Heterocycles

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Modular Access to the Stereoisomers of Fused Bicyclic Azepines: Rhodium-Catalyzed Intramolecular Stereospecific Hetero-[5+2] Cycloaddition of Vinyl Aziridines and Alkenes

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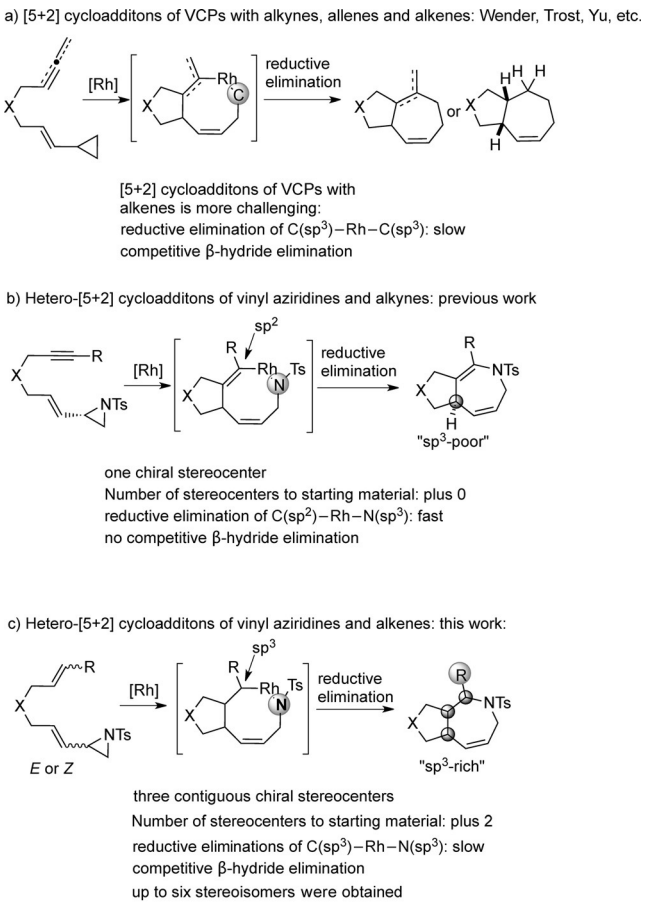
Abstract: *The first rhodium-catalyzed intramolecular hetero-[5+2] cycloaddition reaction of vinyl aziridines and alkenes was realized, wherein both internal and terminal alkenes were applicable. With this method, a variety of unique substituted chiral fused bicyclic azepines, bearing multiple contiguous stereogenic centers, were facilely accessed in a straightforward, high-yielding, and highly stereoselective manner under mild reaction conditions. Notably, the E/Z geometry of the C=C bonds in the vinyl aziridine-alkene substrates impact the cis/trans stereochemistry of the cycloadducts and up to six stereoisomers could be delivered.*

Methodologies that provide stereodefined, sp^3-carbon-rich scaffolds will underpin future advances in small-molecule drug design.[1] Among them, the synthesis of seven-membered carbocycles and heterocycles bearing multiple stereogenic centers is a topic of continued interest because of the presence of this skeletal unit in numerous natural products and pharmaceuticals with diverse biological and medicinal properties, such as antitumor, antibiotic, and antiinflammatory activity.[2] Consequently, considerable effort has been devoted to the development of efficient methods for the synthesis of these seven-membered rings.[3]

Transition-metal-catalyzed cycloadditions represent powerful tools enabling quick and efficient access to polycyclic carbo- and heterocycles in an atom-economical fashion. In particular, using small-ring compounds as cycloaddition partners brings opportunities for developing novel reactions which complement or surpass traditional cycloadditons.[4] Among them, rhodium(I), ruthenium(II), and other transition-metal catalysts catalyze intramolecular [5+2] cycloaddition of vinylcyclopropanes (VCPs) and 2π-components, thus providing a practical way for synthesis of fused bicyclo-[5.3.0.]decane skeletons.[5] Notably, the [5+2] cycloaddition of VCPs and alkenes could efficiently increase sp^3-carbon content in the product and thus attract much interest, but it poses a considerable challenge.[5n,o] An extensive computational study by Wender, Houk, Yu, and co-workers[6c] showed that the reductive elimination involving alkenes is substantially more difficult than those involving alkynes or allenes.[6] This difficulty arises from the formation of complex mixtures resulting from the competing and rapid β-hydride elimination for those substrates bearing internal alkenes. This limitation to terminal alkenes would preclude the rapid access to the bicyclo[5.3.0.]decane cores, bearing two or more chiral centers, in some natural-product families. To overcome this limitation, the [5+2] cycloaddition of VCPs and allenes has been developed as an alternative and efficient solution to this problem (Scheme 1 a).[5k–m]

