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Divergent Catalytic Approach from Cyclic Oxime Esters to Nitrogen-Containing Heterocycles with Group 9 Metal Catalysts

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Supporting Information Placeholder

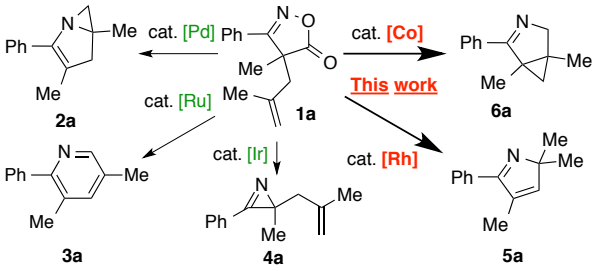
ABSTRACT: We report the divergent catalytic transformation of alkene-tethered isoxazol-5(4*H*)-ones by using rhodium and cobalt catalysts to afford 2*H*-pyrroles (with Rh catalyst) and azabicyclic cyclopropanes (with Co catalyst). The rhodium-catalyzed 2*H*-pyrrole formation involving hydrogen shift is supported by deuterium-labeling experiments. The control experiments in the cobalt-catalyzed reaction indicate that the bicyclic aziridines as the primary product undergo a skeletal rearrangement assisted by metal iodide salts.

Keywords: divergent catalysis, rhodium, cobalt, N-heterocycles, decarboxylation

1. INTRODUCTION

Divergent catalytic transformation of common substrates toward various synthetic scaffolds through the common intermediates by changing transition metals[1,2] or by using different ligands[3,4] is an efficient and powerful strategy as well as a more challenging issue than the usual synthetic strategy aiming at an individual approach to each target. Such kinds of divergent approaches are considered to be effective in the synthesis of various nitrogen-containing heterocycles, which are privileged structural motifs in biologically active molecules, including synthetic drugs.[1,3] Recently, the generation of nitrogen-centered active species generated by catalytic N–O bond cleavage of oxime esters has emerged as one of the most attractive methods for synthesizing various nitrogen-containing heterocycles.[5,6] We have recently found that isoxazol-5(4*H*)-ones (isoxazolones) could act as the alkenylnitrene equivalent (Scheme 1), which is followed by palladium-catalyzed cyclization with the internal olefin to form a bicyclic aziridine.[7,8] During the course of studies, we also found different cyclization reactions of the same isoxazolones, catalyzed by iridium and ruthenium, providing 2*H*-azirines and pyridines, respectively.[9,10] We report herein the divergence of these nitrene-transfer reactions by employing rhodium and cobalt catalysts, affording two different nitrogen-containing heterocycles, 2*H*-pyrroles and azabicyclo[3.1.0]hex-2-enes.

Scheme 1. Divergent synthesis of nitrogen-containing heterocycles by transition metal-catalyzed transformation of alkene-tethered isoxazol-5(4*H*)-ones.



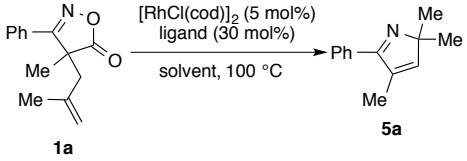
2. RESULTS AND DISCUSSION

2.1. Rhodium-catalyzed 2*H*-Pyrrole Formation

At the outset of this study, we examined the reaction of the model substrate **1a** with a catalyst precursor ([RhCl(cod)]$_2$, 10 mol% per Rh) and various phosphine ligands in 1,4-dioxane at 100 °C for 5 h (Table 1). Trialkylphosphines P(alkyl)$_3$ (alkyl = Me, Cy, *t*-Bu) did not work as ligands for 2*H*-pyrrole formation (entries 1–3). When we employed PPh$_3$ as a ligand, 2*H*-pyrrole **5a** was obtained as the corresponding decarboxylative cyclization product in 67% yield (entry 4). We next examined various triarylphosphine and bisphosphine ligands under similar conditions. Among the various bisphosphine ligands examined, dppf exhibited the highest selectivity for 2*H*-pyrrole formation, 2*H*-pyrrole **5a** being obtained in 74% yield (entries 5–8). When the electronic effect of the triarylphosphine ligands was examined, the use of triarylphosphine with electron-deficient trifluoromethyl group P(4-CF$_3$C$_6$H$_4$)$_3$ resulted in very low conversion (entry 9). This result makes a striking contrast to the palladium-catalyzed aziridination, in which P(4-CF$_3$C$_6$H$_4$)$_3$ is the most effective ligand for obtaining bicyclic aziridine **2a** in the highest yield.[7a] Finally, we found the electron-rich

triarylphosphine, P(4-MeOC$_6$H$_4$)$_3$, was the best ligand in the selective formation of 2*H*-pyrroles (entry 10). Reducing the amount of catalyst loading to 5 mol% Rh diminished the yield of 2*H*-pyrrole significantly in 1,4-dioxane (entry 11). The yield was increased to 84% (73% isolated yield) when acetonitrile was used as the solvent (entries 12–14).

Table 1. Rhodium-catalyzed formation of 2*H*-pyrrole **5a** from isoxazolone **1a**.[a]

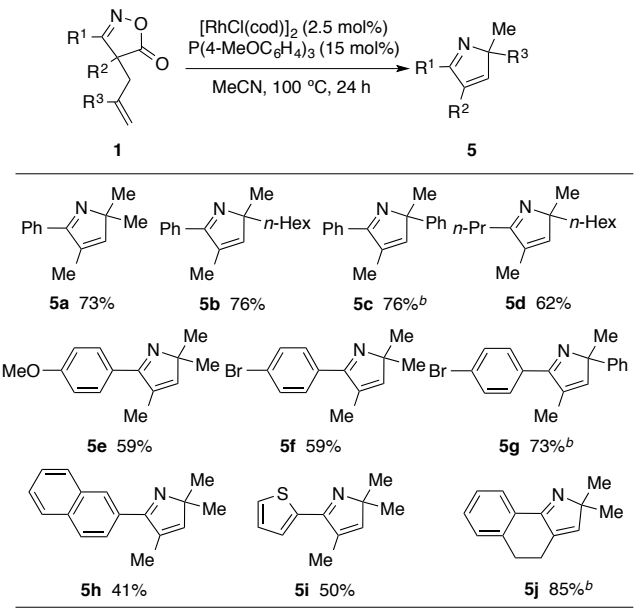


entry	ligand	solvent	time (h)	conv (%)[b]	yield (%)[b]
1	PMe_3	1,4-dioxane	5	31	2
2	PCy_3	1,4-dioxane	5	0	0
3	P(*t*-Bu)$_3$	1,4-dioxane	5	0	0
4	PPh_3	1,4-dioxane	5	99	67
5[c]	dppe	1,4-dioxane	5	88	38
6[c]	dppb	1,4-dioxane	5	86	36
7[c]	dppf	1,4-dioxane	5	96	74
8[c]	*rac*-binap	1,4-dioxane	5	100	33
9	P(4-$CF_3C_6H_4$)$_3$	1,4-dioxane	5	9	2
10	P(4-MeOC$_6$H$_4$)$_3$	1,4-dioxane	5	100	81
11[d]	P(4-MeOC$_6$H$_4$)$_3$	1,4-dioxane	24	73	44
12[d]	P(4-MeOC$_6$H$_4$)$_3$	THF	24	100	69
13[d]	P(4-MeOC$_6$H$_4$)$_3$	DME	24	100	77
14[d]	P(4-MeOC$_6$H$_4$)$_3$	MeCN	24	100	84 (73)[e]

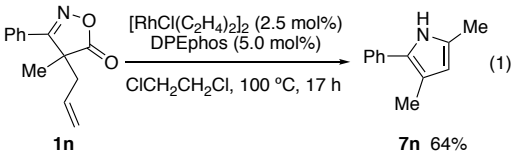
[a] The reaction was carried out with isoxazolone **1a** (0.20 mmol), [RhCl(cod)]$_2$ (5 mol%), and ligand (30 mol%) in 1,4-dioxane (2.0 mL) at 100 °C. [b] Determined by ^{1}H NMR spectra of the crude products. [c] 10 mol% of the ligand was used. [d] [RhCl(cod)]$_2$ (2.5 mol%) and ligand (15 mol%) were used. [e] The yield of isolated product.

