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The Divergent Synthesis of Nitrogen Heterocycles by Rhodium(I)-Catalyzed Intermolecular Cycloadditions of Vinyl Aziridines and Alkynes

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Supporting Information

ABSTRACT: Catalyst-controlled divergent intermolecular cycloadditions of vinylaziridines with alkynes have been developed. By using $[Rh(NBD)_2]BF_4$ as the catalyst, a [3 + 2] cycloaddition reaction was achieved with broad substrate scope and high stereoselectivity under mild reaction conditions. Moreover, the chirality of vinylaziridines can be completely transferred to the [3 + 2] cycloadducts. When the catalyst was changed to $[Rh(\eta^6\text{-}C_{10}H_8)(COD)]SbF_6$, the alternative [5 + 2] cycloadducts were selectively formed under otherwise identical conditions.

A preeminent goal of organic synthesis is to complete control over the product distribution of a catalytic reaction. Efforts to realize this goal would enable the divergent synthesis of different valuable products from common versatile starting materials. Heterocycles such as pyrrolidine and azepine derivatives are ubiquitous structural motifs found in an array of natural products and pharmaceuticals with diverse biological and medicinal properties (Figure 1).[1] Therefore, the development of

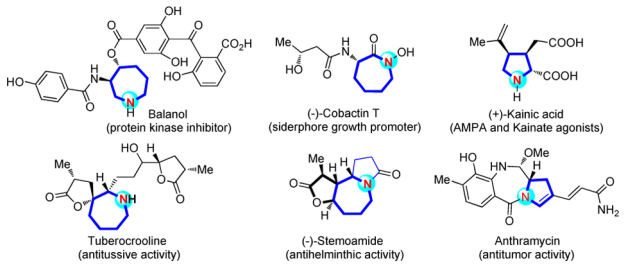
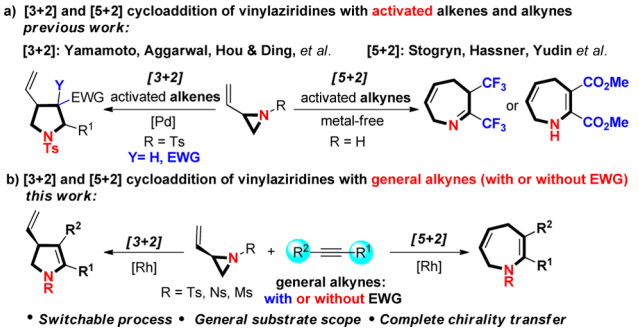


Figure 1. Biologically active natural products containing pyrrolidine and azepine skeletons.

highly efficient synthetic methods to access these compounds has been intensively pursued by the synthetic community.[2] Among them, intermolecular [3 + 2] and [5 + 2] cycloaddition is a viable strategy for synthesis of these valuable aza-heterocycles in an atom-economical fashion.[3,4] While such a strategy has been widely utilized for the formation of pyrrolidine and azepine skeletons from different starting materials, only scarce and specific examples have been reported for the divergent synthesis of different aza-heterocycles from common versatile reactants solely controlled by different catalysts.[4i]

Vinylaziridines are increasingly being exploited as versatile building blocks in organic synthesis, such as nucleophilic ring-opening, rearrangements, carbonylation, and [3 + 2] cycloaddition with heterocumulenes or other activated two-carbon components.[5] Among them, transition-metal-catalyzed formal [3 + 2] cycloadditions of vinylaziridines with electron-deficient alkenes represent powerful tools enabling quick and efficient access to multisubstituted pyrrolidines.[6] For example, the research group of Yamamoto has done pioneering work on the palladium-catalyzed [3 + 2] cycloaddition of *N*-tosylvinylaziridines and alkenes with two activators in 2002.[7] Subsequently, Aggarwal et al. disclosed an elegant palladium-catalyzed [3 + 2] cycloaddition of enantioenriched vinylaziridines with monoactivated alkenes for the stereospecific synthesis of substituted pyrrolidines. The significance of this reaction has been highlighted in the formal synthesis of (−)-α-kainic acid.[8] Recently, the more challenging enantioselective [3 + 2] cycloaddition of racemic vinylaziridines with monoactivated alkenes was reported by Hou and Ding (Scheme 1a).[9] However,

Scheme 1. Intermolecular [3 + 2] and [5 + 2] Cycloadditions of Vinylaziridines



previous reports on the intermolecular [3 + 2] cycloadditions of vinylaziridines are limited to those two-carbon components with one or two activators.[10] Morover, the examples of vinylaziridines as five-atom components in [5 + 2] cycloaddition with general alkynes are rare (Scheme 1a).[11] Therefore, discovering new intermolecular [3 + 2] and [5 + 2] cycloadditions involving general alkynes will advance the vinylaziridine chemistry.

