JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Cite This: J. Am. Chem. Soc. XXXX, XXX, XXX−XXX
Communication
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# A Rh(III)-Catalyzed Formal [4+1] Approach to Pyrrolidines from Unactivated Terminal Alkenes and Nitrene Sources

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Supporting Information

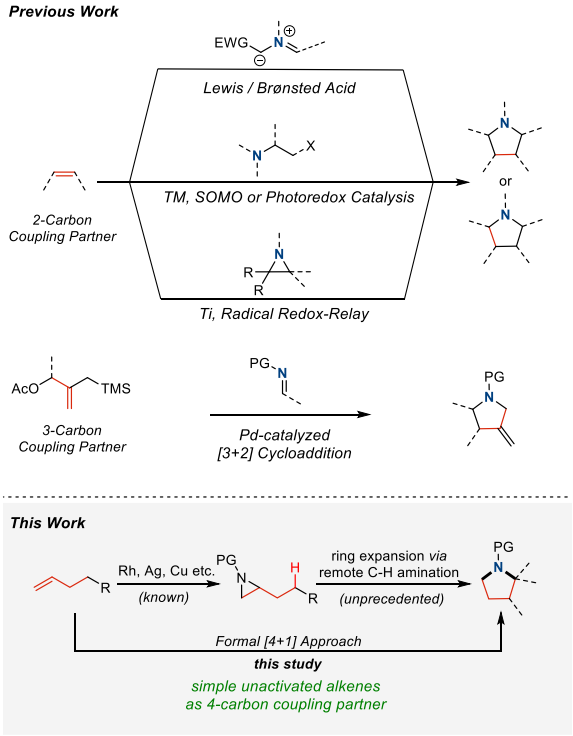
**ABSTRACT:** We have developed a formal [4+1] approach to pyrrolidines from readily available unactivated terminal alkenes as 4-carbon partners. The reaction provides a rapid construction of various pyrrolidine containing structures, especially for the diastereoselective synthesis of spiro-pyrrolidines. Mechanistic investigation suggests a Rh(III)-catalyzed intermolecular aziridination of the alkene and subsequent acid-promoted ring expansion for the pyrrolidine formation.

Pyrrolidine is a prevalent structural unit in pharmaceuticals, biologically active natural products and materials.[1] Consequently, significant efforts have been devoted to the development of efficient routes to pyrrolidines. Early examples can be traced back to the classical Hofmann−Löffler−Freytag reaction in the 19th century.[2] Given the ubiquity of the heterocycle, a myriad of cyclization methods have been developed for its assembly involving nearly every reaction class.[3]

Convergent synthetic strategies involving two or three unique components has also received great attention. Among potential reaction partners, olefins are perhaps the most abundant, general and desirable. The [3+2] cycloaddition between azomethine ylides and alkenes represents a well-studied method among them (Scheme 1).[4] Other recent examples also include the reaction of $\beta$-amino aldehydes, protected cinnamyl amines and aziridines with various types of alkenes as two-carbon sources.[5] Strategies utilizing alkenes as three-carbon coupling partners are relatively rare and often require prefunctionalization. For example, 2-((trimethylsilyl)-methyl) allyl acetate has been reported as a three-carbon source for the formal [3+2] cycloaddition with imines (Scheme 1).[6] Most recently, a visible light-mediated photoredox catalyzed synthesis of spiropyrrolidines was reported using homoallylic amines as 3-carbon/1-nitrogen sources with aliphatic ketones as 1-carbon partners.[7] The use of alkenes as 4-carbon partners is unknown. Herein, we report a Rh(III)-catalyzed formal [4+1] approach to pyrrolidines from $\alpha$-olefins as 4-carbon sources and hydroxylamine derivatives as nitrogen sources.

Recently, we reported a branch-selective allylic amination of simple $\alpha$-olefins using Ir(III) catalysis.[8] During the course of this work, we noted that heptamethylindenyl (Ind*) Rh(III) catalyst[9] delivers the pyrrolidine side product (**3aa**) and linear allylic amination product (**4**) in low yield from 1-hexene (**1a**) and *N*-pivalolyloxy tosylamide (**2a**) (Table 1, entry 1).

