Summer Scholar Report

Ruthenium-Catalyzed Brook Rearrangements for the Rapid Synthesis of Complex Small Molecules

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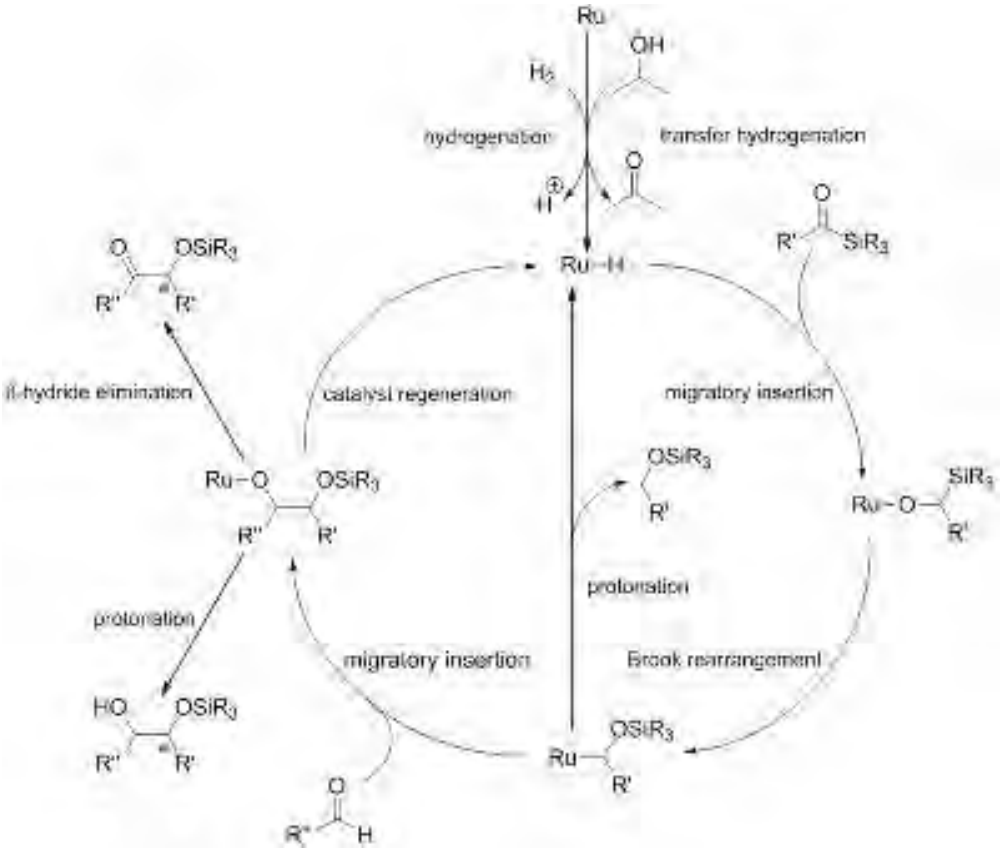
Introduction

"Green" chemistry and atom efficient transformations have garnered increased attention with the reemergence of global climate concerns. Efficient access to and facile derivatization of small complex molecules continues to be an important facet of synthetic organic chemistry. The Brook rearrangement, discovered and studied by Adrian Brook in the 1960's and 70's, provides an unconventional mode for coupling chemistry. Generally initiated by the addition of a nucleophile to a carbonyl, a Brook rearrangement is a silyl group migration from carbon to oxygen. The nucleophile is usually a Grignard or organolithium reagent. The rearrangement is thermodynamically driven and proceeds with high stereochemical fidelity[1]. Anion relay chemistry (ARC) developed by Amos Smith III capitalizes on the mechanism of the Brook rearrangement, employing aldehydes and epoxides to trap the carbanion generated by the Brook rearrangement[2]. The concurrent formation of a C-C bond and a protected alcohol make this a compelling strategy for the rapid assembly of small complex molecules.