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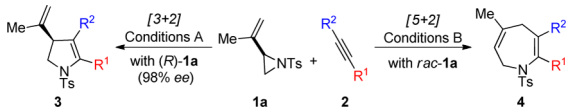
As a part of our continual program in the discovery of new hetero-[5 + 2] cycloaddition reactions of strained rings,[11a,b,12] we recently developed a Rh(I)-catalyzed intramolecular hetero-[5 + 2] cycloaddition of vinyl aziridine-alkyne substrates for synthesis of enantioenriched fused 2,5-dihydro-azepines through chirality transfer strategy.[11a] Hence, we became interested in whether vinylaziridines could be employed in more challenging intermolecular cycloaddition with general alkynes. Herein we report our efforts to selective synthesis of the optically active 2,3-dihydropyroles and valuable 2,5-dihydroazepines from identical starting materials (vinylaziridines and alkynes), by switching the cycloaddition mode with different rhodium(I) catalysts (Scheme 1b).

Initially, our investigation began with phenylacetylene **2a** and *N*-tosyl vinylaziridine substrate (*R*)-**1a**, which can be prepared in 98% ee from commercially available L-serine methyl ester hydrochloride.[5] After many attempts, gratifyingly, with the use of $[Rh(NBD)_2]BF_4$, the [3 + 2] cycloaddition provided the desired 2,3-dihydropyrole **3aa** in 90% NMR yield without loss of chirality information. Interestingly, the reaction favors the formation of [5 + 2]-cycloadduct **4aa** rather than **3aa** when using $[Rh(COD)Cl]_2/AgSbF_6$, $[Rh(COD)Cl]_2/AgBF_4$, or $[Rh(\eta^6\text{-}C_{10}H_8)(COD)]SbF_6$ containing a **COD** ligand as the catalyst, and the structure of **4aa** was further confirmed by X-ray crystallographic analysis.[13] Other commonly used metal catalysts such as $Pd_2(dba)_3$,[8a] $AgSbF_6$,[3g] $FeCl_3$,[3h] and $Sc(OTf)_3$[3j] showed almost no catalytic activity (see Table S1, in the Supporting Information (SI)).

With the optimal reaction conditions in hand, various alkynes **2** were explored to investigate the generality of these product-switchable cycloadditions (Table 1). First, the scope of the [3 + 2] cycloaddition was examined under condition A. A wide range of alkynes, not only terminal alkynes but also internal alkynes are suitable substrates, leading to the corresponding [3 + 2] cycloadduct as a single regioisomer in most cases (Table 1, entries 1−15). The chirality of (*R*)-**1a** can be efficiently or completely transferrred to the valuable 2,3-dihydropyroles with 90−99% ee in moderate to high yields. The structure and absolute configuration of the cycloadduct (*R*)-**3am** were unambiguously determined by X-ray crystallographic analysis.[13] Aliphatic alkynes can give the corresponding [3 + 2] cycloadducts in moderate to high NMR yield, but it is very unstable as a result of the hydrolytically labile property of the enamine skeleton during purification (Table 1, entries 16−26).[14] Gratifyingly, the [5 + 2] cycloadduct **4az** together with [3 + 2] cycloadduct **3az** was obtained when we subjected symmetric internal alkyne **2z** to conditions A. The reaction remained efficient when nonsymmetric internal alkyne **2aa** and **2bb** was used as substrate, providing the corresponding **3aaa** and **3abb** as a single regioisomer. Notably, the reaction is not limited to alkynes without electron-withdrawing group. Monoactivated alkyne **2cc** was also compatible, delivering the [3 + 2] cycloadduct **3acc** under conditions A and B.

