shift.

Carbon−carbon (C−C) and carbon−hydrogen (C−H) bonds constitute the major frameworks of organic molecules. Such nonpolar σ-bonds are kinetically inert and thermodynamically stable in general and, therefore, remain intact under most conventional reaction conditions. The past few decades, however, have seen the rise of methods to selectively transform such intrinsically unreactive bonds with the use of transition-metal catalysts.[1,2]

A 1,4-metal shift is defined as an intramolecular metal−hydrogen exchange process occurring between 1- and 4-positions. This process provides a convenient way to activate a specific C−H bond, and a number of unique reactions involving a 1,4-metal shift have been reported.[3−6] For example, Catellani et al. have reported a palladium-catalyzed reaction of bromobenzenes with norbornenes, in which multiple C−C bonds are introduced on the benzene ring through a 1,4-palladium shift.[4a] A 1,4-rhodium shift has been also successfully exploited.[5] Phenylboronic acid is multiply alkylated with norbornene through repetition of a 1,4-rhodium shift.[5a] Indanones are synthesized through rearrangement of 1-arylpropargyl alcohols.[5c,d] A rearrangement reaction of cyclobutanols affords indanols in an enantio- and diastereoselective way.[5h,i] On the other hand, there are significantly less precedents reported for a 1,5-metal shift.[7] Herein, we report a rearrangement reaction of *N*-arenesulfonylazetidin-3-ols into benzosultams[8] which involves a 1,5-rhodium shift as the key mechanistic element. It provides a stereoselective synthetic pathway starting from natural α-amino acids leading to enantiopure benzosultams, which are substructures of potent pharmaceuticals like piroxicam and meloxicam.[9]

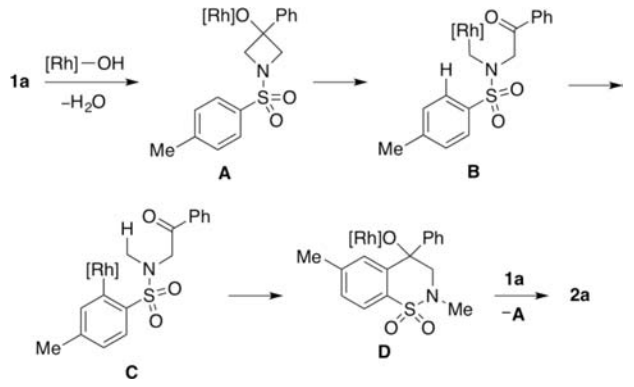
Initially, *N*-*p*-toluenesulfonylazetidinol **1a** was prepared from commercially available azetidin-3-ol in 3 steps.[10] Then, the reaction of **1a** was examined in the presence of $[Rh(OH)(cod)]_2$ (2 mol %) and various phosphine ligands (Rh:P = 1:2.5).[10] Whereas almost no reaction occurred when ligands like PPh_3, DPPB, DPPF were employed, the use of *rac*-BINAP prompted a rearrangement reaction to give **2a** in 46% yield. *rac*-DM-BINAP, which possessed 3,5-xylyl groups in place of phenyl groups on phosphorus, exhibited considerably higher activity to promote quantitative transformation of **1a**. Simple elution of the reaction mixture through a pad of silica gel afforded **2a** in 96% isolated yield (Scheme 1).

Scheme 1. Rhodium-Catalyzed Rearrangement of 1a to 2a



A stepwise mechanism involving a 1,5-rhodium shift from $C(sp^3)$ to $C(sp^2)$ is proposed to explain the formation of **2a** from **1a** (Scheme 2). Initially, the hydroxy group of **1a** is exchanged onto the rhodium hydroxide to generate rhodium alkoxide **A**. Subsequently, β-carbon elimination follows to cleave the C−C bond of the symmetrical azetidine ring, thereby relieving the ring strain.[11] The generated alkylrhodium **B** then undergoes a 1,5-rhodium shift to furnish arylrhodium species **C**. An intramolecular *6-exo* addition to the carbonyl group[12] occurs with **C** to construct the six-membered ring structure of a benzosultam skeleton. Finally, the rhodium alkoxide **D** is exchanged with the hydroxy group of another azetidinol **1a** to release the benzosultam **2a** with regeneration of intermediate **A**.