The rhodium-catalyzed 2*H*-pyrrole formation reaction can be applied to several substrates bearing a variety of substituents (Table 2). When methyl, *n*-hexyl, and phenyl groups were employed as R^3 substituents, the corresponding 2*H*-pyrroles were obtained in good yields (**5a**–**c**). Isoxazolone **1d** having all alkyl substituents for R^1, R^2, and R^3 afforded 2*H*-pyrrole **5d** in 62% yield. Isoxazolones bearing various aromatic substituents on R^1, such as *p*-methoxyphenyl, *p*-bromophenyl, naphthyl, and thienyl groups also afforded 2*H*-pyrroles **5e**–**i** in good yields. Tricyclic product **5j** was also obtained from tetralin-fused isoxazolone **1j**. The reaction of isoxazolone **1n**, which possesses an allyl group (R^3 = H) gave 1*H*-pyrrole **7n** in place of 2*H*-pyrrole in good yield, when the reaction was carried out with [RhCl(C$_2$H$_4$)$_2$]$_2$ and DPEphos in dichloroethane at 100 °C, 17 h (eq 1).

Table 2. Rhodium-catalyzed reaction of isoxazol-5(4*H*)-one **1** giving 2*H*-pyrrole **5**.[a]

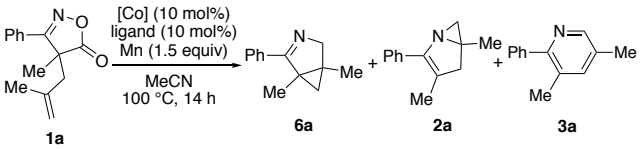


[a] Reaction conditions: isoxazolone **1** (0.20 mmol), [RhCl(cod)]$_2$ (2.5 mol%), and P(4-MeOC$_6$H$_4$)$_3$ (15 mol%) in acetonitrile (2.0 mL). [b] [RhCl(cod)]$_2$ (5 mol%) and P(4-MeOC$_6$H$_4$)$_3$ (30 mol%) were used.



2.2. Cobalt-catalyzed Azabicyclic Cyclopropane Formation

Table 3. Cobalt-catalyzed decarboxylative transformation of isoxazolone **1a**.[a]



entry	[Co]	ligand	conv (%)[b]	**6a** (%)[b]	**2a** (%)[b]	**3a** (%)[b]
1	CoI_2	dppe	100	66 (60)	0	9
2	CoI_2	dppbz	100	66	0	5
3	CoI_2	dppp	57	14	0	1
4	CoI_2	dppf	100	30	0	6
5	CoI_2	DPEphos	58	24	0	4
6	CoI_2	PPh_3	56	10	0	3
7	CoI_2(dppe)	none	100	67	0	7
8	$CoBr_2$	dppe	79	6	32	1
9[c]	CoI_2	dppe	100	0	43	11

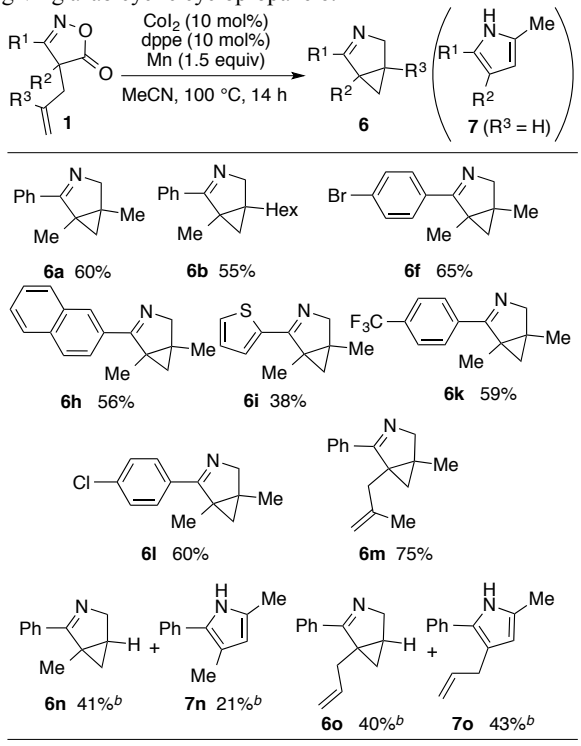
[a] Reaction conditions: isoxazolone **1a** (0.20 mmol), CoI_2 (10 mol%), Mn (0.30 mmol), and ligand (10 mol%) in acetonitrile (2.0 mL) at 100 °C. [b] Determined by ^{1}H NMR analyses of the crude products. [c] Reaction at 60 °C.

During the exploration of catalysis with other metals, we found that a reaction of **1a** catalyzed by a low-valent cobalt-dppe complex, which was generated via reduction of CoI_2 with metallic Mn powder *in situ*,[11] afforded a new product **6a** with a small amount of pyridine **3a** (Table 3,

entry 1). Hence, the reaction conditions of the cobalt-catalyzed reaction of isoxazolone **1a** including ligands, temperature, and solvent were examined. Acetonitrile was also found to be the most effective solvent in the cobalt catalysis.[12] Dppe and dppbz gave the best yields of product **6a** as a result of the screening of various monophosphine and bisphosphine ligands (entries 1–6). The reaction also proceeded smoothly when a presynthesized cobalt–phosphine complex was used (entry 7). In sharp contrast, the employment of a cobalt dibromide complex instead of the iodide complex afforded the product **6a** only in 6% yield. Instead, bicyclic aziridine **2a** was obtained in moderate yield (entry 8). The selective formation of aziridine **2a** was also observed in the reaction at a lower temperature (entry 9).

With the optimized conditions for the selective formation of cyclopropanes established, a variety of **1** was tested (Table 4). Bromo, chloro, thienyl, and trifluoromethyl groups on the aromatic substituent in R^1 could be tolerated under the reaction conditions (**6f–l**). Isoxazolone **1n** and **1o** having one and two allyl groups afforded cyclopropanes **6n** and **6o**, respectively, together with 1*H*-pyrroles **7n** and **7o**.

Table 4. The cobalt-catalyzed reaction of isoxazol-5(4*H*)-one **1** giving azabicyclic cyclopropane **6**.[a]



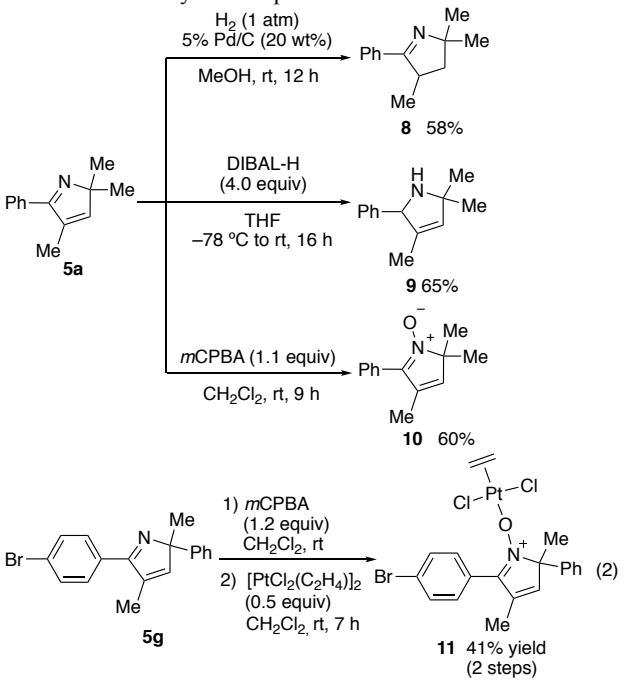
[a] Reaction conditions: isoxazolone **1** (0.20 mmol), CoI_2 (10 mol%), Mn (0.30 mmol), and dppe (10 mol%) in acetonitrile (2.0 mL) at 100 °C.