In parallel, the scope of [5 + 2] cycloadditions was also evaluated. A set of 2,5-dihydroazepines were obtained in high selectivity under condition B. It was found that various alkynes, such as aromatic (**2a−2m**), heteroaromatic (**2n−2o**), and aliphatic terminal alkynes (**2p−2y**), underwent the [5 + 2] cycloadditions with *rac*-**1a** to afford the corresponding [5 + 2] cycloadducts in moderate to excellent yields. In most cases, only one regioisomer is detected, except for aliphatic alkynes **2q**, **2r**, and **2v−2y**, affording corresponding azepines **4** and its regioisomer **4′** in moderate to high ratio. Unfortunately, the internal alkynes are not applicable to the present [5 + 2] cycloaddition.

Table 1. Scope with Respect to Various Alkynes 2



entry	R^1/R^2	Cond. A,[c] Yield (ee) (%)	Cond. B,[c] Yield (%)
1	Ph/H (**2a**)	**3aa**, 80 (97)	**4aa**, 90
2	4-$EtOC_6H_4$/H (**2b**)	**3ab**, 70 (98)	**4ab**, 94
3	4-*t*-BuC_6H_4/H (**2c**)	**3ac**, 93 (96)	**4ac**, 93
4	4-MeC_6H_4/H (**2d**)	**3ad**, 72 (97)	**4ad**, 90
5	3-MeC_6H_4/H (**2e**)	**3ae**, 78 (98)	**4ae**, 97
6	2-MeC_6H_4/H (**2f**)	**3af**, 90 (98)	**4af**, 97
7	4-FC_6H_4/H (**2g**)	**3ag**, 91 (98)	**4ag**, 91
8	4-ClC_6H_4/H (**2h**)	**3ah**, 82 (96)	**4ah**, 75
9	4-BrC_6H_4/H (**2i**)	**3ai**, 86 (94)	**4ai**, 60
10	4-AcC_6H_4/H (**2j**)	**3aj**, 70 (97)	**4aj**, 17
11	4-$MeCO_2C_6H_4$/H (**2k**)	**3ak**, 65 (98)	**4ak**, 61
12	1-naphthyl/H (**2l**)	**3al**, 87 (94)	**4al**, 30
13	2-naphthyl/H (**2m**)	**3am**, 88 (99)	**4am**,93
14	2-thienyl/H (**2n**)	**3an**, 82 (98)	**4an**, 61
15	2-benzofuranyl/H (**2o**)	**3ao**, 89 (98)	**4ao**, 61
16	cyclohexenyl/H (**2p**)	**3ap**, 66 (97)	**4ap**, 82
17	*n*-C_3H_7/H (**2q**)[i]	**3aq**, 90(97)[d,e]	**4aq**, 90[f]
18	*n*-C_5H_{11}/H (**2r**)	**3ar**, 66(98)[d,e]	**4ar**, 76[f]
19	$C_6H_5(CH2)_2$/H (**2s**)	**3as**, 71(96)	**4as**, 74[j]
20	$(CH_3)_2CHCH_2$/H (**2t**)[i]	**3at**, 85(97)[d,e]	**4at**, 75
21	cyclopropyl/H (**2u**)[i]	**3au**, 98(97)[e]	**4au**, 84
22	$(CH_2)_3OTBS$/H (**2v**)	**3av**, 70(−)[e,g]	**4av**, 69[f]
23	$(CH_2)_3OBn$/H (**2w**)	**3aw**, 65(97)[d,e]	**4aw**, 75[f]
24	$(CH_2)_2CO_2Me$/H (**2x**)	**3ax**, 55(90)[d,e]	**4ax**, 78[f,j]
25	$(CH_2)_3Phth$/H (**2y**)	**3ay**, 77(93)[d]	**4ay**, 67[f]
26	Et/Et (**2z**)[h]	**3az**, 52 (92)	**4az**, 18[a]
27	TMS/Me (**2aa**)	**3aaa**, 64(96)	**3aaa**, 40[e]
28	4-$MeOC_6H_4/CH_2OMe$ (**2bb**)	**3abb**, 69(96)	**3abb**, 30[e]
29	Ph/COMe (**2cc**)	**3acc**, 75(94)	**3acc**, 37

[a]Condition A: 0.25 mmol (*R*)-**1a**, 1.2 equiv **2**, and 5 mol % $[Rh(NBD)_2]BF_4$ in 2.5 mL 1,2-dichloroethane (DCE) at rt for 15 min. [b]Condition B: 0.25 mmol *rac*-**1a**, 1.5 equiv **2**, and 5 mol % $[Rh(\eta^6\text{-}C_{10}H_8)(COD)]SbF_6$ in 2.5 mL DCE at 0 °C for 30 min, then it was stirred at rt for 15 min. [c]Isolated yield. [d]The ee value was determined after conversion of **3** to γ-amino ketone **5**. [e]NMR yield. [f]**4aq**:**4aq′** = 14:1, **4ar**: **4ar′** = 10:1, **4av**:**4av′** = 10:1, **4aw**:**4aw′** = 10:1, **4ax**:**4ax′** = 3.3:1, **4ay**:**4ay′** = 6.3:1. [g]The product is very unstable. [h]5.0 equiv of **2**. [i]10.0 equiv of **2**. [j]10 mol % catalyst.