While the use of the traditional Brook rearrangement provides a powerful method for small molecule synthesis, it has several important drawbacks. The stoichiometric use of strong bases such as Grignards and alkyl lithiums can racemize chiral centers α to the carbonyl of an acyl silane substrate. HMPA, a harsh and carcinogenic solvent, is often used to further promote the rearrangement by forming a more reactive alkoxide through the ligation of lithium counterions. Furthermore, the reactivity of a lithiated carbanion is limited to electrophiles such as aldehydes and epoxides. It is also notoriously difficult to control the stereochemistry of the subsequent reaction without the use of a chiral auxiliary. A significant improvement to this method could be the use of a transition metal instead of an organolithium reagent. The absence of strong Lewis bases and harsh solvents presents a more tolerant reaction. Ruthenium-alkyl bonds exhibit unique reactivity and widen the scope of coupling partners to potentially include non-traditional electrophiles, such as olefins. Finally, the stereochemistry of the transformation can be controlled by chirality around the metal center. We envision a catalytic cycle as the one shown in Scheme 1, which illustrates a possible synthesis of benzoin and pinacol condensation type products. Such structural motifs are synthetically valuable building blocks, in addition to being common to natural products. Enantio-enriched variants of these molecules are difficult to access via traditional methods, such as enolate oxidation or benzoin condensation without the use of either chiral auxiliaries or a stereoelectronic bias inherent in the electrophilic coupling partners[3,4].

Before our foray into synthetic endeavors could begin, proof of the existence of a metal-catalyzed Brook rearrangement was necessary. There are only a handful of examples of metal-catalyzed rearrangements in the literature[5]. We chose ruthenium as the first transition metal to research, considering the literature precedence of highly stereoselective ketone hydrogenation developed by Noyori and others[6].



Scheme 1

The first step of the catalytic cycle is analogous to a hydrogenation. Considering the stereochemical fidelity of the Brook rearrangement, asymmetric ruthenium-catalysts could introduce chirality during this hydrogenation step. Herein we report the results of our efforts, which include the first example of a ruthenium catalyzed Brook rearrangement.

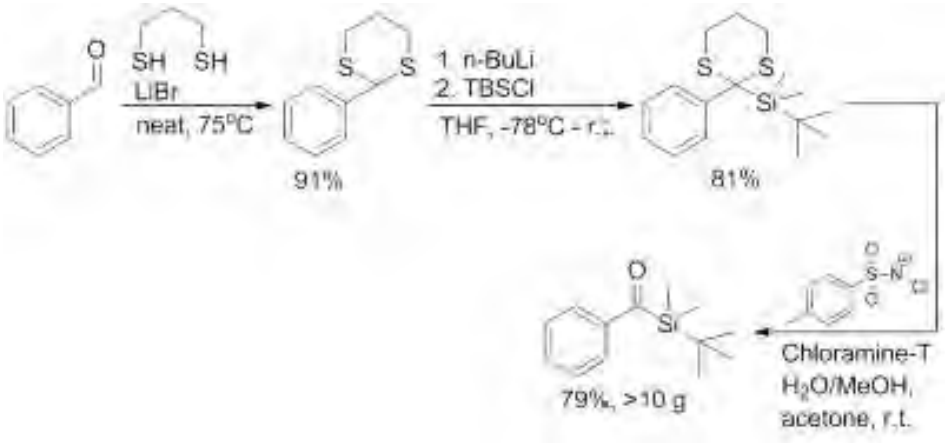
Experimental

General considerations: Unless otherwise stated all manipulations were carried out under an atmosphere of nitrogen, using standard Shlenk techniques. All solvents were passed through a column of alumina and degassed before use. Reagents were purchased from Sigma Aldrich, VWR, or Fischer Scientific and were used without further purification. Nuclear Magnetic Resonance (NMR) spectra for characterization of compounds were recorded on a Varian VNMRS 500 MHz (broadband probe). Gas chromatograph (GC) spectra were recorded on a Shimadzu GC- 2014- FID (Shimadzu SHRXI-5MS column, 15m X 0.25mm X 0.25µm). Acyl silanes[8] and $RuH_2(PPh_3)_4$ [9] were prepared by literature procedures. Transfer hydrogenation reactions general procedure: A 10 ml round bottom flask was charged with acyl silane (0.227 mmol) and ruthenium catalyst (2.4 µmol). The flask was evacuated and placed under an inert atmosphere. The mixture was diluted with 2 ml of a solution of degassed isopropanol and NaOH (2.4 µmol). The reaction was stirred at 82°C for 24 hours under an inert atmosphere. The reaction was monitored by GC. Products were identified by comparing reaction spectra to the spectra of independently synthesized compounds. Digylme was used as an internal standard.