2.3. Derivatization of the reaction products

2*H*-Pyrroles obtained from the rhodium-catalyzed reaction could be transformed into oxidized or reduced five-membered nitrogen-containing heterocycles by simple oxidation and reduction (Scheme 2). Heterogeneous palladium–carbon-catalyzed hydrogenation of 2*H*-pyrrole **5a** afforded pyrroline **8** selectively, while the reaction of 2*H*-pyrrole **5a** with DIBAL-H resulted in the reduction of the C=N double bond to form pyrroline **9** selectively. Oxidation of 2*H*-pyrrole **5a** with *m*-CPBA afforded the corresponding *N*-oxide **10** in good yield. The 2*H*-pyrrole *N*-oxide derived from **5g**, like **5a**, was further converted to the platinum complex **11** in moderate yield. The structure of **11** was determined by X-ray crystallographic analysis (eq 2, Figure 1).

Azabicyclic cyclopropane **6a**, which was obtained in the cobalt-catalyzed reaction, was also applied to hydride reduction with $NaBH_3CN$ to give the corresponding bicyclic amine **12** as a single diastereomer in good yield (eq 3).[13]

Scheme 2. Oxidation and reduction of 2*H*-pyrroles into five-membered heterocyclic compounds



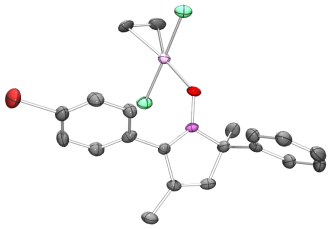
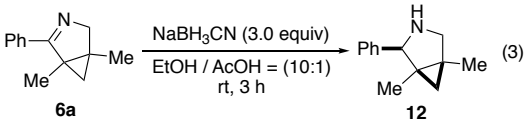


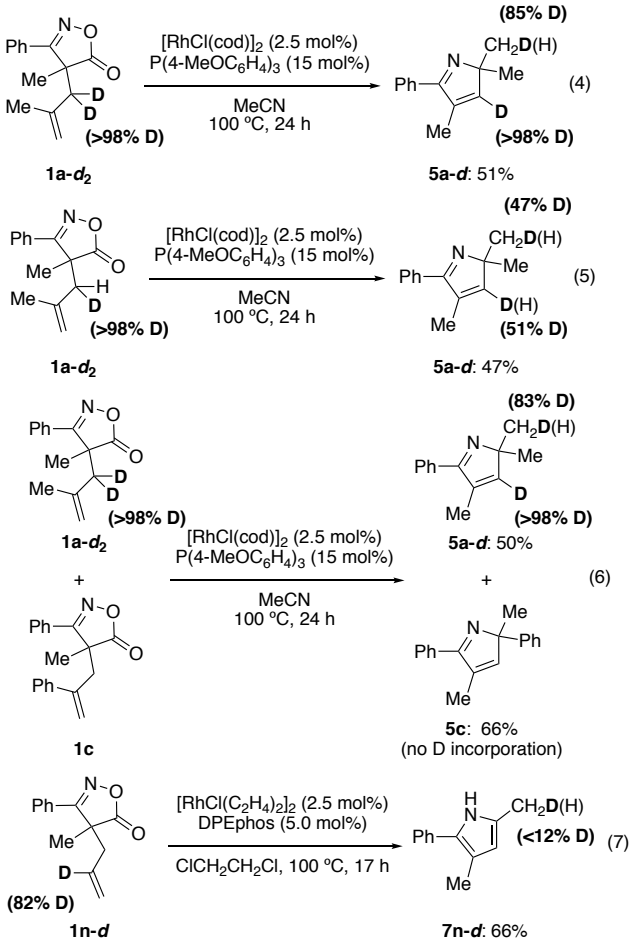
Figure 1. An ORTEP drawing of platinum complex **11**. Hydrogen atoms are omitted for clarity. CCDC 1839972.



2.4. Deuterium-labeling Experiments

Deuterium-labeling experiments were performed to gain insight into the mechanism of the rhodium-catalyzed reaction. Deuterated isoxazolone **1a**-d_2 was reacted under the standard conditions to give 2*H*-pyrrole **5a**-*d*, in which one of the deuterium atoms was incorporated into the methyl group (85% incorporation) and the other deuterium remained attached to the original carbon (eq 4). The reaction

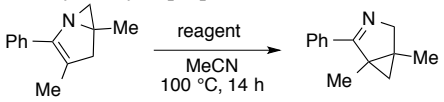
of monodeuterated isoxazolone **1a**-d_1 showed no significant intramolecular kinetic isotope effect (eq 5). A crossover reaction using **1a**-d_2 and **1c** in 1:1 ratio resulted in the formation of deuterated **5a**-*d* and **5c**, which indicates that no intermolecular exchange of hydrogen atoms occurred during the reaction (eq 6). Moreover, allyl-substituted isoxazolone **1n**-*d* with one deuterium at the 2-position of an allyl group was transformed into 1*H*-pyrrole **7n**-*d*, in which the deuterium incorporation ratio at the methyl position was less than 12% (eq 7). This result is in sharp contrast to the palladium-catalyzed formation of 1*H*-pyrroles.[7c] The formation of 1*H*-pyrroles can be explained by assuming the prototropic shift of mechanism from that of the palladium catalyst.[14]



2.5. Control Experiments in Cobalt-catalyzed Reaction

Considering that the cobalt-catalyzed reaction at the lower temperature gave aziridine **2a** as a major product, generation of azabicyclic cyclopropane **6a** by cobalt catalysis would involve the skeletal rearrangement of aziridine **2a**. Therefore, we investigated several conditions of the reaction of isolated aziridine **2a** giving **6a** (Table 5). In the presence of CoI_2, dppe, and metallic Mn, aziridine **2a** was isomerized to product **6a** in good yield, which indicates that aziridine **2a** was a key intermediate for the formation of **6a** (entry 1). The isomerization proceeded in the presence of a catalytic amount of metal iodides such as CoI_2, ZnI_2, SmI_2, and LiI (entries 2–5). While Bu_4NI and $ZnBr_2$ did not show prominent catalytic activity toward the isomerization (entries 6 and 7), the efficacy of metal iodide salts in isomerization was obvious.

Table 5. Skeletal rearrangement of bicyclic aziridine **2a** into azabicyclic cyclopropane **6a**.[a]

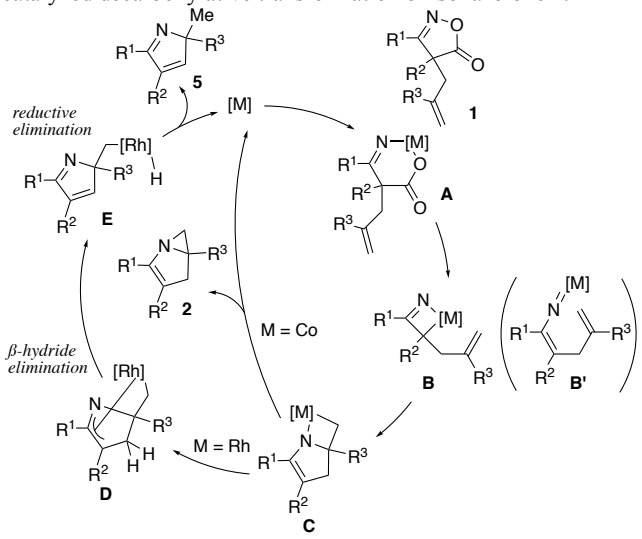


entry	reagents	**6a** (%)[b]
1	CoI_2 (10 mol%), dppe (10 mol%), Mn (1.5 equiv)	68
2	CoI_2 (10 mol%)	49
3	ZnI_2 (10 mol%)	61
4	SmI_2 (10 mol%)	72
5	LiI (10 mol%)	57
6	Bu_4NI (10 mol%)	13
7	$ZnBr_2$ (10 mol%)	0

[a] Reaction conditions: aziridine **2a** (0.20 mmol) and reagents (as described above) in acetonitrile (2.0 mL) at 100 °C. [b] Determined by ^1H NMR analyses of the crude products.