**Scheme 1. Intermolecular Synthetic Approaches for Pyrrolidine Using Alkenes as Coupling Partners**




Inspired by this preliminary result and the rapid access to pyrrolidines, we sought to optimize the transformation. Although desired product could be formed by Rh(III) alone, we found that the yield of pyrrolidine (**3aa**) is greatly improved by prestirring the reaction mixture until full consumption of 1-hexene (**1a**) and then subjecting the reaction mixture with AgOTf at 80 °C (entry 2).

Systematic examination of acid additives revealed that $Sc(OTf)_3$ is more effective than AgOTf, promoting the cyclization even at room temperature (entry 3; for detailed information, see SI). Eventually, TfOH was chosen as optimal, delivering 66% yield of desired 2-ethyl-1-tosylpyrrolidine (**3aa**) (entry 4). The electron-deficient heptamethylindenyl (Ind*) ligand on the Rh(III) catalyst is crucial with the more common $[Cp^*RhCl_2]_2$ providing product in a much lower yield (entry 5).[10] Moreover, other nitrene precursors[11] such as dioxazolone

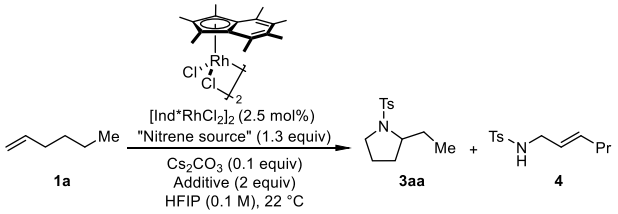
**Received:** July 2, 2019






DOI: 10.1021/jacs.9b07012
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

**Table 1. Reaction Optimization**[a]



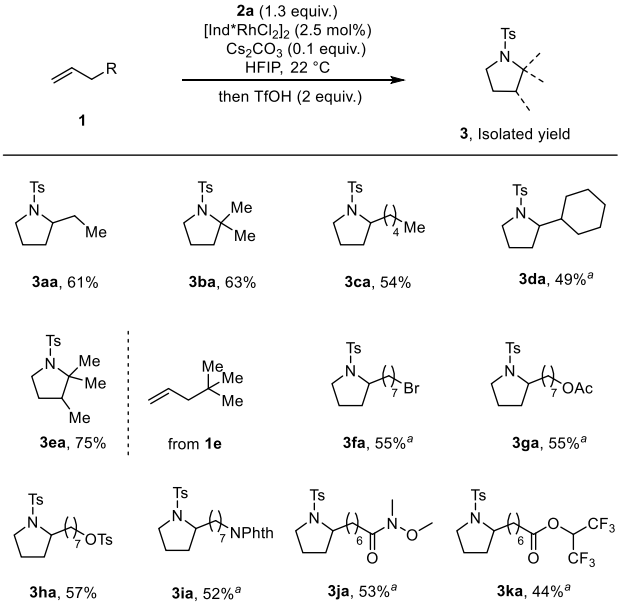

| entry | nitrene source | additive | yield of **3aa** (%)[b] | yield of **4** (%)[b] |
|---|---|---|---|---|
| 1[c] | Ts-NH-OPiv (**2a**) | – | 15 | 15 |
| 2 | Ts-NH-OPiv (**2a**) | AgOTf | 0 (50)[d] | – |
| 3 | Ts-NH-OPiv (**2a**) | $Sc(OTf)_3$ | 45 (58)[d] | – |
| 4 | Ts-NH-OPiv (**2a**) | TfOH | 66 | – |
| 5[e] | Ts-NH-OPiv (**2a**) | TfOH | 15 | – |
| 6 | 3-Phenyl-1,4,2-dioxazol-5-one | TfOH | 0 | – |
| 7 | Ts-$N_3$ | TfOH | 0 | – |

