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Transfer of Chirality in the Rhodium-Catalyzed Intramolecular Formal Hetero-[5 + 2] Cycloaddition of Vinyl Aziridines and Alkynes: Stereoselective Synthesis of Fused Azepine Derivatives

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Supporting Information

ABSTRACT: By taking advantage of vinyl aziridines as a heteroatom-containing five-atom component in rhodium-catalyzed intramolecular formal hetero-[5 + 2] cycloaddition reactions with alkynes, a highly efficient method for the synthesis of fused azepine derivatives at 30 °C was developed. The reaction has broad substrate scope and tolerates a wide range of functional groups. The chirality of vinyl aziridine-alkyne substrates can be completely transferred to the cycloadducts, representing an atom-economic and enantiospecific protocol for the construction of fused 2,5-dihydroazepines for the first time.

The cycloaddition reaction is one of the most powerful and straightforward synthetic tools for the atom-economical construction of cyclic skeletons in modern organic chemistry.[1] However, as compared to those well-established cycloadditions for synthesis of five- and six-membered ring systems, the development of cycloadditions leading to seven-membered rings, particularly seven-membered heterocycles such as azepine derivatives, are still highly desirable, mainly due to the unfavorable enthalpic and entropic reasons.[2,3] Despite the obstacles and challenges in this field, the almost continuous identification of bioactive natural products that contain a seven-membered azaheterocycle in the core structure has driven recent interest.[4] Therefore, a number of methodologies have been developed for the synthesis of these azepine rings.[5] For example, the research group of Wender has done pioneering works on the rhodium-catalyzed hetero-[5 + 2] cycloaddition of cyclopropyl imines with electron-deficient alkyne, leading to a new route to dihydroazepines.[6] Subsequently, the groups of Li,[7a] Fiksdahl,[7b] and France[7c] have realized some other novel formal [5 + 2] cycloadditions of various precursors by using different transition-metal catalysts. Alternatively, the formation of azepine products by [4 + 3][8] and [3 + 2 + 2][9] cycloadditions have also been developed, but only a few approaches exist for the preparation of their ring-fused analogues, which represent a privileged structural motif in many biologically active azepines such as fawcettimine, tetrapetalone A, stemoamide, and akagerine (Figure 1).[4] Thus, the development of new cycloaddition reactions to access polysubstituted, ring-fused azepines from readily available acyclic precursors remains highly desirable. Of note, Sarpong[8a] and Tang[8b] have independently demonstrated an elegant Rh(II)-catalyzed formal [4 + 3] cycloaddition of dienyltriazoles through the carbene intermediate, providing an efficient access to fused

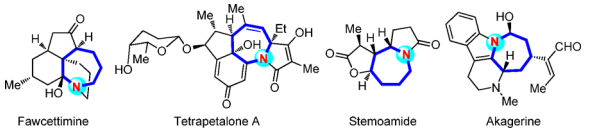
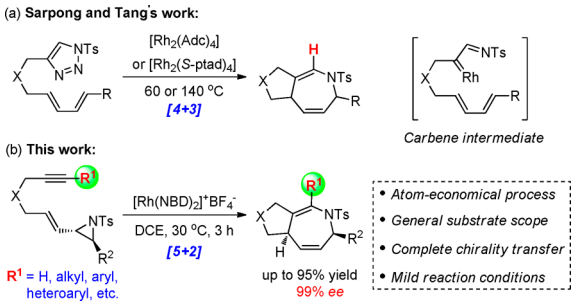


Figure 1. Natural products featuring ring-fused azepines.

2,5-dihydroazepines in racemic form (Scheme 1a). However, there are no examples of enantioselective cycloaddition for the

Scheme 1. Rhodium-Catalyzed Cycloaddition Strategy for Constructing Fused Azepines



construction of chiral azepines. Consequently, the synthesis of enantiomerically pure azepines is in great demand in both organic and medicinal chemistry. Herein, we report a new Rh(I)-catalyzed intramolecular formal hetero-[5 + 2] cycloaddition of optically pure vinyl aziridine-alkyne substrates for synthesis of enantioenriched fused 2,5-dihydroazepines with high *ee* in moderate to good yield through chirality transfer strategy (Scheme 1b).