2.6. Mechanistic Consideration

Scheme 3. A proposed catalytic cycle for rhodium- and cobalt-catalyzed decarboxylative transformation of isoxazolone **1**.

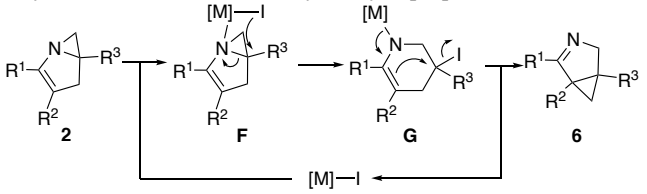


Based on the above experimental results, the proposed mechanism for rhodium-catalyzed 2*H*-pyrrole formation and cobalt-catalyzed bicyclic aziridine formation is shown in Scheme 3. Considering the catalytic cycles proposed for palladium-, ruthenium-, and iridium-catalyzed reactions, the present catalytic cycle also begins from the oxidative addition of isoxazolone **1** to the low-valent metal species to form intermediate **A** via N–O bond cleavage.[7–10] Intermediate **A** rapidly undergoes decarboxylation to form azametallacyclobutene **B** rather than alkenylnitrene species **B′**,[15] which then undergoes intramolecular cycloaddition or 1,2-insertion of olefinic moieties into the metal–nitrogen double bond to form bicyclic metallacycle **C**. In the cobalt-catalyzed reaction, C–N bond-forming reductive elimination from intermediate **C** affords bicyclic aziridine **2** as well as the regenerated catalyst, which is very similar to the palladium-catalyzed system.[7a,16] In the rhodium-catalyzed reaction, on the other hand, intermediate **C** would isomerize into aza-η^3-allylrhodium intermediate **D**. Then the β-hydride elimination followed by reductive elimination

would form 2*H*-pyrrole **5** as well as the regenerated catalyst. These reaction pathways are in good agreement with deuterium-labeling experiments as described above. 1*H*-Pyrrole **7** is considered as the prototropically isomerized product of 2*H*-pyrrole **5**, which has also been confirmed by the deuterium-labeling experiment described above.

It is assumed that the skeletal rearrangement of bicyclic aziridine **2** to azabicyclic cyclopropane **6** would be triggered by the coordination of the nitrogen atom to the Lewis acidic metal species,[17,18] taking the control experiments as shown in Table 3 into consideration. Then complex **F** undergoes a C–N bond-cleaving ring expansion simultaneously with the formation of the C–I bond to form six-membered species **G**,[19] which readily undergoes the C–C bond-forming recyclization to give bicyclic product **6**, regenerating the metal iodide species (Scheme 4).

Scheme 4. Proposed mechanism for skeletal rearrangement of bicyclic aziriridne **2** into azabicyclic cyclopropane **6**.



3. CONCLUSION

We have explored divergence in the decarboxylative ring-reconstruction of alkene-tethered isoxazol-5(4*H*)-ones by employing rhodium and cobalt catalysts. 2*H*-Pyrroles[20] and azabicyclo[3.1.0]hexanes,[13,21] both of which have been obtained in the present catalyst system, are both promising candidates of a framework for the synthesis of biologically active molecules, including drugs and natural products.[20c,22,23] Mechanistic elucidations using deuterium-labeling experiments and control experiments have supported the mechanism for the formation of the target heterocycles. The divergence of the catalytic transformation of isoxazolones that can be switched by changing transition metals may provide a new guiding principle in the development of divergent methods for nitrogen-containing heterocyclic molecules by transition metal catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Details on experimental procedures for the catalytic reactions, spectroscopic data for the products, and crystallographic data (PDF)
X-ray crystallographic structure of complex **11** (CIF)

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Notes

No competing financial interests have been declared.

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REFERENCES

1) For selected examples for the synthesis of *N*-heterocycles, see: (a) Cuny, G.; Bois-Choussy, M.; Zhu, J. Palladium- and Copper-Catalyzed Synthesis of Medium- and Large-Sized Ring-Fused Dihydroazaphenanthrenes and 1,4-Benzodiazepine-2,5-diones. Control of Reaction Pathway by Metal-Switching. *J. Am. Chem. Soc.* **2004**, *126*, 14475–14484. (b) Zhou, G.; Zhang, J. Product-selectivity control by the nature of the catalyst: Lewis acid-catalyzed selective formation of ring-fused tetrahydroquinolines and tetrahydroazepines via intramolecular redox reaction. *Chem. Commun.* **2010**, *46*, 6593–6595. (c) Zeng, Q.; Zhang, L.; Yang, J.; Xu, B.; Xiao, Y.; Zhang, J. Pyrroles versus cyclic nitrones: catalyst-controlled divergent cyclization of N-(2-perfluoroalkyl-3-alkynyl) hydroxylamines. *Chem. Commun.* **2014**, *50*, 4203–4206. (d) Rao, W.-H.; Yin, X.-S.; Shi, B.-F. Catalyst-Controlled Amino- versus Oxy-Acetoxylation of Urea-Tethered Alkenes: Efficient Synthesis of Cyclic Ureas and Isoureas. *Org. Lett.* **2015**, *17*, 3758–3761. (e) Zhu, P.-L.; Zhang, Z.; Tang, X.-Y.; Marek, I.; Shi, M. Gold- and Silver-Catalyzed Intramolecular Cyclizations of Indolylcyclopropenes for the Divergent Synthesis of Azepinoindoles and Spiroindoline Piperidines. *ChemCatChem* **2015**, *7*, 595–600. (f) Ding, D.; Mou, T.; Xue, J.; Jiang, X. Access to divergent benzo-heterocycles via a catalyst-dependent strategy in the controllable cyclization of *o*-alkynyl-*N*-methoxyl-benzamides. *Chem. Commun.* **2017**, *53*, 5279–5282. (g) Alam, K.; Hong, S. W.; Oh, K. H.; Park, J. K. Divergent C-H Annulation for Multifused *N*-Heterocycles: Regio- and Stereospecific Cyclizations of *N*-Alkynylindoles. *Angew. Chem. Int. Ed.* **2017**, *56*, 13387–13391.

2) For examples for the other divergent synthesis, see: (a) Liu, L.; Zhang, J. Selectivity Control in Lewis Acid Catalyzed Regiodivergent Tandem Cationic Cyclization/Ring Expansion Terminated by Pinacol Rearrangement. *Angew. Chem. Int. Ed.* **2009**, *48*, 6093–6096. (b) Chen, Z.; Tian, Z.; Zhang, J.; Ma, J.; Zhang, J. C–O Versus C–C Bond Cleavage: Selectivity Control in Lewis Acid Catalyzed Chemodivergent Cycloadditions of Aryl Oxiranyldicarboxylates with Aldehydes, and Theoretical Rationalizations of Reaction Pathways.

