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C_{sp^3}–C_{sp^3} Bond Cleavage in the Palladium-Catalyzed Aminohydroxylation of Allylic Hydrazones Using Atmospheric Oxygen as the Sole Oxidant

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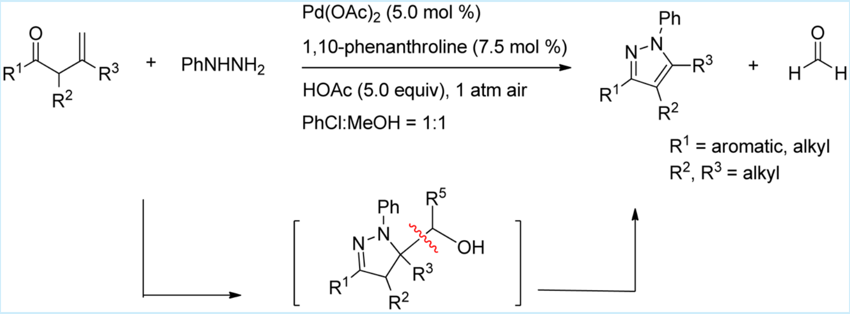
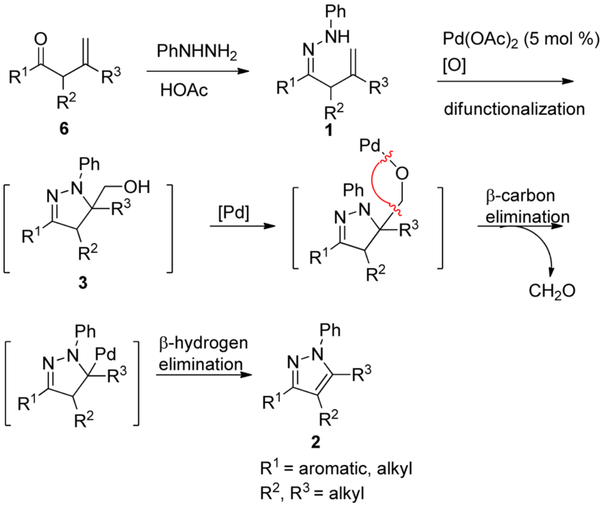
Supporting Information



ABSTRACT: A C–C bond cleavage was observed in the palladium-catalyzed aminohydroxylation of allylic hydrazones, using atmospheric oxygen as the sole oxidant. This reaction could also proceed in a one-pot manner, starting from keto-alkene compounds and phenylhydrazine.

Transition-metal-catalyzed cleavage of carbon–carbon σ-bonds in a selective manner is a very important reaction in organometallic chemistry.[1] Accordingly, it has attracted tremendous attention among synthetic chemists. Various transition metals such as rhodium complexes or palladium complexes have been shown to be efficient catalysts for C–C bond cleavage.[2−6] Common strategies employed the use of a decarboxylation strategy or the use of special latent groups such as tertiary alcohol. Both these strategies have limitations in terms of substrate scope, working only for substrates which can ensure facile retro processes. Furthermore, among the various reported C_{sp^3}–C_{sp^3} bond cleavage reactions, examples involving primary alcohol β-carbon elimination were very rare.[6] Therefore, new carbon–carbon bond cleavage reactions involving β-carbon elimination of a primary alcohol will be useful. During the course of our attempts to functionalize alkenes using allylic hydrazones, we observed the formation of 1*H*-pyrazole instead of the expected amino hydroxyl product.[7−9] The loss of one carbon in the final product clearly indicates that carbon–carbon bond cleavage has occurred in the reaction. In this paper, we report a palladium-catalyzed C–C cleavage reaction with an allylic hydrazone using atmospheric oxygen as the sole oxidant to synthesize 1*H*-pyrazoles[10] (Scheme 1). The scope as well the mechanistic studies of this reaction will also be reported.

Scheme 1. Pd-Catalyzed C–C Bond Cleavage Reactions



Initially, (*E*)-1-phenyl-2-(2,2,5-trimethylhex-5-en-3-ylidene)hydrazine (**1a**) under atmospheric oxygen was treated with 5.0 mol % $Pd(OAc)_2$, 7.5 mol % 1,10-phenanthroline, and 5.0 equiv of HOAc, and **2a** was obtained as a major product in moderate yield (Scheme 2, entry 1). Upon screening various