To further extend the substrate scope, we next examined several different substituted vinylaziridines. As depicted in Table 2, *N*-nosyl vinylaziridine **1c** and *N*-mesyl vinylaziridine **1d** proceeded smoothly in current transformation, providing options for *N*-protection and deprotection. The R^5 group in **1** could be replaced by H, *n*-butyl, isopropyl, or phenyl groups without a notable negative effect to the cycloaddition under conditions A or B (**1b−1g**). Notably, aziridinyl enolsilanes **1h** and **1i** underwent [3 + 2] and [5 + 2] cycloadditions with acceptable yields, albeit that products **3ia** and **4ia** are moisture sensitive.[15] Vinylaziridines **1j**[16] and **1k** could also successfully deliver the desired products, incorporating a quaternary carbon into the 2,3-dihydropyroles. Furthermore, **1l** is also applicable to

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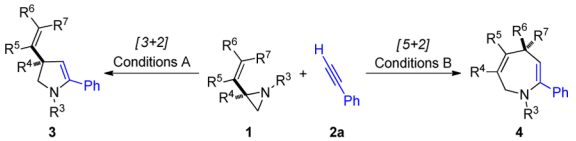
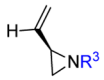
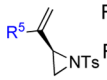
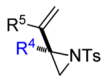
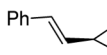
Table 2. Scope with Respect to Various VAs 1[a]

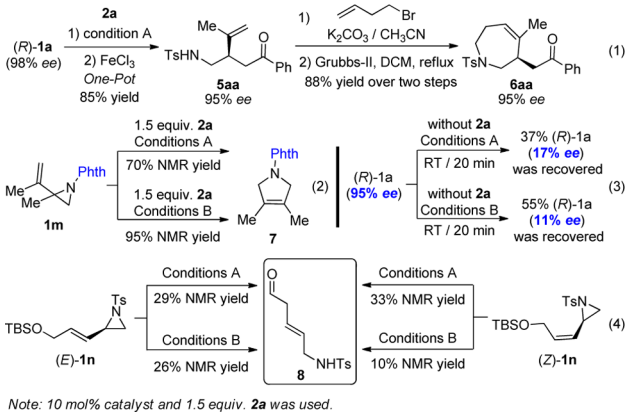


entry	(1)(ee%)	Cond. A Yield(ee)(%)	Cond. B Yield(%)
1	 R^3 = Ts(**1b**)(99)	**3ba**, 75 (97)	**4ba**, 40[b]
2	R^3 = Ns(**1c**)(92)	**3ca**, 84 (92)	**4ca**, 70
3	R^3 = Ms(**1d**)(86)	**3da**, 50(86)	**4da**, 62
4	 R^5 = *i*-Pr(**1e**)(90)	**3ea**, 72 (90)	**4ea**, 92
5	R^5 = *n*-Bu(**1f**)(88)	**3fa**, 65 (93)	**4fa**, 91
6	R^5 = Ph(**1g**)(97)	**3ga**, 75 (99)	**4ga**, 90
7	R^5 = OTBS(**1h**)(95)	**3ha**,84 (95)	**4ha**, 78
8	R^5 = OTES(**1i**)(94)	**3ia**, 75[c] (-)	**4ia**, 76[c]
9	 R^5 = H, R^4 = *i*-Pr ((*R*)-**1j**)(85)	**3ja**, 78 (84)	**4ja**, 48[d]
10	R^5 = Me, R^4 = Me ((*S*)-**1k**)(86)	**3ka**, 55 (85)[e]	**4ka**, 40[f]
11	 **1l** (98)	**3la**, 53 (32)[c]	**4la**,40[g]

[a]Conditions A and B are the same as those described in Table 1. Isolated yield. [b]**3ba** was obtained in 20% yield. [c]NMR yield, the product is very unstable. [d]**3ja** and **4ja** were obtained in 48% total yield together with **9** in 45% yield, see ref 16, **4ja**:**3ja** = 1.0:0.7. [e]Reaction was run at room temperature with 10 mol % catalyst for 1 h. [f]Reaction was run at room temperature with 5 mol % $[Rh(COD)Cl]_2/AgSbF_6$ for 1 h. [g]**3la** (59% ee) and **4la** (72% ee) were obtained in 40% total yield, **4la**:**3la** = 1.0:1.2.

the [3 + 2] and [5 + 2] cycloadditions, but gave the corresponding cycloadducts with lower ee value and yield.