While the systematic study of the [5+2] cycloaddition of VCPs and 2π-components has been carried out for construction of fused bicycle[5.3.0.]decane skeletons, the synthesis of fused azepine derivatives by hetero-[5+2] cycloaddition still lags behind.[7] The ubiquity of these units in many biologically



Scheme 1. [5+2] cycloadditions and hetero-[5+2] cycloadditions. Ts = 4-toluenesulfonyl.

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active alkaloids, such as tetrapetalone A, fawcettimine, stemoamide, and cephalotaxine, make the development of new stereoselective strategies to access stereoisomers of fused bicyclic azepines in one step, from readily available acyclic precursors, highly desirable (Figure 1).[2c,8] Inspired by the

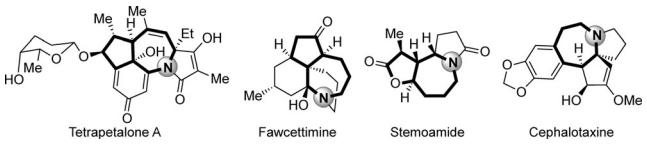
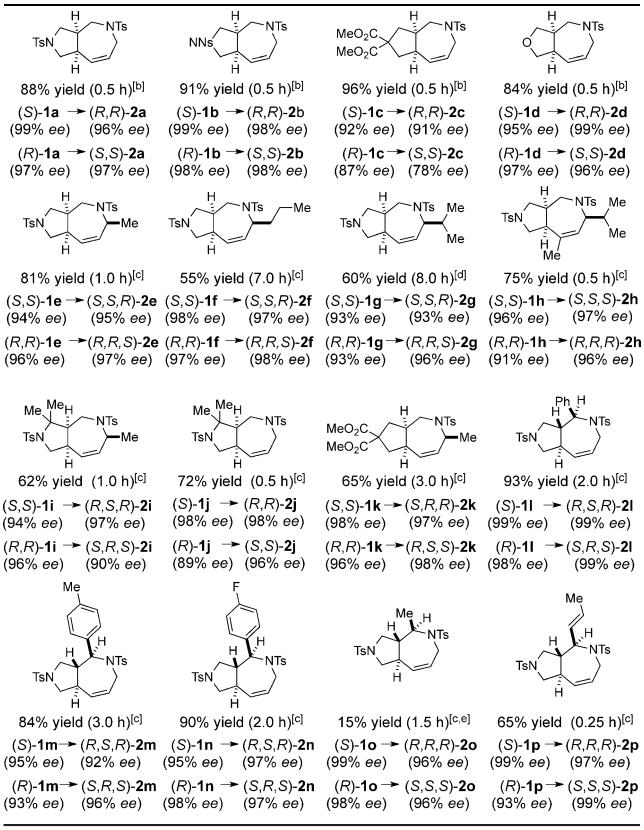


Figure 1. Natural products featuring ring-fused azepines.

pioneering works on the rhodium-catalyzed hetero-[5+2] cycloaddition of cyclopropyl imines with electron-deficient alkynes, developed by the research group of Wender,[7a] we recently developed a rhodium(I)-catalyzed intramolecular hetero-[5+2] cycloaddition of optically pure vinyl aziridine-alkyne substrates for the synthesis of enantioenriched fused 2,5-dihydroazepines through a chirality-transfer strategy (Scheme 1 b),[9a] which is complementary to the [4+3] method reported by the groups of Sarpong and Tang.[10] For increasing the sp^3-carbon content in the cycloadduct, one straightforward but challenging way is to replace of the alkynes by the alkenes in this reaction, thus leading to previously unexplored issues of mechanism [reductive elimination of an C(sp^3)–Rh–N(sp^3) intermediate versus competitive β-hydride elimination] and stereochemistry. Herein, we report the first example of rhodium(I)-catalyzed hetero-[5+2] cycloadditions between vinyl aziridines and alkenes (Scheme 1 c). Several points are noteworthy: 1) the reaction proceeds under mild reaction conditions with a broad substrate scope; 2) the transformation is very practical and completely regio- and stereoselective; 3) it provides an atom-economic and stereospecific protocol to valuable chiral fused bicyclic azepines bearing two or three contiguous stereogenic centers through a chirality-transfer strategy; 4) theoretically, a compound bearing three chiral centers will afford eight stereoisomers, thus, the development of methodology which provides most of the stereoisomers is highly desirable but poses considerable challenges. We found that a slight structural variation of the *E/Z* geometry of the C=C bonds and the stereochemistry of the aziridine moiety in the vinyl aziridine-alkene substrates could yield up to six stereoisomers of the cycloadducts.