Chem.—Eur. J. **2012**, *18*, 8591–8595. (c) Dooley, J. D.; Chidipudi, S. R.; Lam, H. W. Catalyst-Controlled Divergent C–H Functionalization of Unsymmetrical 2-Aryl Cyclic 1,3-Dicarbonyl Compounds with Alkynes and Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 10829–10836. (d) Huang, G.; Xia, Y. Catalyst-Controlled C–C σ Bond Cleavages in Metal Halide-Catalyzed Cycloisomerization of 3-Acylcyclopropenes via a Formal 1,1-Halometalation Mechanism: Insights from Quantum Chemical Calculations. *ACS Catal.* **2015**, *5*, 859–868. (e) Lee, S.; Mah, S.; Hong, S. Catalyst Controlled Divergent C4/C8 Site-Selective C–H Arylation of Isoquinolones. *Org. Lett.* **2015**, *17*, 3864–3867.

3) For selected examples for the synthesis of *N*-heterocycles, see: (a) Strambeanu, I. I.; White, M. C. Catalyst-Controlled C–O versus C–N Allylic Functionalization of Terminal Olefins. *J. Am. Chem. Soc.* **2013**, *135*, 12032–12037. (b) Hyster, T. K.; Farwell, C. C.; Buller, A. R.; McIntosh, J. A.; Arnold, F. H. Enzyme-Controlled Nitrogen-Atom Transfer Enables Regiodivergent C–H Amination. *J. Am. Chem. Soc.* **2014**, *136*, 15505–15508. (c) Undeela, S.; Thadkapally, S.; Nanubolu, J. B.; Singarapu, K. K.; Menon, R. S. Catalyst-controlled divergence in cycloisomerisation reactions of N-propargyl-N-vinyl sulfonamides: gold-catalysed synthesis of 2-sulfonylmethyl pyrroles and dihydropyridines. *Chem. Commun.* **2015**, *51*, 13748–13751. (d) Cheng, Q.-Q.; Yedoyan, J.; Arman, H.; Doyle, M. P. Copper-Catalyzed Divergent Addition Reactions of Enoldiazoacetamides with Nitrones. *J. Am. Chem. Soc.* **2016**, *138*, 44–47. (e) Feng, J.-J.; Lin, T.-Y.; Zhu, C.-Z.; Wang, H.; Wu, H.-H.; Zhang, J. The Divergent Synthesis of Nitrogen Heterocycles by Rhodium(I)-Catalyzed Intermolecular Cycloadditions of Vinyl Aziridines and Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 2178–2181. (f) Cheng, Q.-Q.; Lankelma, M.; Wherritt, D.; Arman, H.; Doyle, M. P. Divergent Rhodium-Catalyzed Cyclization Reactions of Enoldiazoacetamides with Nitrosoarenes. *J. Am. Chem. Soc.* **2017**, *139*, 9839–9842.

4) For examples for the other divergent synthesis, see: (a) Panne, P.; Fox, J. M. Rh-Catalyzed Intermolecular Reactions of Alkynes with α-Diazoesters That Possess β-Hydrogens: Ligand-Based Control over Divergent Pathways. *J. Am. Chem. Soc.* **2007**, *129*, 22–23. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. Catalyst and base controlled site-selective sp^2 and sp^3 direct arylation of azine N-oxides. *Tetrahedron* **2009**, *65*, 3155–3164. (c) Gao, H.; Wu, X.; Zhang, J. *Exo/endo* selectivity-control in Lewis-acid catalyzed tandem heterocyclization/formal [4+3] cycloaddition: synthesis of polyheterocycles from 2-(1-alkynyl)-2-alken-1-ones and 1,3-diphenylisobenzofuran. *Chem. Commun.* **2010**, *46*, 8764–8766. (d) Chen, P.-h.; Xu, T.; Dong, G. Divergent Syntheses of Fused β-Naphthol and Indene Scaffolds by Rhodium-Catalyzed Direct and Decarbonylative Alkyne − Benzocyclobutenone Couplings. *Angew. Chem. Int. Ed.* **2014**, *53*, 1674–1678. (e) Fujino, D.; Yorimitsu, H.; Osuka, A. Regiocontrolled Palladium-Catalyzed Arylative Cyclizations of Alkynols. *J. Am. Chem. Soc.* **2014**, *136*, 6255–6258. (f) Zhang, Z.-M.; Chen, P.; Li, W.; Niu, Y.; Zhao, X.-L.; Zhang, J. New Type of Chiral Sulfinamide Monophosphine Ligands: Stereodivergent Synthesis and Application in Enantioselective Gold(I)-Catalyzed Cycloaddition Reactions. *Angew. Chem. Int. Ed.* **2014**, *53*, 4350–4354. (g) Martos-Redruejo, A.; López-Durán, R.; Buñuel, E.; Cárdenas, D. J. Ligand-controlled divergent formation of alkenyl- or allylboronates catalyzed by Pd, and synthetic applications. *Chem. Commun.* **2014**, *50*, 10094–10097. (h) Martínez, A. M.; Echavarren, J.; Alonso, I.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. Rh^{I}/Rh^{III} catalyst-controlled divergent aryl/heteroaryl C–H bond functionalization of picolinamides with alkynes. *Chem. Sci.* **2015**, *6*, 5802–5814. (i) Wang, Y.; Zhang, P.; Qian, D.; Zhang, J. Highly Regio-, Diastereo-, and Enantioselective Gold(I)-Catalyzed Intermolecular Annulations with N-Allenamides at the Proximal C=C Bond. *Angew. Chem. Int. Ed.* **2015**, *54*, 14849–14852. (j) Santhoshkumar, R.; Mannathan, S.; Cheng, C.-H. Ligand-Controlled Divergent C—H Functionalization of Aldehydes with Enynes by Cobalt Catalysts. *J. Am. Chem. Soc.* **2015**, *137*, 16116–16120. (k) Zhang, J.; Sha, S.-C.; Bellomo, A.; Trongsiriwat, N.; Gao, F.; Tomson, N. C.; Walsh, P. J. Positional Selectivity in C–H Functionalizations of 2-Benzylfurans with Bimetallic Catalysts. *J. Am. Chem. Soc.* **2016**, *138*, 4260–4266. (l) Sun, P.; Gao, S.; Yang, C.; Guo, S.; Lin, A.; Yao, H. Controllable Rh(III)-Catalyzed Annulation between Salicylaldehydes and Diazo Compounds: Divergent Synthesis of Chromones and Benzofurans. *Org. Lett.* **2016**, *18*, 6464–6467. (m) Alcaide, B.; Almendros, P.; Cembellín, S.; Fernández, I.; Martínez del Campo, T. Cationic Au^{III} versus Au^{I} : Catalyst-Controlled Divergent Reactivity of Alkyne-Tethered Lactams. *Chem.—Eur. J.* **2017**, *23*, 3012–3015. (n) Lee, Y.-C.; Patil1, S.; Golz, C.; Strohmann, C.; Ziegler, S.; Kumar, K.; Waldmann, H. A ligand-directed divergent catalytic approach to establish structural and functional scaffold diversity. *Nature Comm.* **2017**, 8, 14043.