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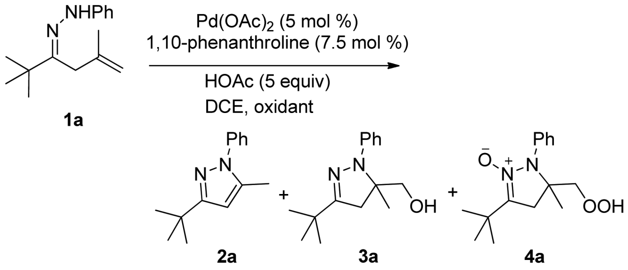
Scheme 2. Screening of Reaction Conditions[a]



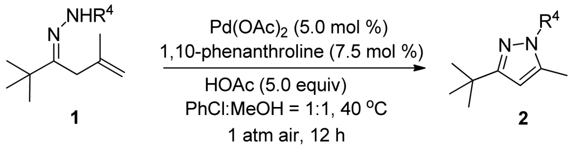
entry	oxidant	time (h)	yield (%)[b]	ratio (**2a**: **3a**: **4a**) (%)[c]
1	air	4	38	47:37:16
2	O_2	4	39	48:40:12
3	$Cu(OAc)_2$	24	<10	-
4	$PhI(OAc)_2$	24	<10	-
5	$K_2S_2O_8$	24	<10	-
6	^{t}BuOO^{t}Bu	24	<10	-
7	BQ	24	<10	-
8[d]	air	5	69	78:15:7
9[e]	air	2	52	60:35:5
10[d]	O_2	5	73	79:17:4
11[f]	air	2	75	80:15:5
12[g]	air	2	72	77:19:4
13[h]	air	8	62	78:18:4
14[i]	air	24	<10	-

[a] Unless noted otherwise, the reactions were carried out on a 0.15 mmol scale of **1a** with 5 equiv of HOAc, 7.5 mol % of 1,10-phenanthroline, and 5 mol % of $Pd(OAc)_2$ in 1,2-dichloroethane (1.0 mL) at rt under 1 atm of air. [b] The yield of **2a**. [c] The ratio of **2a**/**3a**/**4a** was determined by crude ^{1}H NMR. [d] PhCl/MeOH = 0.5 mL/0.5 mL. [e] 15 equiv of HOAc. [f] The reaction at 40 °C. [g] 10 mol % of $Pd(OAc)_2$. [h] 3 mol % of $Pd(OAc)_2$. [i] Without $Pd(OAc)_2$.

oxidants, the best result was obtained under atmospheric oxygen in terms of reaction efficiency, practicality, and economical reasons (Scheme 2, entry 1). This transformation proceeded smoothly at room temperature while higher efficiency was achieved at 40 °C (Scheme 2, entry 11). The mixed solvents of chlorobenzene and methanol were found to increase the yield to 69% (Scheme 2, entry 8). A higher loading of $Pd(OAc)_2$ provided a higher 72% yield of the desired product **2a** (Scheme 2, entries 12, 13). The best result was obtained with 5.0 mol % of $Pd(OAc)_2$ and 7.5 mol % of 1,10-phenanthroline, using a mixture of chlorobenzene and methanol as the solvent under 1 atm of air at 40 °C in 2 h.

Next we investigated the effect of the nitrogen protecting groups. A number of protecting groups, such as acetyl, benzoyl, benzyl, and aromatic, were examined, and they revealed that this transformation proceeded smoothly only with the aromatic protecting groups. Further studies unveiled that a substituent on the aromatic ring may also play an important role in the reaction. Substrates with a 4-OMe phenyl protecting group delivered the desired product in good yield, whose protecting group could be easily removed (Scheme 3, entry 2). Substrates with electron-withdrawing groups on the aromatic ring afforded the desired products in moderate yields (Scheme 3, entries 4, 5). No desired product was obtained for a substrate with a 4-nitrile phenyl protecting group (Scheme 3, entry 9). Hydrazone (**1j**) with *ortho*-methyl on the aromatic group did not yield any product probably due to the steric factor of the methyl group (Scheme 3, entry 10).

Scheme 3. Screening of Nitrogen Protecting Groups[a,b]



entry	R^4	yield (%)[c]
1	C_6H_5 (**1a**)	75 (**2a**)
2	4-OMe-C_6H_4 (**1b**)	61 (**2b**)
3	4-Me-C_6H_4 (**1c**)	73 (**2c**)
4	4-F-C_6H_4 (**1d**)	75 (**2d**)
5	4-Cl-C_6H_4 (**1e**)	60 (**2e**)
6	3-Me-C_6H_4 (**1f**)	65 (**2f**)
7	3,4-OMe-C_6H_3 (**1g**)	63 (**2g**)
8	3-Cl, 4-F-C_6H_3 (**1h**)	72 (**2h**)
9	4-CN-C_6H_4 (**1i**)	-
10	2-Me-C_6H_4 (**1j**)	-

