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A Pd(II)-Catalyzed Ring-Expansion Reaction of Cyclic 2-Azidoalcohol Derivatives: Synthesis of Azaheterocycles

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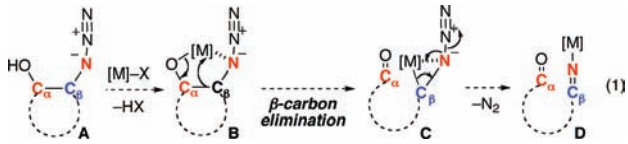
Transition metal-catalyzed C—C bond cleavage has attracted attention as a versatile tool in organic synthesis, and various modes of catalytic processes have been reported to activate inert C—C bonds.[1] Among them, β-carbon elimination of transition metal alcoholates ([M]—O—C_α—C_β → O=C_α + C_β—[M]) has recently been developed, in which formation of a relatively stable C_β—[M] bond or release of ring strain or steric congestion by cleavage of the C_α—C_β bond contributes significantly to the driving force of such reactions.[2,3] Our attention was drawn to the potential chemical reactivity of readily available 2-azidoalcohols. We hypothesized that transition metal alcoholates **B** generated from 2-azidoalcohols **A** would undergo β-carbon elimination to give α-azidocarbometal species **C** (eq 1). Subsequent metal migration from C to N with elimination of dinitrogen[4] might afford alkylideneaminometal species **D**, which could be used for further C—N bond forming reactions.[5] It was speculated that these processes might be promoted by coordination of the internal nitrogen of the azido moiety to the metal center.[6,7]



Herein, we report a Pd(II)-catalyzed ring-expansion reaction of cyclic 2-azidoalcohols, which involves an unprecedented C—C bond cleavage and C—N bond formation sequence to provide azaheterocycles such as pyridine, isoquinoline, and γ-carboline derivatives. As outlined in Scheme 1, our strategy relies on β-carbon elimination of palladium(II) alcoholate **II** generated from azidoalcohol **I** with a Pd(II) complex in the presence of a base followed by elimination of dinitrogen to give alkylideneaminopalladium(II) species **III**. Consecutive intramolecular nucleophilic attack of the iminyl palladium part of **III** to the resulting formyl group then leads to cyclized intermediate **IV**. Protonation of **IV** followed by dehydration affords six-membered azaheterocycles **VI** along with the Pd(II)

Scheme 1. Proposed Catalytic Cycle

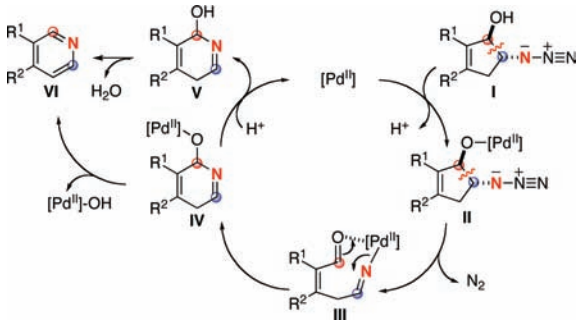
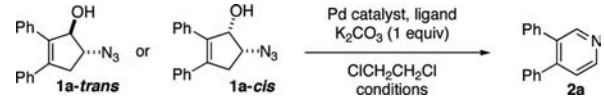


Table 1. Screening of Conditions for the Pd-Catalyzed Pyridine Formation from Azidoalcohols **1a-*trans*** and **1a-*cis***



entry	substrate	Pd catalyst (mol %)	ligand (mol %)	conditions	yield (%)[b,c]
1	**1a-*trans***	$Pd(OAc)_2$ (10)	—	60 °C, 3 h	0 (91)
2	**1a-*trans***	$Pd(OAc)_2$ (10)	PPh_3 (20)	60 °C, 6.5 h	44 (51)
3	**1a-*trans***	$Pd(OAc)_2$ (20)	PPh_3 (40)	60 °C, 6 h	55 (5)
4	**1a-*trans***	$Pd(OAc)_2$ (10)	$P(t\text{-}Bu)_3$ (20)	60 °C, 6 h	0 (79)
5	**1a-*trans***	$Pd(OAc)_2$ (15)	dppb (15)	60 °C, 5 h	72
6	**1a-*trans***	$Pd(OAc)_2$ (15)	dppf (15)	80 °C, 2.5 h	70
7	**1a-*trans***	$PdCl_2$(dppb) (15)	—	80 °C, 8 h	64 (11)
8	**1a-*trans***	$PdCl_2$(dppf) (15)	—	80 °C, 5 h	88
9	**1a-*trans***	$Pd(OAc)_2$ (15)	2,2′-bipyridine (15)	80 °C, 0.5 h	80
10	**1a-*trans***	$Pd(OAc)_2$ (15)	TMEDA (15)	80 °C, 8 h	69 (19)
11	**1a-*cis***	$PdCl_2$(dppf) (15)	—	80 °C, 4 h	59
12	**1a-*cis***	$Pd(OAc)_2$ (15)	2,2′-bipyridine (15)	80 °C, 6 h	51 (34)