The vinyl aziridine-alkene substrate (*S*,6*E*)-**1a** can be easily prepared in 99% *ee* from commercially available D-serine methyl ester hydrochloride.[11] After many attempts, gratifyingly, with the use of [Rh(IPr)(COD)Cl]/$AgSbF_6$ (COD = 1,5-cyclooctadiene), the cycloaddition reaction provided the desired product in 90% yield (NMR) and 99% *ee* in DCE at 80 °C. [Rh(η^6-$C_{10}H_8$)(COD)]$^+SbF_6^-$ and [Rh(NBD)Cl]$_2$/$AgSbF_6$ (NBD = norbornadiene) were more efficient for the reaction, and can catalyze the reaction at 30 °C. Different silver salts, such as AgOTf and $C_3F_7CO_2Ag$, were investigated but failed to improve the process (see Table S1, in the Supporting Information).

Table 1: Exploration of substrate scope.[d]

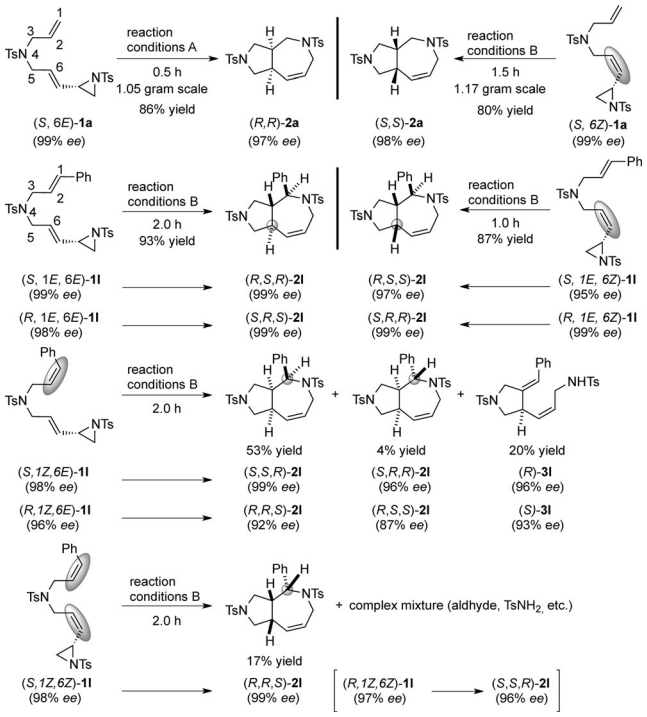


[a] Average yield of products isolated form the reactions of (+)-**1** and its enantiomer. For all substrates in Table 1 the *E*-configured alkene was used. [b] Reaction conditions A: [Rh(η^6-$C_{10}H_8$)(COD)]SbF_6 (5 mol%), DCE (0.067 M), 30 °C. [c] Reaction conditions B: [{Rh(NBD)Cl}$_2$]/$AgSbF_6$ (5 mol%), DCE (0.067 M), 80 °C. [d] Reaction conditions C: [Rh(IPr)(COD)Cl]/$AgSbF_6$ (5 mol%), DCE (0.067 M), 80 °C. [e] 10 mol% catalyst.