5) For reviews, see: (a) Kitamura, M.; Narasaka, K. Synthesis of Aza‐Heterocycles from Oximes by Amino‐Heck Reaction. *Chem. Rec.* **2002**, *2*, 268–277. (b) Narasaka, K.; Kitamura, M. Amination with Oximes. *Eur. J. Org. Chem.* **2005**, 4505–4519. (c) Kitamura, M.; Narasaka, K. Catalytic Radical Cyclization of Oximes Induced by One-Electron Transfer. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 539–547. (d) Chiba, S. Cu–Rh Redox Relay Catalysts for Synthesis of Azaheterocycles. *Chem. Lett.* **2012**, *41*, 1554–1559. (e) Huang, H.; Ji, X.; Wu, W.; Jiang, H. Transition metal-catalyzed C–H functionalization of N-oxyenamine internal oxidants. *Chem. Soc. Rev.* **2015**, *44*, 1155–1171. (f) Huang, H.; Caia, J.; Deng, G.-J. O-Acyl oximes: versatile building blocks for N-heterocycle formation in recent transition metal catalysis. *Org. Biomol. Chem.* **2016**, *14*, 1519–1530. (g) Race, N. J.; Hazelden, I. R.; Faulkner, A.; Bower, J. F. Recent developments in the use of aza-Heck cyclizations for the synthesis of chiral N-heterocycles. *Chem. Sci.* **2017**, *8*, 5248–5260. (h) Bolotin, D. S.; Bokach, N. A.; Demakova, M. Y.; Kukushkin, V. Y. Metal-Involving Synthesis and Reactions of Oximes. *Chem. Rev.* **2017**, *117*, 13039–13122. (i) Gao, Q.; Liu, Z.; Wang, Y.; Wu, X.; Zhang, J.; Wu, A. I_2-Triggered Reductive Generation of N-Centered Iminyl Radicals: An Isatin-to-Quinoline Strategy for the Introduction of Primary Amides. *Adv. Synth. Catal.* **2018**, *360*, 1364–1369.

6) For selected examples, see: (a) Tsutsui, H.; Narasaka, K. Syn-

thesis of Pyrrole Derivatives by the Heck-Type Cyclization of γ,δ-Unsaturated Ketone O-Pentafluorobenzoyloximes. *Chem. Lett.* **1999**, *28*, 45–46. (b) Koganemaru, Y.; Kitamura, M.; Narasaka, K. Synthesis of Dihydropyrrole Derivatives by Copper-Catalyzed Cyclization of γ,δ-Unsaturated Ketone O-Methoxycarbonyloximes. *Chem. Lett.* **2002**, *31*, 784–785. (c) Tan, Y.; Hartwig, J. F. Palladium-Catalyzed Amination of Aromatic C−H Bonds with Oxime Esters. *J. Am. Chem. Soc.* **2010**, *132*, 3676–3677. (d) Wei, Y.; Yoshikai, N. Modular Pyridine Synthesis from Oximes and Enals through Synergistic Copper/Iminium Catalysis. *J. Am. Chem. Soc.* **2013**, *135*, 3756–3759. (e) Faulkner, A.; Scott, J. S.; Bower, J. F. An Umpolung Approach to Alkene Carboamination: Palladium Catalyzed 1,2-Amino-Acylation, -Carboxylation, -Arylation, -Vinylation, and -Alkynylation. *J. Am. Chem. Soc.* **2015**, *137*, 7224–7230. (f) Davies, J.; Booth, S. G.; Essafi, S.; Dryfe, R. A. W.; Leonori, D. Visible-Light-Mediated Generation of Nitrogen-Centered Radicals: Metal-Free Hydroimination and Iminohydroxylation Cyclization Reactions. *Angew. Chem. Int. Ed.* **2015**, *54*, 14017–14021. (g) Race, N. J.; Faulkner, A.; Shaw, M. H.; Bower, J. F. Dichotomous mechanistic behavior in Narasaka–Heck cyclizations: electron rich Pd-catalysts generate iminyl radicals. *Chem. Sci.* **2016**, *7*, 1508–1513. (h) Yang, H.-B.; Selander, N. Divergent Iron–Catalyzed Coupling of O-Acyloximes with Silyl Enol Ethers. *Chem.—Eur. J.* **2017**, *23*, 1779–1783. (i) Jiang, H.; Studer, A. Iminyl-Radicals by Oxidation of α-Imino-oxy Acids: Photoredox-Neutral Alkene Carboimination for the Synthesis of Pyrrolines. *Angew. Chem. Int. Ed.* **2017**, *56*, 12273–12276. (j) Shimbayashi, T.; Okamoto, K.; Ohe, K. Iron-Catalyzed Aminative Cyclization/Intermolecular Homolytic Aromatic Substitution Using Oxime Esters and Simple Arenes. *Chem.—Asian J.* **2018**, *13*, 395–399.

7) (a) Okamoto, K.; Oda, T.; Kohigashi, S.; Ohe, K. Palladium-Catalyzed Decarboxylative Intramolecular Aziridination from *4H*-Isoxazol-5-ones Leading to 1-Azabicyclo[3.1.0]hex-2-enes. *Angew. Chem. Int. Ed.* **2011**, *50*, 11470–11473. (b) Okamoto, K.; Shimbayashi, T.; Tamura, E.; Ohe, K. Palladium-Catalyzed Aza-Wittig-Type Condensation of Isoxazol-5(4*H*)-ones with Aldehydes. *Chem.—Eur. J.* **2014**, *20*, 1490–1494. (c) Palladium-Catalyzed Selective Formation of substituted pyrroles from alkene-tethered cyclic oxime esters. Okamoto, K.; Oda, T.; Matsushita, G.; Shimbayashi, T.; Sasakura, K.; Ohe, K. *Heterocycles*, in press (DOI: 10.3987/COM-17-S(T)4).

8) In the most recent decade, other cyclic molecules having N–O bonds have also emerged as nitrene equivalents under transition metal catalysis. See: (a) Zhong, C. L.; Tang, B. Y.; Yin, P.; Chen, Y.; He, L. Synthesis of 2,5-Disubstituted Oxazoles and Oxazolines Catalyzed by Ruthenium(II) Porphyrin and Simple Copper Salts. *J. Org. Chem.* **2012**, *77*, 4271–4277. (b) Shimbayashi, T.; Okamoto, K.; Ohe, K. Synthesis of Imidazoles and Pyrimidines Using Palladium-Catalyzed Decar-boxylative Intramolecular Condensation of 1,2,4-Oxadiazol-5(4*H*)-ones. *Synlett* **2014**, *25*, 1916–1920. (c) Bizet, V.; Buglioni, L.; Bolm, C. Light-induced ruthenium-catalyzed nitrene transfer reactions: a photochemical approach towards N-acyl sulfimides and sulfoximines. *Angew. Chem. Int. Ed.* **2014**, *53*, 5639–5642. (d) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. Mechanistic Studies on the Rh(III)-Mediated Amido Transfer Process Leading to Robust C–H Amination with a New Type of Amidating Reagent. *J. Am. Chem. Soc.* **2015**, *137*, 4534–4542. (e) Park, J.; Chang, S. Comparative Catalytic Activity of Group 9 [Cp*M(III)] Complexes: Cobalt-Catalyzed C-H Amidation of Arenes with Dioxazolones as Amidating Reagents. *Angew. Chem. Int. Ed.* **2015**, *54*, 14103–14107. (f) Mei, R.; Loup, J.; Ackermann, L. Oxazolinyl-Assisted C–H Amidation by Cobalt(III) Catalysis. *ACS Catal.* **2016**, *6*, 793–797. (g) Hermann, G. N.; Bolm, C. Mechanochemical Rhodium(III)-Catalyzed C–H Bond Amidation of Arenes with Dioxazolones under Solventless Conditions in a Ball Mill. *ACS Catal.* **2017**, *7*, 4592–4596. (h) Halskov, K. S.; Roth, H. S.; Ellman, J. A. Synthesis of [5,6]-Bicyclic Heterocycles with a Ring-Junction Nitrogen Atom: Rhodium(III)-Catalyzed C-H Functionalization of Alkenyl Azoles. *Angew. Chem. Int. Ed.* **2017**, *56*, 9183–9187. (i) Tan, P. W.; Mak, A. M.; Sullivan, M. B.; Dixon, D. J.; Seayad, J. Thioamide-Directed Cobalt(III)-Catalyzed Selective Amidation of C(sp^3)-H Bonds. *Angew. Chem. Int. Ed.* **2017**, *56*, 16550–16554. (j) Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.-H.; Chang, S. Selective formation of γ-lactams via C‑H amidation enabled by tailored iridium catalysts. *Science* **2018**, *359*, 1016–1021.