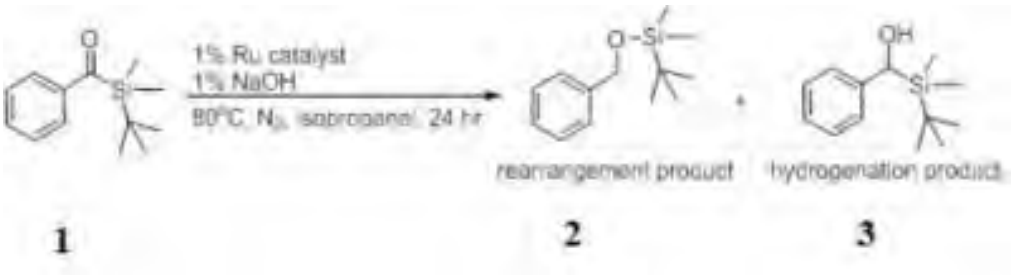
Results and Discussion

A mechanistic probe was required to probe the possibility of a Brook rearrangement occurring during the course of the reaction. As shown in Scheme 3, the acyl silane substrate we chose was benzoyl-*tert*-butyldimethylsilane[**1**]. An electron withdrawing group α to the carbonyl stabilizes the negative charge

generated by the rearrangement and large silyl groups are less labile under reaction conditions. These acyl silanes are easy to access and are derived from cheap starting materials[8] (Scheme 2). Benzaldehyde can be treated with 1,3-propanedithiol to yield a 1,3-dithiane. This dithiane can be deprotonated, treated with an electrophilic silyl group, and deprotected to yield the final acyl silane. Brevity allows a fairly modular synthesis with derivatization available by changing either the starting aldehyde or electrophilic silyl group.



Scheme 2



Scheme 3

If the ruthenium catalyst only hydrogenated the acyl silane the α-hydroxysilane product **3** would be observed. However if a rearrangement occurred the silyl-ether product **2** would be observed. The catalyst we first explored, $RuCl_2(PPh_3)_3$, is air and moisture stable and has a proclivity for ketone hydrogenation. When **1** was treated with 1% $RuCl_2(PPh_3)_3$ and 1% NaOH under transfer hydrogenation conditions for 24 hours the silyl ether product **2** was isolated in 58% yield. The hydrogenation product **3**, tertbutyldimethylsilanol, and an unknown byproduct were observed in lower yields. Control reactions were then run to confirm that the rearrangement was metal catalyzed and not catalyzed by base, PPh_3, or solvent. The results are shown in Table 1.

Substrate	Reactant(s)	Result
1	isopropanol	No reaction
1	3 eq PPh_3	No reaction
3	1% NaOH	No reaction
2	1% $RuCl_2(PPh_3)_3$/NaOH	No reaction

All reactions were stirred under inert atmosphere at 82°C for 24 hours in degassed isopropanol. Digylme was used as an internal standard. Reactions were followed by GC.

Table 1

The first three entries show the reaction is not base, ligand, or solvent catalyzed. The last entry shows that the final silyl ether product does not react further under reaction conditions. Due to the low solubility of NaOH (and most common activators) in isopropanol, it was proposed that treating **1** with a ruthenium hydride, which is presumably generated *in situ*, would be logistically and chemically more efficient. Two ruthenium hydride complexes were synthesized[9]. $RuHCl(PPh_3)_3$ was prepared by treating $RuCl_2(PPh_3)_3$ with a solution of methanol, excess PPh_3, and 1 equivalent of sodium borohydride yielding a red purple solid. $RuH_2(PPh_3)_3$ was synthesized analogously by treating $RuCl_2(PPh_3)_3$ with a solution of methanol, excess PPh_3, and an excess of sodium borohydride yielding a bright yellow solid. Both complexes are crystalline solids that are mildly sensitive to oxygen and moisture. The results of treating **1** with the ruthenium hydride complexes are summarized in Table 2.

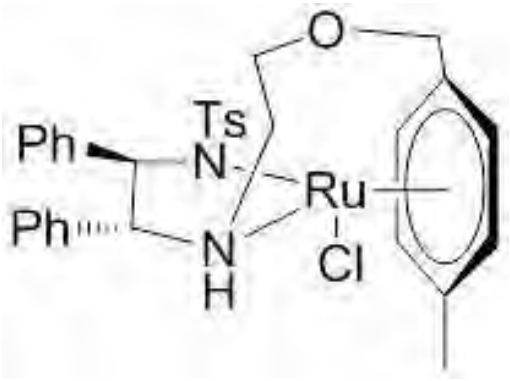
Substrate	Catalyst	Yield 2
1	1% $RuHCl(PPh_3)_3$	0%
1	1% $RuH_2(PPh_3)_3$	24%

Yields were calculated based an internal standard of digylme All reactions were stirred under inert atmosphere at 82°C for 24 hours in degassed isopropanol. No base or activator was present in the reactions.