Under the optimal reaction conditions, a series of vinyl aziridine-alkenes (**1**) were prepared and examined (Table 1). The results indicate that the present transformation is tolerant of tethers incorporating sulfonamide (**1a**,**b**), geminal diester (**1c**), and ether (**1d**) functionalities under reaction conditions A, thus delivering the corresponding cycloadducts as single *cis*-fused diastereomers. The structure and absolute configuration of the product (*S,S*)-**2a** were established by X-ray crystallographic analysis.[12] Variation of the substitution patterns on the aziridine moiety, and using the reaction conditions A, resulted in the undesired decomposition of the substrates **1e**–**h** and **1k**. Gratifyingly, treatment of these substrates with 5 mol% [{Rh(NBD)Cl}$_2$]/$AgSbF_6$ in DCE at 80 °C delivered the corresponding products in moderate to good yields (reaction conditions B). Importantly, the substrate **1h**, having a trisubstituted alkene moiety, reacted well under reaction conditions B without any detectable amount of olefin isomerization. In contrast, **1g**, lacking methyl substitution of the alkene group, gave **2g** in 34% yield (NMR). The use of [Rh(IPr)(COD)Cl]/$AgSbF_6$ as the catalyst significantly improved the yield to 60%. The substrates **1i** and **1j**, bearing two methyl groups at the allylic position, were also successfully converted into the desired cycloadducts **2i** and **2j**, respectively. Notably, both terminal and internal alkenes

were compatible and afforded the corresponding substituted fused 2,3,6,7-tetrahydroazepine scaffolds (**2l–p**). Interestingly but surprisingly, the cycloadducts from vinyl aziridine-internal alkenes prefers a *trans* ring-fusion rather than a *cis* ring-fusion from the terminal alkenes (**2l** versus **2a**). Unfortunately, the substrate **1o**, bearing a methyl group at the alkene terminus, delivered the corresponding **2o** in only 15% yield, along with some byproducts from the competitive β-hydride elimination.[13] Gratifyingly, the compound **1p**, bearing an alkenyl group, which serves as a masked alkyl group at the alkene terminus, reacted smoothly to afford the product **2p**. Moreover, complete chirality transfer could be achieved for substrates (+)-**1** and (−)-**1**, thus indicating the present transformation is highly stereospecific.

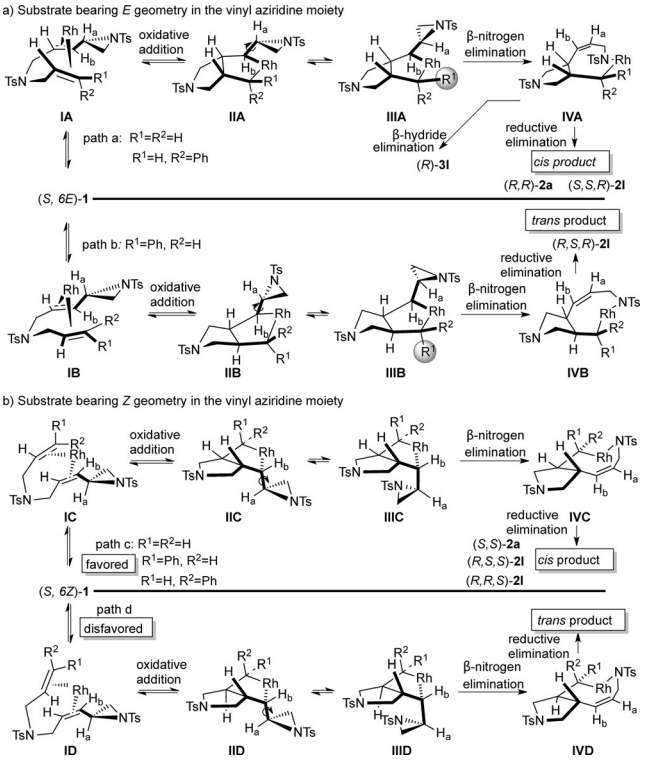
To further explore the scope and mechanistic details of this hetero-[5+2] cycloaddition, we extensively studied the influence of the *E/Z* geometry of the C=C bonds and the stereochemistry of the aziridine moiety on the stereochemistry of the cycloadducts (Scheme 2). Interestingly, the



Scheme 2. Gram-scale reaction and access to the six stereoisomers of the fused azepine derivatives.

reactions of the substrates (*S*,6*E*)-**1a** and (*S*,6*Z*)**1a** are amenable to a gram-scale synthesis of the corresponding products (*R*,*R*)-**2a** and (*S*,*S*)-**2a**, featuring a *cis* ring-fusion but with opposite configurations. However, the stereoselectivity was shifted toward the formation of a *trans*-ring-fusion product for substrate (*S*,1*E*,6*E*)-**1l**. More surprisingly, a slight structural variation of the *E/Z* geometry of the C=C bonds in the vinyl aziridine moiety [(*S*,1*E*,6*Z*)-**1l**] allowed switching of the reaction to yield (*R*,*S*,*S*)-**2l** as a single diastereomer with *cis*-ring-fusion. Subsequently, the *E/Z* geometry of the double bond in the two-carbon synthons of the hetero-[5+2] cycloaddition was investigated. Interestingly, the third diastereomer (*S*,*S*,*R*)-**2l**, and (*R*)-**3l** together with (*S*,*R*,*R*)-**2l** were obtained when (*S*,1*Z*,6*E*)-**1l** was employed as the starting material. Whereas (*R*,*R*,*S*)-**2l** was observed when we subjected (*S*,1*Z*,6*Z*)-**1l** to the same reaction conditions. The structures of (*R,S,R*)-**2l**, (*R*,*S*,*S*)-**2l**, and (*S*,*S*,*R*)-**2l** were confirmed by single-crystal X-ray diffraction.[12]