As a part of our continual program in the discovery of rhodium-catalyzed cycloaddition reactions,[10] we became interested in whether readily available optically pure vinyl aziridines[11] could be employed in formal hetero-[5 + 2] cycloaddition with unactivated alkynes. If this approach is successful, it will provide an atom-economic and enantiospecific protocol access to valuable chiral fused 2,5-dihydroazepines through chirality transfer strategy. However, this hypothesis may face considerable challenges such as (1) vinyl aziridines are commonly used as three-atom components in [3 + 2] cycloadditions,[12] and the

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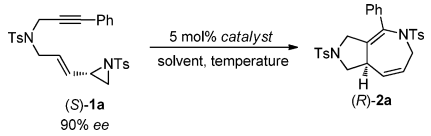
example of vinyl aziridines as five-atom components in [5 + 2] cycloaddition with unactivated alkynes is extremely rare.[13] (2) vinyl aziridines easily undergo rearrangement[14a] and isomerization[14b] to corresponding 3-pyrrolines and ketimines in the presence of transition-metal catalysts.

To examine the above hypothesis, substrate (*S*)-**1a** was selected as the model substrate, which can be easily prepared in 90% *ee* from commercially available D-serine methyl ester hydrochloride. Initially, (*S*)-**1a** was treated with $[Rh(CO)_2Cl]_2$ in DCE at 80 °C for 15 h, resulting in the decomposition of starting material (Table 1, entry 1). After several attempts, we

Table 1. Optimization of Reaction Conditions[a]



(*S*)-**1a** 90% *ee* → (*R*)-**2a**

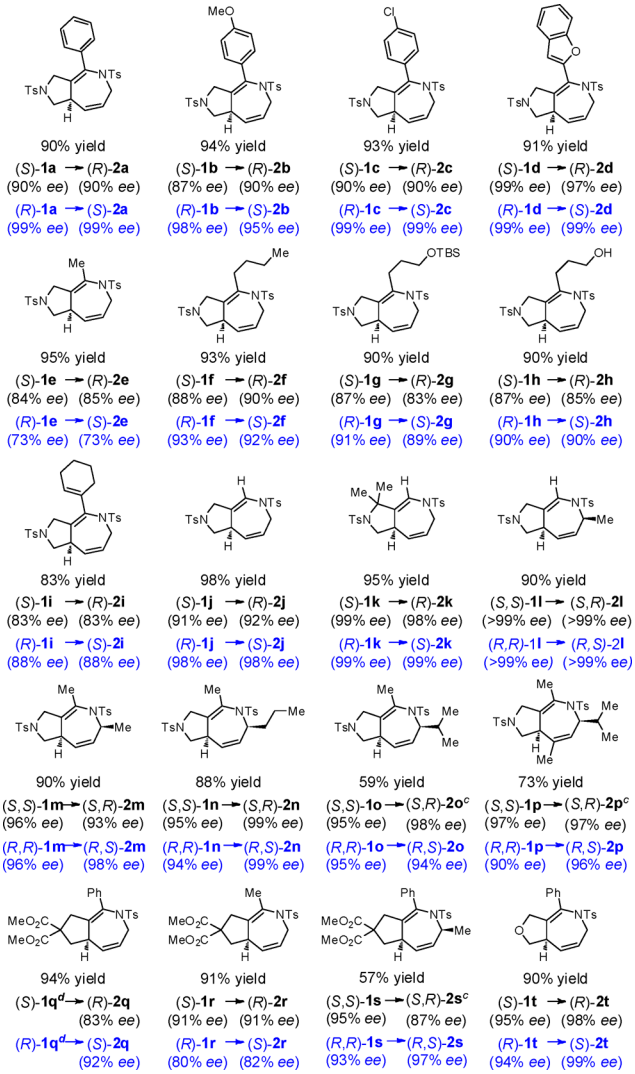
entry	catalyst	time (h)	yield (%)[b]	ee (%)
1[c]	$[Rh(CO)_2Cl]_2$	15	*f*	
2	$[Rh(\eta^6\text{-}C_{10}H_8)(COD)]\ SbF_6$	15	92	87
3	$[Rh(dnCOT)(MeCN)_2]\ SbF_6$	15	40	83
4	$RhCl(IPr)(COD)/AgSbF_6$	15	92	84
5	$[Rh(NBD)dppe]\ BF_4$	15	56	88
6	$[Rh(NBD)Cl]_2/AgSbF_6$	5	99	90
7	$[Rh(NBD)Cl]_2/AgOTf$	5	99	90
8	$[Rh(NBD)Cl]_2/AgPF_6$	5	92	90
9	$[Rh(NBD)Cl]_2/AgClO_4$	5	88	90
10	$[Rh(NBD)Cl]_2/C_3F_7CO_2Ag$	5	47	70
11[c]	$[Rh(NBD)_2]\ BF_4$	5	99	91
12[d]	$[Rh(NBD)_2]\ BF_4$	3	99	90
13[e]	$[Rh(NBD)_2]\ BF_4$	3	99(90)	90
14[e]	$[Rh(COD)_2]\ BF_4$	3	90	90