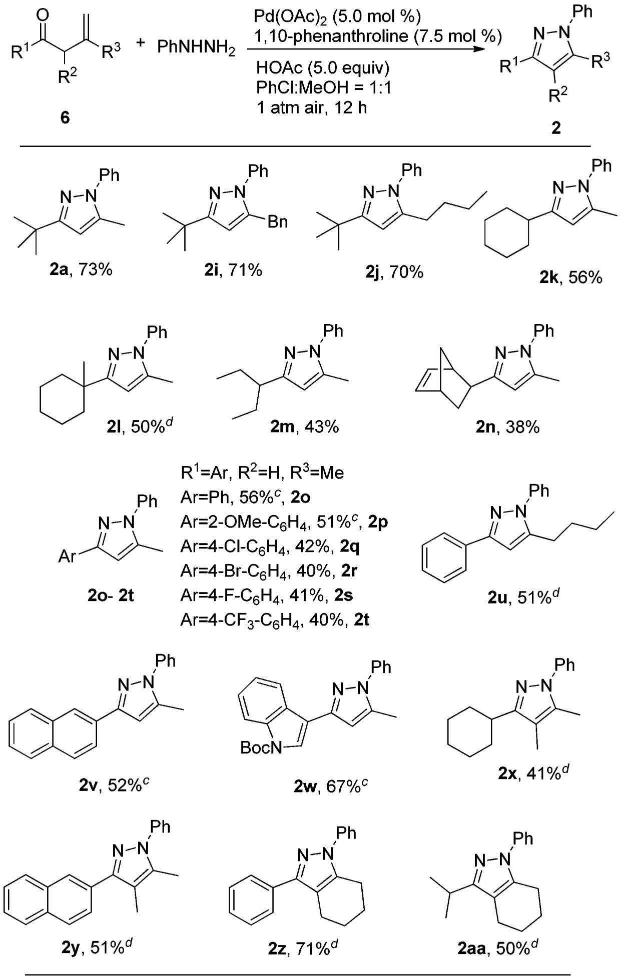
[a] Unless noted otherwise, the reactions were carried out on a 0.15 mmol of **1** with HOAc (5.0 equiv), 1,10-phenanthroline (7.5 mol %), and $Pd(OAc)_2$ (5.0 mol %) in PhCl/MeOH = 1:1 (0.25 mL/0.25 mL) at 40 °C under 1 atm of air. [b] In all cases, **3** and **4** were obtained in less than 20% yield. [c] Isolated yield of **2**.

Hydrazones are usually made of the corresponding ketones and hydrazines in acidic conditions. We proposed that hydrazones could be made *in situ* to carry out the amino-hydroxylative reaction in a one pot manner. Next, we have examined the reaction scope through a variety of *β*-keto alkenes and the phenylhydrazine in a one-pot manner (Scheme 4). The substituents on the alkene moiety have no significant influence on the efficiency of this reaction. Both aromatic and aliphatic groups were tolerated and afforded the target products in comparable yields. The substitutions at the *α*-position of the alkenes delivered the products in moderate yields (Scheme 4, compounds **2x**−**2aa**).

Three possible pathways leading to the final product are proposed as shown in Scheme 5. In path 1, primary alcohol **3** was first formed through aminohydroxylation of alkene **1**, which upon *β*-carbon elimination of alcohol led to the formation of final product **2**. In path 2, intermediate aldehyde **5** might be formed through oxidation of alcohol **3**, which might have undergone decarbonylation to form the desired product **2** by *β*-carbon elimination. In path 3, intermediate carboxylic acid **6** could be generated from the oxidation of intermediate aldehyde **5**, which would have further undergone decarboxylation to achieve the desired product **2**.

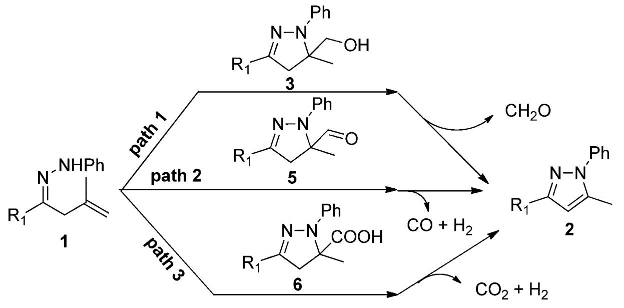
To further probe the mechanism, a series of control experiments have been carried out. Results showed that **2o** was obtained from alcohol **3o** under the standard reaction conditions in 68% yield (Scheme 6). When aldehyde **5o** and carboxylic acid **6o** were treated with the standard conditions separately, only **6o** gave the desired product in a moderate yield (Scheme 6). During the preparation of **6o**, complete conversion from **6o** to final product **2o** has been observed under ethyl acetate at room temperature. But conversion from alcohol **3** to aldehyde **5** could not take place under our reaction conditions. Therefore, pathways 2 and 3 are unlikely to occur in our reactions. Since the byproduct formaldehyde was difficult to detect, a secondary alcohol **7** was synthesized and subjected to the standard conditions (Scheme 7). In addition to the pyrazole product, we observed a hexanal peak in the crude ^{1}H NMR spectrum.[11] Therefore, pathway 1 was proposed to be the most likely route in this palladium-catalyzed C−C bond cleavage reaction. Primary alcohol **3** should be the key intermediate, which was obtained through aminohydroxylation