Based on the above chirality-transfer experiment, a rationalization is outlined in Scheme 3 to address this stereocontrol issue. As exemplified in Scheme 3a for (*S,6E*)-**1**, having



Scheme 3. Proposed mechanism.

E geometry in the vinyl aziridine moiety. Firstly, the rhodium catalyst π-facial selectivity coordination to ene-ene moieties of the enantioenriched **1** would give either the intermediate **IA** or **IB**, which would in turn undergo oxidative cyclometallation of the 1,6-diene moiety to afford the diastereomeric metallacyclo-pentenes **IIA** and **IIB**, respectively. After rotating around the H_a–C–C–H_b bond to align the carbon–rhodium and aziridine C–N bonds for cleavage, and to position the remaining group in the geometry required for the formation of the *cis*-alkene, the β-nitrogen elimination of the intermediates **IIIA** and **IIIB** take place, thus leading to **IVA** and **IVB**, respectively. Finally, reductive eliminations of the C(sp^3)–Rh–N(sp^3) bond from these species produce the *cis* ring-fused and *trans* ring-fused products **2**, and regenerate the rhodium catalyst. When $R^1 = Ph$ and $R^2 = H$, the steric interaction between the R^1 and the aziridine moiety in **IIIA** likely disfavors the formation of the intermediate that leads to **IVA**. Thus the reaction gave the *trans* ring-fused products *(R,S,R)*-**2l** by path b. In contrast, when $R^1 = R^2 = H$ [(*S*,6*E*)-

1a] or $R^1 = H$, $R^2 = Ph$ [(*S*,1*Z*,6*E*)-**11**], the formation of **IIIA** is intrinsically favored and leads to the *cis* ring-fused product **2** by path a and (*R*)-**31** through the competitive β-hydride elimination pathway. 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 stereocontrol issue with respect to substrate the (*S,6Z*)-**1**, bearing *Z* geometry in the vinyl aziridine moiety, is also in agreement with the model (Scheme 3b).[14]

In summary, we have developed a general approach to sp^3-carbon-rich fused tetrahydroazepine scaffolds by a rhodium-catalyed intramolecular stereospecific hetero-[5+2] cycloaddition of vinyl aziridines and alkenes under mild reaction conditions. This method delivers valuable fused azepines bearing multiple contiguous stereogenic centers with broad substrate scope and high enantioselectivity (up to 99% *ee*) by a chirality-transfer strategy. Moreover, our studies highlight that a slight structural variation of the *E/Z* geometry of the C=C bonds and the stereochemistry of the aziridine moiety in the vinyl aziridine-alkene substrates can enable reactions to afford up to six stereoisomers of the cycloadducts. Further mechanism and synthetic application of this transformation are underway.

Acknowledgements

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Keywords: chirality · cycloaddition · heterocycles · rhodium · stereoselectivity

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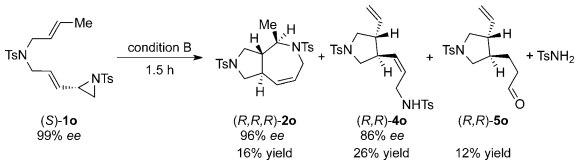
[12] CCDC 1426872 [(*S*,*S*)-**2a**], 1426970 [(*R*,*S*,*R*)-**2l**], 1426971 [(*R*,*S*,*S*)-**2l**], and 1426972 [(*S*,*S*,*R*)-**2l**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[13] The byproducts arising from β-hydride elimination pathways:



[14] An alternative mechanism was suggested by a reviewer, and it involves the formation of six-membered metallacycle derived from the oxidative addition of rhodium catalyst with vinyl aziridine moiety (see Figure S2 in the Supporting Information).

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