[a]All reactions were carried out with 0.2 mmol of **1a** and 5 mol % of catalyst (Rh to $AgSbF_6$ = 1:1) in 3.0 mL of 1,2-dichloroethane (DCE) at 80 °C. [b]NMR yield with CH_2Br_2 as an internal standard; values in the parentheses are isolated yield. [c]Ten mole percent of catalyst was used. [d]Reaction was run at 60 °C. [e]Reaction was run at 30 °C. [f]Complex mixture.

were pleased to find that product (*R*)-**2a** could be obtained in 92% NMR yield and 87% *ee* in the presence of cationic $[Rh(\eta^6\text{-}C_{10}H_8)(COD)]SbF_6$ catalyst (Table 1, entry 2). Subsequently, a number of other cationic catalysts derived from weak counteranion, including $[Rh(dnCOT)(MeCN)_2]SbF_6$,[3c] $[Rh(IPr)(COD)]SbF_6$, and $[Rh(NBD)dppe]BF_4$ were tested, but leading to lower *ee* values and yields (Table 1, entries 3−5). Gratifyingly, we found that $[Rh(NBD)Cl]_2/AgSbF_6$ affords the desired dihydroazepine in 99% NMR yield without loss of chirality information (Table 1, entry 6). Different silver salts, such as AgOTf, $AgPF_6$, $AgClO_4$, and $C_3F_7CO_2Ag$ were investigated (Table 1, entries 7−10). Similar results were obtained with $[Rh(NBD)Cl]_2/AgOTf$ and $[Rh(NBD)Cl]_2/AgPF_6$ catalysts (Table 1, entries 7 and 8). Treatment of **1a** with $[Rh(NBD)Cl]_2/AgClO_4$ afford the product with lower yield (Table 1, entry 9). Remarkably, the use of $[Rh(NBD)Cl]_2/C_3F_7CO_2Ag$ bearing a more nucleophilic counteranion $C_3F_7CO_2^-$ resulted in both lower yield and lower *ee* (Table 1, entry 10). Given that the commercially available $[Rh(NBD)_2]BF_4$ showed the same good performance as $[Rh(NBD)Cl]_2/AgSbF_6$ and the reaction temperature can be reduced to 30 °C (Table 1, entries 11−14), the final reaction conditions are described as follows: **1** (0.2 mmol), 5 mol % $[Rh(NBD)_2]\ BF_4$, 1,2-dichloroethane (DCE), 30 °C, and 3 h.