Scheme 2. Proposed Mechanism for the Rearrangement of 1a to 2a



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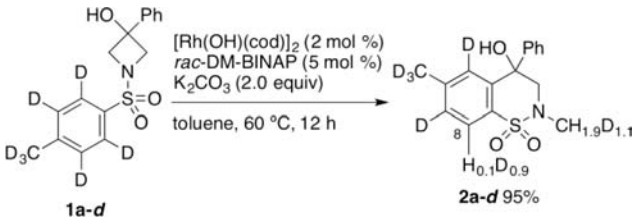
We next carried out the reaction of **1a-*d***, whose *p*-tolyl group was fully deuterated (Scheme 3). One of the deuterium atoms

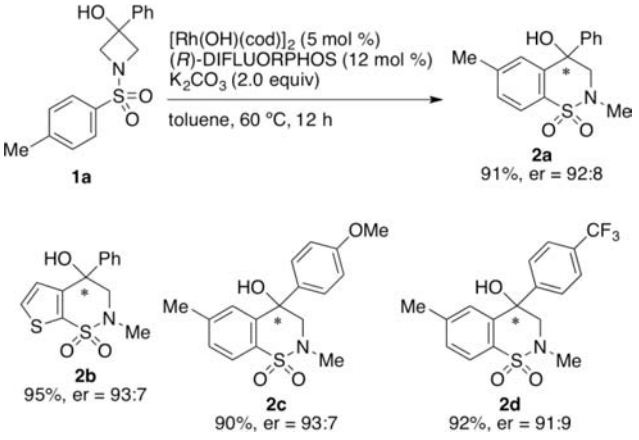
Scheme 3. Rhodium-Catalyzed Reaction of 1a-*d* to 2a-*d*



on the *ortho* positions of the *p*-tolyl moiety was transferred onto the *N*-methyl group of **2a-*d***, being consistent with the proposed mechanism. The H/D ratio of the *N*-methyl group and the 8-position were 1.9/1.1 and 0.1/0.9, respectively. The slightly lower than expected H/D ratios at the *N*-methyl and the slightly higher than expected at the 8-positions may suggest the microscopic reversibility between the intermediary arylrhodium **C** and the alkylrhodium **B**.

Next, optically active diphosphine ligands were examined to induce enantioselectivity at the step of intramolecular carbonyl addition, i.e., from **C** leading to **D**.[12] Although (*R*)-DM-BINAP exhibited the best reactivity among the chiral ligands examined to give **2a** in 94% yield, the enantiomeric ratio (er) was low (62:38).[10] (*R*)-DIFLUORPHOS afforded the best selectivity of 92:8 er (91% yield) (Scheme 4). Application of this reaction conditions to various azetidinols **1** furnished benzosultams **2** in the range of 91:9 to 93:7 er.[13]

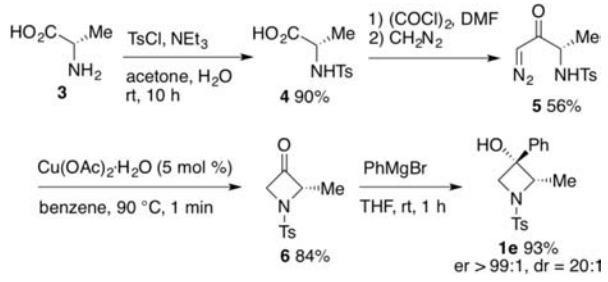
Scheme 4. Enantioselective Rearrangement of 1



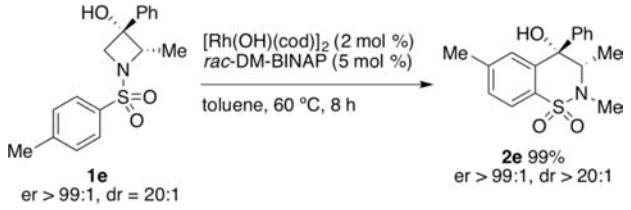
Asymmetrical azetidinol **1e** was prepared in an enantiopure form from (L)-alanine according to a modified version of Seebach's method (Scheme 5).[14] Initially, (L)-alanine (**3**) was treated with *p*-toluenesulfonyl chloride to afford *N*-tosylate **4**. Subsequent treatment with oxalyl chloride followed by coupling with diazomethane gave diazo ketone **5**. Copper-catalyzed denitrogenative cyclization of **5** afforded azetidinone **6**. Addition of phenylmagnesium bromide to **6** occurred selectively from the face opposite to the methyl group to furnish azetidinol **1e** in an enantiopure form.

The azetidinol **1e** was heated at 60 °C in toluene for 8 h in the presence of $[Rh(OH)(cod)]_2$ (2 mol %) and *rac*-DM-BINAP (5 mol %) (Scheme 6). The rearrangement reaction proceeded diastereoselectively to furnish benzosultam **2e** in

Scheme 5. Synthesis of Enantiopure Azetidinol 1e



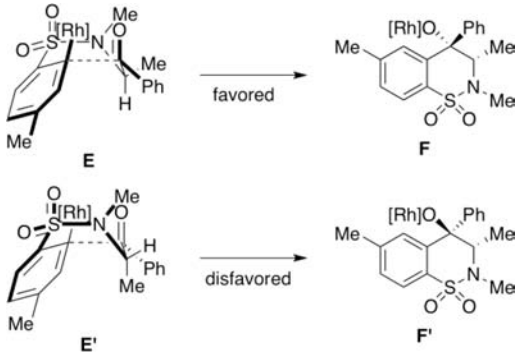
Scheme 6. Rearrangement of 1e to 2e



quantitative yield with the enantiopurity retained. The stereochemistry was confirmed by X-ray crystallography.[10]