9) (a) Okamoto, K.; Shimbayashi, T.; Yoshida, M.; Nanya, A.; Ohe, K. Synthesis of 2*H*-Azirines by Iridium-Catalyzed Decarboxylative Ring Contraction of Isoxazol-5(4*H*)-ones. *Angew. Chem. Int. Ed.* **2016**, *55*, 7199–7202. (b) Okamoto, K.; Sasakura, K.; Shimbayashi, T.; Ohe, K. Ruthenium-catalyzed Decarboxylative and Dehydrogenative Formation of Highly Substituted Pyridines from Alkene-tethered Isoxazol-5(4*H*)-ones. *Chem. Lett.* **2016**, *45*, 988–990. (c) Okamoto, K.; Nanya, A.; Eguchi, A.; Ohe, K. Asymmetric Synthesis of 2*H*-Azirines with a Tetrasubstituted Stereocenter by Enantioselective Ring Contraction of Isoxazoles. *Angew. Chem. Int. Ed.* **2018**, *57*, 1039–1043.

10) Peters has also reported transition metal-catalyzed transformation of isoxazolones. See: (a) Rieckhoff, S.; Frey, W.; Peters, R. Regioselective Catalytic Asymmetric C-Alkylation of Isoxazolinones by a Base-Free Palladacycle-Catalyzed Direct 1,4-Addition. *Angew. Chem. Int. Ed.* **2015**, *54*, 2788–2791. (b) Rieckhoff, S.; Hellmuth, T.; Peters, R. Regioselective Pd-Catalyzed Synthesis of 2,3,6-Trisubstituted Pyridines from Isoxazolinones. *J. Org. Chem.* **2015**, *80*, 6822–6830. (c) Rieckhoff, S.; Titze, M.; Frey, W.; Peters, R. Ruthenium-Catalyzed Synthesis of 2*H*-Azirines from Isoxazolinones. *Org. Lett.* **2017**, *19*, 4436–4439. (d) Rieckhoff, S.; Meisner, J.; Kästner, J.; Frey, W.; Peters, R. Double Regioselective Asymmetric C-Allylation of Isoxazolinones: Iridium-Catalyzed N-Allylation Followed by an Aza-Cope Rearrangement. *Angew. Chem. Int. Ed.* **2018**, *57*, 1404–1408. (e) Rieckhoff, S.; Frey, W.; Peters, R. Regio-, Diastereo- and Enantioselective Synthesis of Piperidines with Three Stereogenic Centers from Isoxazolinones by Palladium/Iridium Relay Catalysis. *Eur. J. Org.Chem.* **2018**, 1797–1805.

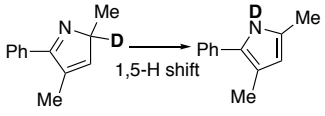
11) For selected reviews and examples, see: (a) Wei, C. H.; Mannathan, S.; Cheng, C. H. Regio- and Enantioselective Cobalt-

Catalyzed Reductive [3+2] Cycloaddition Reaction of Alkynes with Cyclic Enones: A Route to Bicyclic Tertiary Alcohols. *Angew. Chem. Int. Ed.* **2012**, *51*, 10592–10595. (b) Gandeepan, P.; Cheng, C. H. Cobalt Catalysis Involving π Components in Organic Synthesis. *Acc. Chem. Res.* **2015**, *48*, 1194–1206. (c) Sen, M.; Kalsi, D.; Sundararaju, B. Cobalt(III)-Catalyzed Dehydrative [4+2] Annulation of Oxime with Alkyne by C-H and N-OH Activation. *Chem.—Eur. J,* **2015**, *21*, 15529–15533. (d) Nogi, K.; Fujihara, T.; Terao, J.; Tsuji, Y. Carboxyzincation Employing Carbon Dioxide and Zinc Powder: Cobalt-Catalyzed Multicomponent Coupling Reactions with Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 5547–5550.

12) We assume the one-electron reduction of Co(II) precursor with metallic manganese to form Co(I) species as the primary low-valent catalyst. See also ref. 12 for other cobalt-catalyzed reactions.

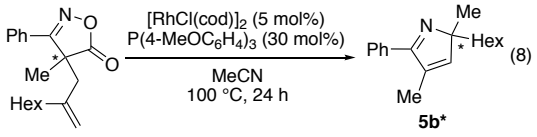
13) Toh, K. K.; Biswas, A.; Wang, Y.-F.; Tan, Y. Y.; Chiba, S. Copper-Mediated Oxidative Transformation of N-Allyl Enamine Carboxylates toward Synthesis of Azaheterocycles. *J. Am. Chem. Soc.* **2014**, *136*, 6011–6020.

14) We assume that the rhodium-catalyzed reaction of **1n**-*d* may first afford 2*H*-pyrrole **5n**-*d*, which readily undergoes 1,5-hydrogen shift to form **7n**-*d*. The deuterium on the nitrogen atom could not be detected due to the fast H–D exchange.



5n-*d* **7n**-*d*

15) We have prepared the enantiopure isoxazolone **1b*** by chiral HPLC resolution and examined this for rhodium-catalyzed 2*H*-pyrrole formation. As a result, center chirality of isoxazolone **1b*** was transferred into the different carbon center of **5b*** almost completely. This result indicates that the reaction should proceed through intermediates preserving chiral information derived from starting isoxazolone **1b***.



1b*
>99% ee

5b*
86% yield
>99% ee

16) For examples of aza-vinylcyclopropane rearrangement of *N*-vinylaziridines, see: (a) Whitlock, H. W., Jr.; Smith, G. L. The rearrangement of an N-vinylaziridine. *Tetrahedron Lett.* **1965**, *6*, 1389–1393. (b) Ito, M. M.; Nomura, Y.; Takeuchi, Y.; Tomoda, S. Formation of Unusual Pyrroles by Photolysis of 1-Vinyl-4,5-Dihydro-1*H*-1,2,3-Triazoles *Chem. Lett.* **1981**, 1519–1522. (c) More, S. S.; Mohan, T. K.; Kumar, Y. S.; Kumar, U. K. S.; Patel, N. B. Synthesis of novel 5-alkyl/aryl/heteroaryl substituted diethyl 3,4-dihydro-2*H*-pyrrole-4,4-dicarboxylates by aziridine ring expansion of 2-[(aziridin-1-yl)-1-alkyl/aryl/heteroaryl-methylene]malonic acid diethyl esters *Beilstein J. Org. Chem.* **2011**, *7*, 831–838.

17) Theoritical studies for palladium-catalyzed decarboxylative aziridination using isoxazolones have been reported. See: Xie, H.; Lin, F.; Yang, L.; Chen, X.; Ye, X.; Tian, X.; Lei, Q.; Fang, W. A DFT study on palladium-catalyzed decarboxylative intramolecular aziridination reaction mechanism. *J. Organomet. Chem.* **2013**, *417*, 745–746.

18) For examples of aza-vinylcyclopropane rearrangement of 2-vinylaziridines, see: (a) Atkinson, R. S.; Rees, C. W. A vinylaziridine to pyrroline rearrangement. *Chem. Commun.* **1967**, 1232. (b) Atkinson, R. S.; Rees, C. W. Reactive intermediates. Part VIII. Thermolysis of N-(vinylaziridinyl)-benzoxazolinones. Some new heterocyclic rearrangements. *J. Chem. Soc. C* **1969**, 778–782. (c) Hirner, S.; Somfai, P. Microwave-Assisted Rearrangement of Vinylaziridines to 3-Pyrrolines: Formal Synthesis of (-)-Anisomycin. *Synlett* **2005**, 3099–3102. (d) Birchacek, M.; Lee, D.-E.; Njardarson, J. T. Lewis Acid Catalyzed [1,3]-Sigmatropic Rearrangement of Vinyl Aziridines. *Org. Lett.* **2008**, *10*, 5023–5026.