With the optimal reaction conditions in hand, we next examined the scope of this cycloaddition by variation of the substitution patterns on alkynes and aziridines moieties (Table 2). The alkyne substitution could be an aryl (**2a**-**2c**), heteroaryl

Table 2. Exploration of Substrate Scope[a,b]



[a]Standard conditions: $[Rh(NBD)^2]^+BF_4^-$ (5 mol %), DCE (0.067 M), 30 °C, 3 h. [b]Average isolated yield of the reactions from (*S*)-**1** and its enantiomer. [c]The reaction was run at 80 °C for 4 h with 10 mol % catalyst. [d]The *ee* value of **1q** can not be determined by HPLC analysis using a chiral stationary phase.

(**2d**), alkyl (**2e**−**2f**), or cyclohexenyl group (**2i**). The hydroxyl group in **2h** was tolerated under the reaction conditions (**2g** versus **2h**). Notably, both internal and terminal alkynes were compatible to afford the corresponding substituted fused 2,5-dihydroazepine scaffolds (**2j**−**2l**), which is complementary to Sarpong and Tang's method.[8a,b] The structure and absolute configuration of the product (*S*, *R*)-**2l** were established by X-ray crystallographic analysis.[15] The stereochemistry of other azepine products was then assigned accordingly. A substrate (**2k**) bearing two methyl groups at the propargylic position was also successfully converted to the desired product. The reaction remained efficient when the aziridines moiety was changed from

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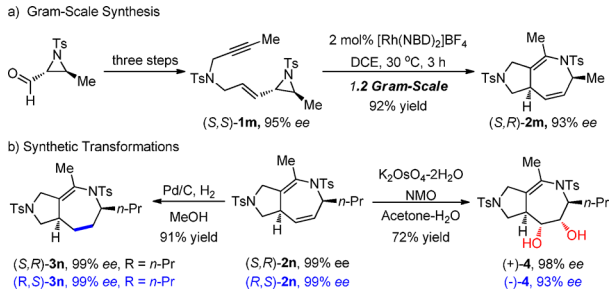
methyl to *n*-propyl (**2m** and **2n**), whereas substrate **1o** possessing isopropyl group on aziridine moiety afforded the corresponding product **20** in moderate yield, but required increased catalyst loading and reaction temperature. Importantly, substrate **1p** with trisubstituted alkene moiety reacted smoothly at 80 °C to afford cycloadduct **2p** without any detectable amount of olefin isomerization. Substrates with a geminal diester or oxygen tether in the 1,6-enyne yielded the corresponding azepines successfully (**2q**−**2t**). It should be noted that enantiomerically enriched substrate (+)-**1** and (−)-**1** was easily prepared from the corresponding chiral aziridine aldehydes; its absolute stereochemistry was determined by comparison with known intermediates. Moderate to high yield and complete chirality transfer could be achieved for substrate (+)-**1** and (−)-**1** respectively, under the standard conditions.

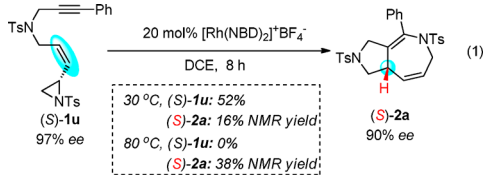
Moreover, this stereospecific cycloaddition is easy to scale-up. A gram-scale reaction of 1.2 g of (*S*, *S*)-**1m** (95% *ee*) was subjected to the current reaction conditions with a reduced catalyst loading (2 mol % Rh), delivering the corresponding (*S*,*R*)-**2m** in 92% yield and 93% *ee* (Scheme 2a). To demonstrate