[a]Reactions were conducted on a 0.1 mmol scale using **1a** (1.0 equiv). Additive was added after 24 h. [b]Determined by analysis of $^1$H nuclear magnetic resonance (NMR) of the unpurified reaction mixture. [c]Reaction was conducted at 40 °C with 1 equiv of **2a**, with $[Ind^*RhCl_2]_2$/AgOTf as the catalyst precursor. [d]Temperature increased to 80 °C after addition of the additive. [e]$[Cp^*RhCl_2]_2$ was used.

or tosyl azide (entry 6, 7) lead to no pyrrolidine product formation.

We next sought to examine the scope of this method with various terminal alkenes (Scheme 2). The reaction proceeds

**Scheme 2. Alkene Substrate Scope**

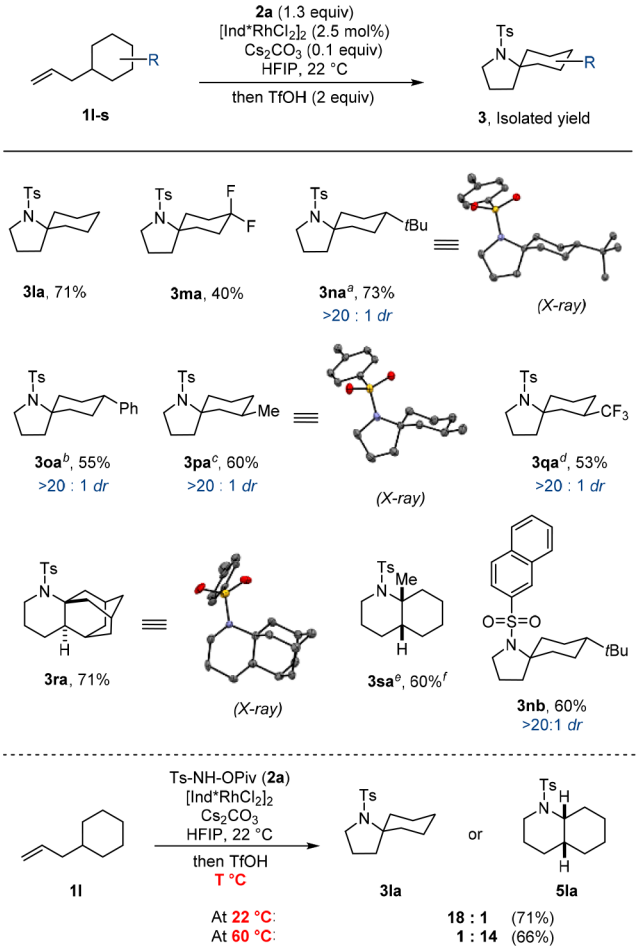



[a]Reaction conducted at 40 °C.

smoothly with alkenes containing substituents at C4 and C5 positions, giving desired products (**3aa**–**3da**) in good yield. Interestingly, in the case of 4,4-dimethyl-1-pentene (**1e**) where the C4 position is blocked, one of the methyl groups migrates to the C3 position, forming 2,2,3-trimethyl-1-tosylpyrrolidine (**3ea**) selectively. Additionally, a variety of functional groups such as –Br, –OAc, –OTs, –NPhth, $-CONR_2$ and $-CO_2R$ are tolerated when located far from the reaction center,[12] providing corresponding products (**3fa**–**3ka**) in moderate to good yield.

In consideration of the importance of spirocyclic pyrrolidines among pharmaceuticals, we tested synthetic utility of this method for the synthesis of spiro-pyrrolidines with a variety of allyl cyclohexane substrates (Scheme 3). Allyl cyclohexane (**1l**)

**Scheme 3. Allyl Cyclohexane Substrate Scope**




[a]From **1n** (3.1:1 dr). [b]From **1o** (2.8:1 dr). [c]From **1p** (3.0:1 dr). [d]From **1q** (3.8:1 dr). [e]From **1s** (1.6:1 dr). [f]Reaction conducted at 4 °C.