19) The mechanism for the formation of pyridine **3a** might be attributed to the side pathway from intermediate **G**. Otherwise, there might be a similar reaction pathway to the ruthenium-catalyzed pyridine formation (ref. 9b).

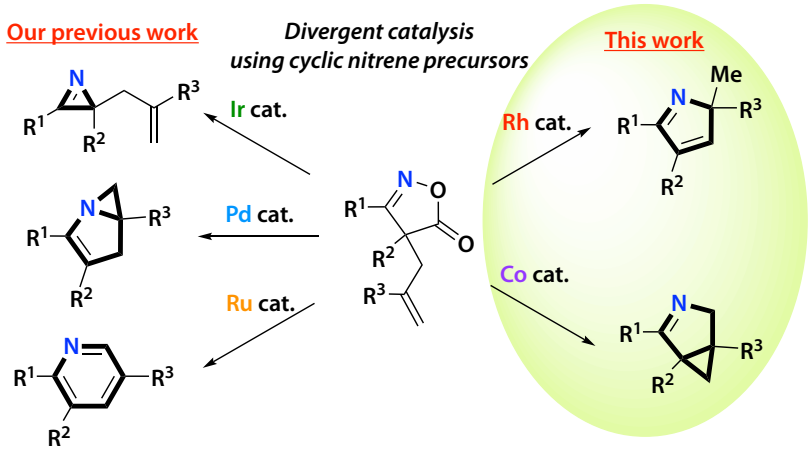
20) (a) Zhuo, C.-X.; Zhou, Y.; You, S.-L. Highly Regio- and Enantioselective Synthesis of Polysubstituted 2*H*-Pyrroles via Pd-Catalyzed Intermolecular Asymmetric Allylic Dearomatization of Pyrroles. *J. Am. Chem. Soc.* **2014**, *136*, 6590–6593. (b) Zhuo, C.-X.; Cheng, Q.; Liu, W.-B.; Zhao, Q.; You, S.-L. Enantioselective Synthesis of Pyrrole-Based Spiro- and Polycyclic Derivatives by Iridium-Catalyzed Asymmetric Allylic Dearomatization and Controllable Migration Reactions. *Angew. Chem. Int. Ed.* **2015**, *54*, 8475–8479. (c) The Organocatalytic Approach to Enantiopure 2*H*- and 3*H*-Pyrroles: Inhibitors of the Hedgehog Signaling Pathway. Kötzner, L.; Leutzsch, M.; Sievers, S.; Patil, S.; Waldmann, H.; Zheng, Y.; Thiel, W.; List, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 7693–7697. (d) Polaḱ, P.; Tobrman, T. Dearomatization Strategy for the Synthesis of Arylated 2*H*-Pyrroles and 2,3,5-Trisubstituted 1*H*-Pyrroles. *Org. Lett.* **2017**, *19*, 4608–4611.

21) (a) Wu, K.; Meng, L.; Huai, M.; Huang, Z.; Liu, C.; Qi, X.; Lei, A. Palladium-catalyzed aerobic (1+2) annulation of Csp^3–H bonds with olefin for the synthesis of 3-azabicyclo[3.1.0]hex-2-ene. *Chem. Commun.* **2017**, *53*, 2294–2297. (b) Veeranna, K. D.; Das, K. K.; Baskaran, S. One-Pot Synthesis of Cyclopropane-Fused Cyclic Amidines: An Oxidative Carbanion Cyclization. *Angew. Chem. Int. Ed.* **2017**, *56*, 16197–16201. (c) Ershov, O. V.; Bardasov, I. N. Methods of assembling 3-azabicyclo[3.1.0]hexane skeleton. *Chem. Heterocycl. Compd.* **2016**, *52*, 447–449 (microreview).

22) For selected examples of biological studies on 2*H*-pyrroles and their derivatives, see: (a) Saito, S.; Kubota, T.; Kobayashi, J. Calyciphylline G, a novel alkaloid with an unprecedented fused-hexacyclic skeleton from *Daphniphyllum calycinum*. *Tetrahedron Lett.* **2007**, *48*, 5693–5695. (b) Zhang, Y.-M.; Tan, N.-H.; Lu, Y.; Chang, Y.; Jia, R.-R. Chamobtusin A, a Novel Skeleton Diterpenoid Alkaloid from *Chamaecyparis obtusa cv. tetragon*. *Org. Lett.* **2007**, *9*, 4579–4581. (c) Deery, E.; Schroeder, S.; Lawrence, A. D.; Taylor, S. L.; Seyedarabi, A.; Waterman, J.; Wilson, K. S.; Brown, D.; Geeves, M. A.; Howard, M. J.; Pickersgill, R. W.; Warren, M. J. An enzyme-trap approach allows isolation of intermediates in cobalamin biosynthesis. *Nature Chem. Biol.*

2012, *8*, 933-940. (d) Jeppsson, F.; Eketjäll, S.; Janson, J.; Karlström, S.; Gustavsson, S.; Olsson, L.-L.; Radesäter, A.-C.; Ploeger, B.; Cebers, G.; Kolmodin, K.; Swahn, B.-M.; von Berg, S.; Bueters, T.; Fälting, J. Discovery of AZD3839, a Potent and Selective BACE1 Inhibitor Clinical Candidate for the Treatment of Alzheimer Disease. *J. Biol. Chem.* **2012**, *287*, 41245-41247.

23) For selected examples of biological studies on 3-azabicyclo[3.1.0]hexanes, see: (a) Epstein, J. W.; Brabander, H. J.; Fanshawe, W. J.; Hofmann, C. M.; McKenzie, T. C.; Safir, S. R.; Osterberg, A. C.; Cosulich, D. B.; Lovell, F. M. 1-Aryl-3-azabicyclo[3.1.0]hexanes, a New Series of Nonnarcotic Analgesic Agents. *J. Med. Chem.* **1981**, *24*, 481-490. (b) Rowlands, M. G.; Bunnett, M. A.; Foster, A. B.; Jarman, M.; Stanek, J.; Schweizer, E. Analogs of Aminoglutethimide Based on 1-Phenyl-3-azabicyclo[3.1.0]hexane-2,4-dione: Selective Inhibition of Aromatase Activity. *J. Med. Chem.* **1988**, *31*, 971-976. (c) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. CC-1065 and the Duocarmycins: Synthetic Studies. *Chem. Rev.* **1997**, *97*, 787–828. (d) Sorbera, L.A.; Castaner, J.; Leeson, P. A. Bicifadine. *Drugs Future* **2005**, *30*, 7. (d) Njoroge, F. G.; Chen, K. X.; Shih, N.-Y.; Piwinski, J. J. Challenges in Modern Drug Discovery: A Case Study of Boceprevir, an HCV Protease Inhibitor for the Treatment of Hepatitis C Virus Infection. *Acc. Chem. Res.* **2008**, *41*, 50–59. (e) Bymaster, F. P.; Golembiowska, K.; Kowalska, M.; Choi, Y. K.; Tarazi, F. I. Pharmacological characterization of the norepinephrine and dopamine reuptake inhibitor EB-1020: Implications for treatment of attention–deficit hyperactivity disorder. *Synapse* **2012**, *66*, 522. (f) Warnock, K. T.; Yang, A. R. S. T.; Yi, H. S.; June, H. L., Jr.; Kelly, T.; Basile, A. S.; Skolnick, P.; June, H. L. Rate dependent effects of acute nicotine on risk taking in young adults are not related to ADHD diagnosis. *Pharmacol., Biochem. Behav.* **2012**, *103*, 111.


Our previous work
Divergent catalysis
using cyclic nitrene precursors
This work
Ir cat.
Pd cat.
Ru cat.
Rh cat.
Co cat.
Me