Table 2

The results in Table 2 show the first example of a ruthenium-catalyzed Brook rearrangement and indicates that a monohydride species is most likely not the active catalyst for the reaction. It is hard to ascertain the identity of the active catalyst for the rearrangement, but further investigation is underway. Treatment of the acyl silane with the dihydride species alone did not produce yields equivalent to analogous reaction conditions with $RuCl_2(PPh_3)$/NaOH, which indicated that a more complex mechanism may be operating during the reaction. Two more reactions were of note. When **1** was treated with 1% NaOH and 1% of catalyst **4** under transfer hydrogenation conditions, **2** was observed in 81% yield. When **1** was treated with $RuCl_2(PPh_3)_3$, the reaction required roughly 18 hours before **1** converted completely. However, when **1** was treated with catalyst **4**, the reaction only required roughly 5 hours

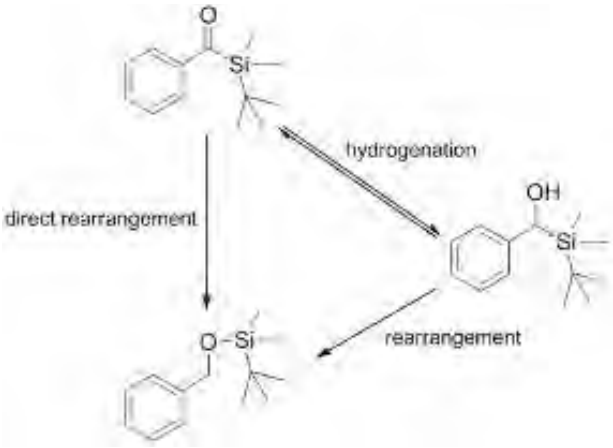
before **1** converted completely. Furthermore, when **1** was treated with catalyst **4**, the rearrangement and hydrogenation product formed concurrently, though at drastically different rates. This suggests that the rearrangement product may be forming via two pathways. As shown in **Scheme 4**, the rearrangement product may be accessed directly from the acyl silane or through a α-hydroxyl silane intermediate. It was surprising that treatment of **1** with the DENEB catalyst **4** yielded rearrangement product **2,** considering the catalyst is known to operate via an outer-sphere mechanism[7]. Literature precedence would suggest that synchronous delivery of a hydride and proton would yield the hydrogenation product **3** exclusively, but formation of the rearrangement product implies that the [1,2] Brook rearrangement occurs faster than the asynchronous delivery of the final proton. This kinetic phenomenon is akin to a radical clock experiment and could allow study of the persistence of alkoxides by comparing the rate of Brook rearrangement to protonation. Finally, changing from aryl to alkyl acyl silane substrates leads to no observation of a Brook rearrangement with either $RuCl_2(PPh_3)_3$ or the DENEB catalyst. This emphasizes the importance of an electron withdrawing group alpha to the carbonyl and its role in stabilizing the carbanion in the transition state.



DENEB/Oxo-tethered ruthenium (II) catalyst 4

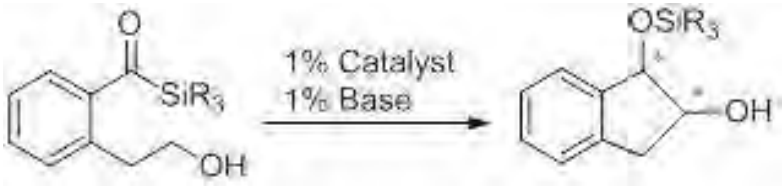
Conclusion and Future Directions

Treatment of aryl acyl silane **1** with $RuH_2(PPh_3)_3$ without base or activator under transfer hydrogenation conditions yielded rearrangement product **2**, which is the first example of a ruthenium-catalyzed Brook rearrangement. The active catalyst is most likely not a monohydride species, although the identity of the active species is difficult to ascertain at this time. Furthermore, mechanistic experiments indicate that a [1, 2] Brook rearrangement can occur with a catalyst that operates with either an innersphere or outer-sphere mechanism.



Scheme 4

We have also determined that an electron-withdrawing group alpha to the carbonyl is required for the transformation to occur. Evidence of a metal-catalyzed Brook rearrangement suggests that such rearrangements could be a viable architecture for asymmetric small molecule synthesis. Future work will focus on developing a coupling reaction between acyl silanes and aldehydes to yield silyl-benzoin condensation or silyl-pinacol type products. Condition optimization and catalyst screenings are already under way. Future work will also focus on intramolecular Brook rearrangements by synthesizing the substrate shown in Scheme 5 and subjecting it to the reaction conditions tested previously. [1, 2] – Dioxygenated bicyclic compounds are difficult to synthesize but are a common motif found in nature[10], making the facile synthesis of these complex small molecules very attractive in natural product total synthesis.



Scheme 5

Acknowledgements

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