[a] All reactions were carried out in the scale of 0.3 mmol of **1a** in $ClCH_2CH_2Cl$ (2 mL) under N_2. [b] Isolated yield. [c] Recovery yield of **1a** is in parentheses. dppb: 1,4-bis(diphenylphosphino) butane; dppf: 1,1′-bis(diphenylphosphino)ferrocene. TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

complex. Alternatively, elimination of hydroxy Pd(II) species from **IV** provides **VI** directly.

First, reactions of (1*R**,5*R**)-5-azido-2,3-diphenylcyclopent-2-enol (**1a-*trans***) with some transition metal catalysts (with 1 equiv of K_2CO_3 in 1,2-dichloroethane) were examined, and Table 1 lists representative data using palladium catalyst systems. While $Pd(OAc)_2$ itself (10 mol %) did not exhibit any reactivity to **1a** (entry 1), it showed some catalytic effect in the presence of PPh_3 (20 mol %) at 60 °C, giving a ring expansion product, 3,4-diphenylpyridine (**2a**) in 44% yield with 51% recovery of **1a** (entry 2). Higher catalytic loading, however, did not improve the chemical yield of **1a** (entry 3). Although the reaction with bulky $P(t\text{-}Bu)_3$ did not proceed at all (entry 4), bidentate phosphine ligands like dppb and dppf proved to be optimal ligands for the pyridine formation (entries 5—8). The use of $PdCl_2$(dppf) (15 mol %) at 80 °C gave **2a** in the best yield (88%) (entry 8). Interestingly, nitrogen ligands such as 2,2′-bipyridine and TMEDA with $Pd(OAc)_2$ also exhibited good catalytic activity (entries 9 and 10). The reactions of the corresponding *cis*-azidoalcohols **1a-*cis*** were also found to proceed to afford pyridine **2a**, although the yield of **2a** was lower than that from *trans*-azidoalcohol **1a-*trans*** (entries 11 and 12). Such a C—C bond fission of the unstrained five-membered ring is quite rare.[2h,8] Other metal complexes like Ni(II), Cu(I), Rh(I), and Au(I) were not viable catalysts for this transformation (see Supporting Information).

With the identification of the optimized conditions in hand, we next examined the generality of this catalytic method for the synthesis of substituted pyridines using *trans*-azidoalcohol **1** (Table

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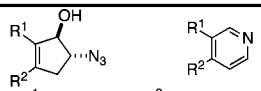
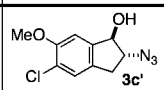
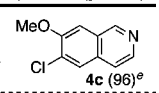
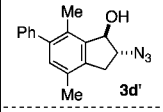
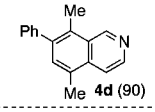
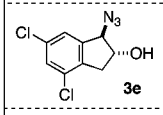
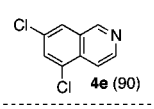
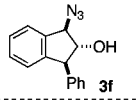
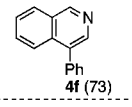
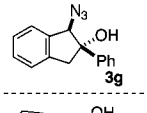
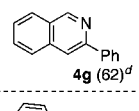
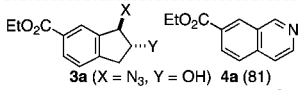
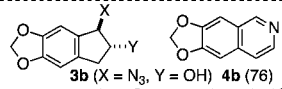
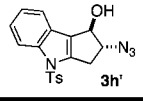
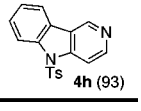
Table 2. Synthesis of Pyridines, Isoquinolines and γ-Carboline[a,b]

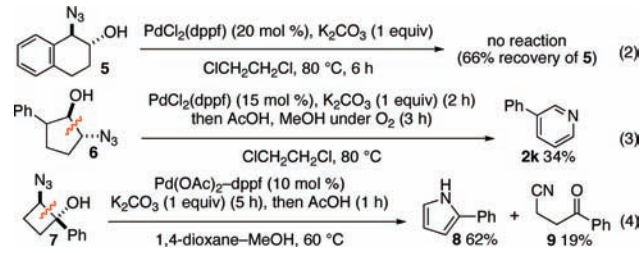
trans-azidoalcohols	products (yield/%)[b]	azidoalcohols	products (yield/%)[b]
			