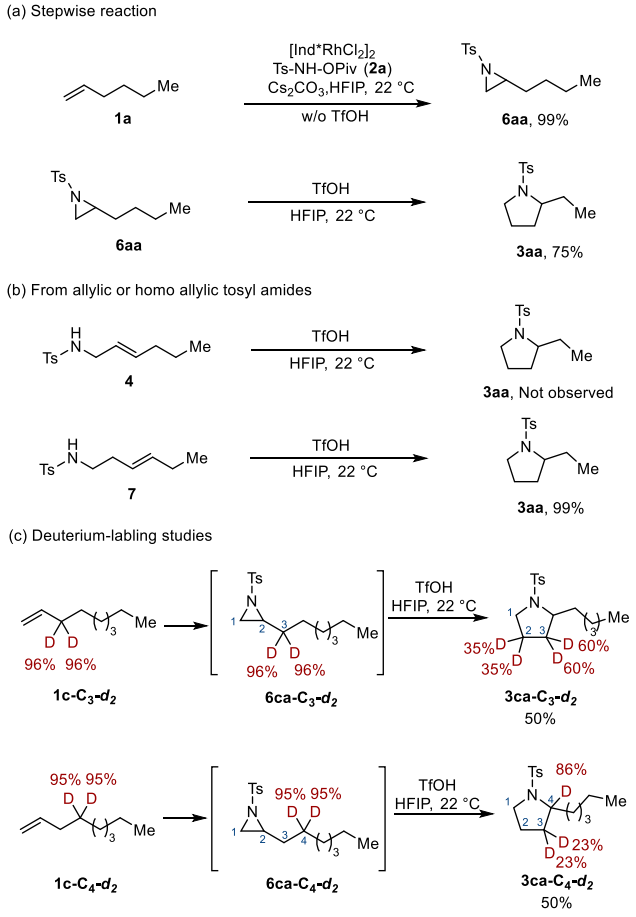
was successfully converted to the 1-tosyl-1-azaspiro[4.5]decane (**3la**) product in excellent yield. A conformational bias in the cyclohexane ring (4-*tert*-butyl, 4-phenyl, 3-methyl and 3-trifluoromethyl) produced corresponding spiro-pyrrolidine products with excellent diastereoselectivity (**3na**, **3oa**, **3pa** and **3qa**). It is also worth noting that >20:1 diastereoselectivities are achieved regardless of trans/cis ratio of the starting cyclohexane. The relative stereochemistry of **3na** and **3pa** was unambiguously determined by X-ray crystallography. Interestingly, the reaction with 2-allyl adamantane (**1r**) causes a 1,2-hydride shift before cyclization, leading to the formation of an unprecedented structure **3ra**. A similar hydride shift event was also observed with 1-allyl-2-methylcyclohexane (**1s**), giving rise to 6,6-fused bicyclic, decahydroquinoline (**3sa**). Moreover, naphthyl sulfonyl group was introduced as an alternative tosyl protecting group due to its milder deprotection conditions (**3nb**).[13] Last, regiodivergent synthesis of pyrrolidine-based


DOI: 10.1021/jacs.9b07012
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

spirocycle (**3la**) and fused bicyclic compound (**5la**) was achieved from allyl cyclohexane (**1l**) with exquisite selectivity by simply changing reaction temperature.

To obtain mechanistic insights, we first conducted the reaction with 1-hexene (**1a**) using the standard reaction conditions without the sequential treatment of TfOH. *N*-Tosyl aziridine **6aa** was isolated in quantitative yield. The aziridination of unactivated alkenes catalyzed by Ind*Rh(III) is unprecedented, although it is a well-explored research area.[14] Further subjecting the resulting aziridine to TfOH leads to pyrrolidine product in 75% yield (**3aa**) (Scheme 4a).[5c,15]