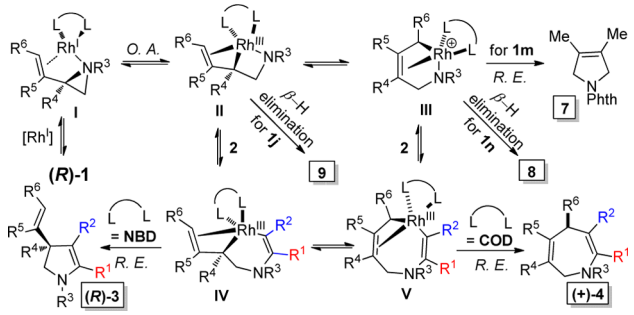
Given the fact that synthesis of chiral azepine is in great demand in both organic and medicinal chemistry, a method was developed to convert the [3 + 2] cycloadducts to chiral azepines. (*R*)-**1a** and **2a** can be transformed into a useful building block, γ-amino ketone **5aa**, using a one-pot protocol. Subsequently, the transformation of **5aa** to the enantiomerically pure azepines **6aa** was accomplished by a sequence of S_N2 reaction followed by ring-closing metathesis (eq 1).



To clarify the mechanism, we examined the reaction of vinylaziridines without the activated sulfonamide group. The reaction turned out to be messy when the unactivated vinylaziridines were employed in the current cycloadditions (see Figure S1, in the SI), whereas 3-pyrroline **7** can be accessed from vinylaziridine **1m** with phthalimido (Phth) group under condition A or B (eq 2).[17] Interestingly, the (*R*)-**1a** would undergo racemization rapidly in the absence of alkyne (eq 3).

Based on the results above, a plausible mechanism is proposed in Scheme 2. Coordination of rhodium catalyst to vinylaziridine

Scheme 2. Proposed Mechanism



(*R*)-**1** via the olefin and the nitrogen gives complex **I**. Subsequent oxidative addition with retention gives enyl (σ + π) rhodium species **II** and **III** reported by Evans.[18,19] The direct reductive elimination of rhodium species **III** would afford the 3-pyrroline **7** when the vinylaziridine **1m** was used as starting material. The competitive β-H elimination of rhodium species **III** (or **II**) derived from **1n** (or **1j**) would give the aldehyde **8** (eq 4) or (diene **9**)[16] after further reductive elimination. In the presence of alkynes **2**, rhodium species **II** and **III** could be regioselectively captured by alkynes to deliver another two interconvertible enyl (σ + π) rhodium species **IV** and **V**, followed by irreversible reductive elimination to yield [3 + 2] cycloadduct (*R*)-**3** and [5 + 2] cycloadduct (+)-**4**, respectively, under the catalysis of two different rhodium catalysts. Although the exact mechanism of this intriguing transformation remains unclear at this stage, both the diene ligands (NBD versus COD) and the property of the substrates play a central role on the mode of the current cycloadditions.

In summary, a product-switchable rhodium(I)-catalyzed intermolecular cycloaddition of vinylaziridines and alkynes has been developed and enables the efficient and divergent synthesis of two types of aza-heterocycles, 2,3-dihydropyroles and 2,5-dihydroazepines from identical starting materials, respectively, through [3 + 2] and [5 + 2] cycloadditions. Notably, the chirality of vinylaziridines can be efficiently transferred to the [3 + 2] cycloadducts. The salient features of this transformation include an atom-economic and switchable process, mild reaction conditions, stereospecificity, and general substrate scope. Further mechanism and synthetic application of this efficient transformation are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00386.

Experimental details and data (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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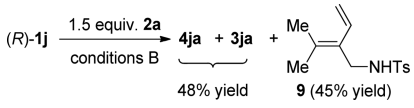

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