Scheme 4. One-Pot C–C Cleavage Reaction with Atmospheric Oxygen as the Sole Oxidant to 1*H*-Pyrazole[a,b]



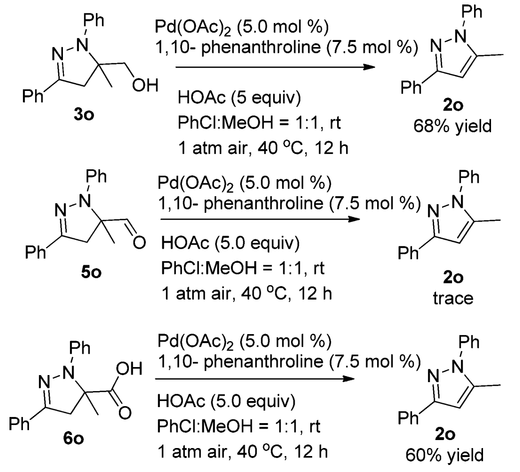
[a] Unless noted otherwise, the reactions were carried out on a 0.15 mmol scale of **6**, and 0.225 mmol scale of $PhNHNH_2$ (1.5 equiv) with HOAc (5.0 equiv), 1,10-phenanthroline (7.5 mol %), and $Pd(OAc)_2$ (5.0 mol %) in PhCl/MeOH = 1:1 (0.25 mL/0.25 mL) at 40 °C under 1 atm of air. [b] In all cases, **3** and **4** were obtained in less than 20% yield. [c] Hydrazones were used directly at rt. [d] The reaction at 60 °C.

Scheme 5. Possible Pathways for Palladium-Catalyzed C–C Cleavage Reaction

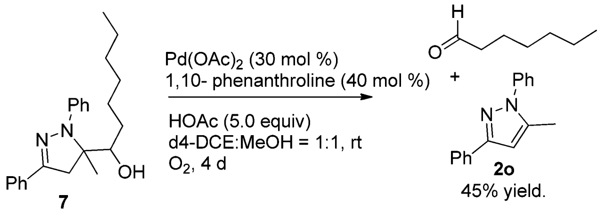


of alkene **1**. This primary alcohol **3** released formaldehyde through *β*-carbon elimination, followed by further *β*-hydrogen elimination to form the final product **2**.[3b,c] On the basis of all the above-mentioned results, we proposed the mechanism as shown in Scheme 8.

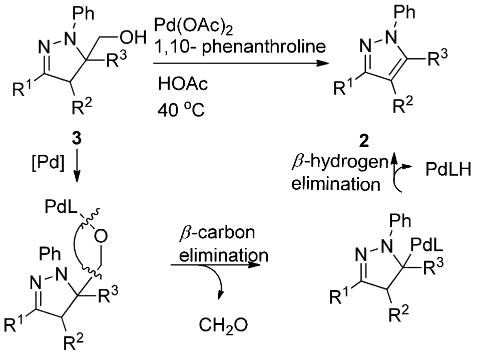
Scheme 6. Transformation from 3o, 5o, or 6o to 2o



Scheme 7. Transformation from 7 to 2o



Scheme 8. Proposed Mechanism



In conclusion, we have developed a palladium-catalyzed C_{sp^3}–C_{sp^3} cleavage reaction toward the formation of 1*H*-pyrazoles, using 1 atm of air as the sole oxidant and reagent. This atmospheric oxygen incorporated methodology can be utilized to synthesize useful regents. Understanding the mechanistic information obtained in this study, we are currently developing other new C–C bond cleavage reactions. Further studies toward the mechanism and application are currently in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full analytical data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01127.

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Notes

The authors declare no competing financial interest.

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(11) This reaction was conducted with d_4-dichloroethane and normal methanol as solvent. A hexanal peak could be observed in the crude NMR spectrum. See details in the Supporting Information.