**Scheme 4. Mechanistic Investigation**

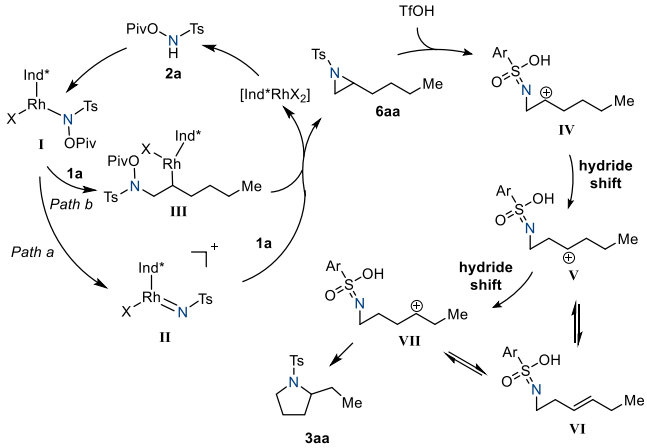



These results suggest that the Rh(III)-catalyzed intermolecular aziridination of the alkene and subsequent acid-promoted ring expansion is likely responsible for the reaction mechanism.

In order to investigate the reaction mechanism, allylic and homoallylic tosyl amides (**4** and **7**) were subjected to TfOH (Scheme 4b). Allylic amine (**4**) does not lead to pyrrolidine product, while a quantitative yield was achieved from homoallylic amine (**7**).[16] Furthermore, we continued to test the mechanism with C1 to C4 deuterated alkenes (Scheme 4c). In the case of C3 deuterated aziridine (**6ca-C$_3$-$d_2$**), extensive deuterium incorporation is observed at the C2 position. In addition, significant erosion of deuterium is observed in the case of **6ca-C$_4$-$d_2$**.

Taken together, these experiments suggest a plausible reaction mechanism (Scheme 5). *N*-Pivalolyloxy tosylamide (**2a**) first coordinates to the Rh(III) catalyst and undergoes Rh-nitrene formation (**II**).[17] Alkene aziridination proceeds

**Scheme 5. Proposed Mechanism**




subsequently to form *N*-tosyl aziridine (**6aa**). It is also possible that the aziridine (**6aa**) is formed through the alkene migratory insertion of intermediate **I**, followed by a concerted C−N bond formation and N−O bond cleavage. Upon treatment with triflic acid, aziridine ring expansion is initiated by 1,2-hydride shift, followed by a combination of 1,2-hydride shift and elimination/protonation pathways, and eventually quenches the carbocation at C4 position to form the pyrrolidine product (**3aa**). The possible intervention of homoallylic amide **VI** explains the modest loss of deuteration in the deuterium labeling experiments noted above.

In summary, we have developed a Rh(III)-catalyzed formal [4+1] synthesis of pyrrolidines from readily available unactivated alkenes. Mechanistic studies show that the reaction proceeds through a Rh(III)-catalyzed aziridination of the alkene and subsequent ring expansion from aziridine to pyrrolidine promoted by the acid. This method offers a new strategy for pyrrolidine synthesis by employing a simple alkene as a four-carbon source. With this method, various types of pyrrolidines, especially spiro-pyrrolidines, were rapidly constructed. Further efforts at elucidating the mechanism and expanding this chemistry are currently underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07012.

Crystallographic data for **3na**, **3pa**, **3ra** and **5la** (ZIP)

Experimental procedures, detailed optimization table, characterization, copies of $^1$H, $^{13}$C and $^{19}$F NMR spectra for all new compounds (PDF)

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§S.L. and H.L. contributed equally to this work.

### Notes

The authors declare no competing financial interest.



DOI: 10.1021/jacs.9b07012
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

## ■ ACKNOWLEDGMENTS

We gratefully acknowledge NIGMS (GM80442) for funding. Single crystal X-ray diffraction was performed at the Shared Materials Characterization Laboratory (SMCL) at Columbia University. Use of the SMCL was made possible by funding from Columbia University.

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DOI: 10.1021/jacs.9b07012
*J. Am. Chem. Soc.* XXXX, XXX, XXX−XXX