1b: R^1 = 4-Me-C_6H_4, R^2 = Ph	**2b** (78)	**3c'**	**4c** (96)[e]
1c: R^1 = 4-Cl-C_6H_4, R^2 = Ph	**2c** (88)		
1d: R^1 = 4-F-C_6H_4, R^2 = Ph	**2d** (89)		
1e: R^1 = Me, R^2 = Ph	**2e** (83)	**3d'**	**4d** (90)
1f : R^1 = Me, R^2 = 3,5-Me_2-C_6H_3	**2f** (74)		
1g: R^1 = allyl, R^2 = Ph	**2g** (80)		
1h: R^1 = Me, R^2 = $PhCH_2CH_2$	**2h** (65)	**3e**	**4e** (90)
1i : R^1 = Cl, R^2 = Ph	**2i** (90)		
1j : R^1 = Br, R^2 = Ph	**2j** (72)[c]		
1k: R^1 = Ph, R^2 = H	**2k** (83)[d]	**3f**	**4f** (73)
1l : R^1 = 4-Me-C_6H_4, R^2 = H	**2l** (64)		
1m: R^1 = 2-Me-C_6H_4, R^2 = H	**2m** (66)		
1n: R^1 = 4-Cl-C_6H_4, R^2 = H	**2n** (84)	**3g**	**4g** (62)[d]
1o: R^1 = 4-F-C_6H_4, R^2 = H	**2o** (86)		
1p: R^1 = 4-CF_3-C_6H_4, R^2 = H	**2p** (93)		
			
3a (X = N_3, Y = OH) **4a** (81)			
3a' (X = OH, Y = N_3) **4a** (96)[e]			
			
3b (X = N_3, Y = OH) **4b** (76)		**3h'**	**4h** (93)
3b' (X = OH, Y = N_3) **4b** (92)[e]			

[a] Unless otherwise noted, the reactions were carried out using 0.3 mmol of azidoalcohols **1** or **3** in the presence of 15 mol % of $PdCl_2$(dppf) and 1 equiv of K_2CO_3 in $ClCH_2CH_2Cl$ (2 mL) under N_2. [b] Isolated yields are recorded above. [c] The reaction was run using 10 mol % of $Pd(OAc)_2$ and 2,2′-bipyridine as a catalyst. [d] 20 mol % of $PdCl_2$(dppf) was used. [e] The reaction was carried out using 10 mol % of $Pd(OAc)_2$ and 10 mol % of dppf at *room temperature*.

2). The reaction allowed installing not only aryl substituents but also methyl and allyl moieties at C-3 on the pyridine ring (**2b**−**2g**). 3,4-Dialkylsubstituted pyridines **2h** could also be synthesized in good yield. Importantly, 3-chloro- and 3-bromopyridines **2i** and **2j** were successfully formed with keeping the C−Cl or C−Br bond intact. 3-Arylpyridines with some substituents were prepared using this method (**2k**−**2p**). In addition to pyridines, this catalytic ring expansion provided substituted isoquinoline derivatives. It is noted that the reactions of both *trans*-1-azido-2-indanol **3** and 2-azido-1-indanol **3′** proceeded to afford the same isoquinolines using a 10 mol % catalyst (**4a** and **4b**). Interestingly, the reactions of 2-azido-1-indanols **3a′**−**c′** proceeded at room temperature using a $Pd(OAc)_2$−dppf system in excellent yields. Both electron-withdrawing (**4a**) and electron-donating groups (**4b**−**d**) were incorporated on the isoquinoline ring. Chloride substituents on the benzene ring were tolerated (**4c** and **4e**). Azidoalcohols bearing a phenyl group at C-3 (**3f**) and C-2 (tertiary alcohol **3g**) were converted into corresponding isoquinolines in good yields. Moreover, this method afforded γ-carboline **4h** from **3h′**.

Next, we envisioned applying this method to the other ring systems (eqs 2−4). Although no C−C bond fission was observed from six-membered ring azidoalcohol **5** (eq 2), formations of pyridine and pyrrole occurred from 2-azidocyclopentanol **6** bearing a saturated five-membered ring and strained 2-azidocyclobutanol **7**, respectively (eqs 3 and 4). The reaction of 2-azidocyclopentanol **6** provided pyridine **2k** in moderate yield after treatment with AcOH under an oxygen atmosphere for further oxidation of a formed dihydropyridine intermediate (eq 3). In the case of the reaction of 2-azidocyclobutanol **7**, selective C−C bond fission involving the azido-substituted carbon was observed to afford 2-phenylpyrrole (**8**) in 62% yield, while a sterically less hindered β-carbon in the substituted *tert*-cyclobutanol ring is normally eliminated[2c−e] (eq 4). Along with pyrrole **8**, 19% yield of γ-keto nitrile **9** was formed presumably via β-H elimination from an iminyl palladium(II) intermediate,[2g,9] although such nitriles were not obtained in the other systems.

Further studies on the scope, mechanistic evaluation, and synthetic applications of this intriguing Pd(II)-catalyzed ring expansion of cyclic 2-azidoalcohol derivatives are in progress.



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Supporting Information Available: Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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