The exclusive formation of **2e** demonstrates that β-carbon elimination occurs site-selectively at the methylene side rather than at the methyne side, probably due to steric reasons. In addition, intramolecular carbonyl addition takes place in a diastereoselective fashion. We assume that the six-membered ring transition state adopts a boat-like conformation, in which the C−Rh bond can align with the C═O bond for the maximum orbital interaction as shown in Scheme 7. With the

Scheme 7. Models for Diastereoselective 6-*exo-trig* Cyclization



conformer **E**, the methyl group at the α-position adopts a pseudoequatorial position, whereas the α-methyl group of the conformer **E′** takes a pseudoaxial position. Thus, the conformer **E** is favored over the conformer **E′** to produce the adduct **F** diastereoselectively.

Various benzosultams were synthesized in an enantio- and diastereopure form (Table 1). The reaction of *N*-*p*-toluenesulfonylazetidinol **1f**, the diastereomer of **1e**, also furnished the same stereoisomer **2e** exclusively, being consistent with the proposed mechanism; the stereochemistry of the alcohol moiety once disappears upon β-carbon elimination to produce the same intermediate **C**. Azetidinols **1g−j** having various aryl groups on the sulfonyl moiety gave the corresponding products **2g−j** (entries 2−5). The reaction of *N*-

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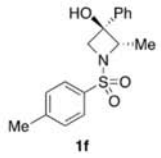
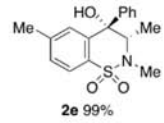
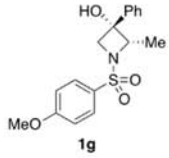
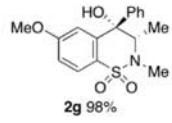
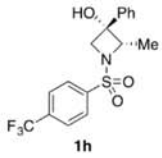
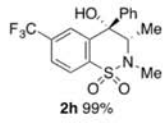
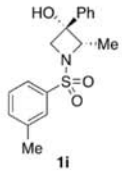
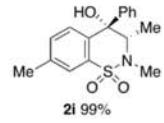
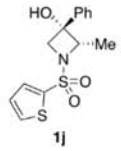
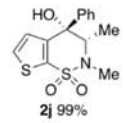
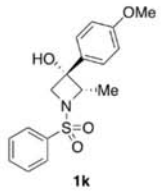
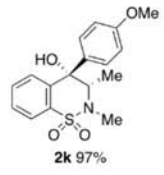
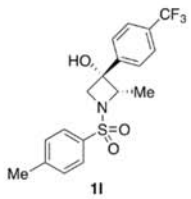
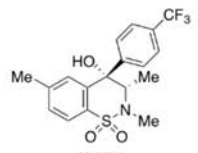
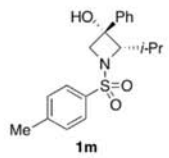
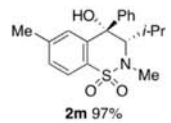
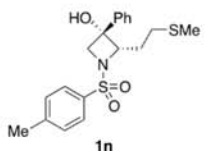
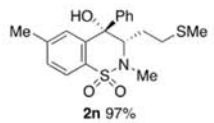
Table 1. Rhodium-Catalyzed Rearrangement of 1 to 2[a]

entry	1	2[b]
1	 **1f**	 **2e** 99%
2	 **1g**	 **2g** 98%
3	 **1h**	 **2h** 99%
4	 **1i**	 **2i** 99%
5	 **1j**	 **2j** 99%
6	 **1k**	 **2k** 97%
7	 **1l**	 **2l** 97%
8	 **1m**	 **2m** 97%
9	 **1n**	 **2n** 97%

[a]Reaction conditions: $[Rh(OH)(cod)]_2$ (2 mol %), *rac*-DM-BINAP (5 mol %, Rh:P = 1:2.5), toluene, 60 °C, 8 h. [b]Isolated yield.

m-toluenesulfonylazetidinol **1i** gave product **2i** with complete regioselectivity (entry 4), suggesting that rhodium preferred the sterically less hindered position as the destination of its 1,5-shift. Substituted aryl groups were allowed at the C3-position (entries 6, 7).[15] Benzosultam **2m** was obtained from azetidinol **1m**, which was prepared from valine (entry 8). The reaction of methionine-derived **1n** successfully furnished **2n**, demonstrating the compatibility of a sulfide functionality (entry 9).

In summary, we have described the rhodium-catalyzed rearrangement reaction of *N*-arenesulfonylazetidin-3-ols into benzosultams. The unique transformation mechanistically involves reorganization of nonpolar σ-bonds via a 1,5-rhodium shift and provides a method to synthesize enantio- and diastereopure benzosultams starting from natural α-amino acids.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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