Scheme 2. Gram-Scale Reaction and Synthetic Transformations



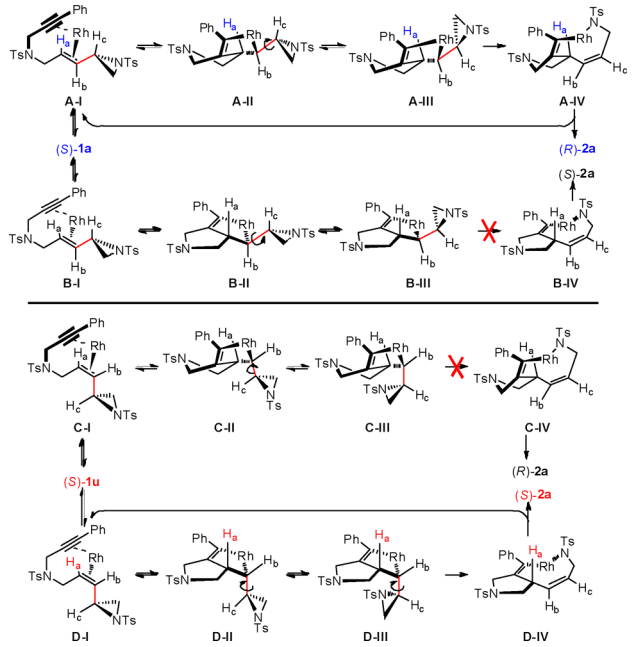
potential synthetic utilities of this protocol, the diastereoselective dihydroxylation was realized with K_2OsO_4-$2H_2O$/NMO, providing the corresponding (+)-**4** and (−)-**4** in 72% yield with 98% *ee* and 93% *ee*, respectively. Alternatively, the disubstituted double bond could be selectively hydrogenated to produce the corresponding **3** in 91% yield with complete chirality transfer (Scheme 2b).

To gain further insights into the reaction mechanism, we prepared substrate (*S*)-**1u** with a *Z*-alkene moiety. However, substrate (*S*)-**1u** was far less reactive than its *E*-siomer (*S*)-**1a** (eq 1). What's more surprising, treatment of (*S*)-**1u** (97% *ee*) with 20



mol % $[Rh(NBD)_2]$ BF_4 in DCE for 8 h at 80 °C gave (*S*)-**2a** rather than (*R*)-**2a** in 38% NMR yield with 90% *ee*. On the basis of the above chirality transfer experiment, we proposed a plausible mechanism to account for this rhodium-catalyzed stereospecific formal hetero-[5 + 2] cycloaddition (Scheme 3). First, both the *re*-face and *si*-face of the carbon−carbon double bond in (*S*)-**1a** could coordinate to the rhodium complex, which lead to diastereomeric metallacyclopentenes **A-II** or **B**−**II** formed by oxidative cyclometalation of the 1,6-enyne moiety. The subsequent formation of a *Z*-olefin in **A-IV** and **B**−**IV**

Scheme 3. Proposed Mechanism



requires a *syn* alignment of the protons H_b and H_c along the C−C bond, which is achieved through rotation around this bond to give **A-III** and **B**−**III**. However, only the conformation of **A-III** allow the C−N bond in the aziridine moiety to properly overlap with the C−Rh bond as required for concerted ring expansion to afford the species **A-IV**. Finally, reductive elimination from this species produces the fused 2,5-dihydroazepine (*R*)-**2a** and regenerates the rhodium catalyst. The observed highly efficient chirality transfer is thus a consequence of the reversibility of the initial mechanistic steps and the influence of the substituent on a later step, putatively involving irreversible cleavage of the aziridine. The stereospecificity with respect to (*S*)-**1u** is in agreement with the model outlined in Scheme 3.

In summary, we have demonstrated that the chirality of vinyl aziridine-alkyne substrates, which are readily available in optically pure form, can be efficiently transferred to the fused 2,5-dihydroazepine products of a formal hetero-[5 + 2] cycloaddition. This method provides strategically novel, atom-economic, and mild access to the azepine architectures with both excellent functional-group compatibility and high enantioselectivity (up to >99% *ee*). Moreover, the further transformations of the products and mechanistic study have also been carried out. The salient features of this transformation include mild reaction conditions, readily available starting materials, ease of scale-up, stereospecificity, general substrate scope, and commercially available rhodium catalyst. Further synthetic applications of this efficient transformation to the synthesis of natural products and pharmaceutical agents are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for the substrates and products (PDF), and crystallographic data (CIF) for (*S*,*R*)-**2l**. 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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