Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2024, **22**, 3262

Palladium-catalyzed C–C bond cleavage of *N*-cyclopropyl acylhydrazones†

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Received 4th March 2024,
Accepted 28th March 2024

DOI: 10.1039/d4ob00349g

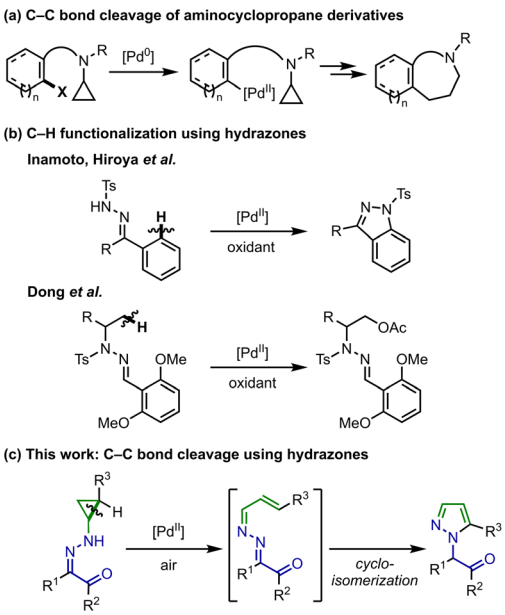
rsc.li/obc

Despite their utility as directing groups, the C–C bond cleavage of cyclopropanes utilizing hydrazones has not been explored. Herein, Pd-catalyzed C–C bond cleavage reaction of *N*-cyclopropyl acylhydrazones, followed by cycloisomerization to yield pyrazoles, has been developed. The protocol enables the synthesis of various α-pyrazole carbonyl compounds, which have a potential of biological activity. Control experiments and DFT calculations suggest that β-carbon elimination of a stable 6-membered chelate palladium complex occurs, generating a conjugated azine as a reaction intermediate for the following cycloisomerization.

Introduction

Deconstructive strategy *via* C–C bond cleavage is valuable for synthesizing complex compounds.[1–3] Since cyclopropanes have 27.5 kcal mol^{-1} of strain energy, the strain-released ring-opening reaction of cyclopropanes is thermodynamically advantageous to the C–C bond cleavage process.[4] Therefore, cyclopropanes are often used as a synthetic intermediate for producing complex compounds.[4,5] As the most typical examples, Lewis acid-mediated ring-opening reactions of donor–acceptor cyclopropanes, which have an electronically-biased C–C bond, have been reported.[6] For cyclopropanes bearing a less electronically-biased C–C bond, ring-opening reactions mostly proceed *via* oxidative addition of a transition metal complex to a C–C bond.[7] Among them, cyclopropanes having an adjacent electron-withdrawing group, such as ketones and imines or alkylidene cyclopropanes, have been employed. In contrast, the treatment of cyclopropanes linked to an electron-donating group (EDG), such as the hydroxy, siloxy, amino, and thio groups with appropriate transition metals, undergoes β-carbon cleavage[8] or EDG-assisted ring-opening.[9] Moreover, indirect C–C bond cleavage *via* palladium-catalyzed C(sp^3)–H activation of aminocyclopropane derivatives has been also reported.[10,11]

The proximity of transition metals to a reaction site is important for the activation of inactive bonds such as C–H or C–C bonds.[12] In the cleavage of C–C bonds in aminocyclopropane derivatives, only examples of covalent proximity effects *via* oxidative addition to C–X bond (X = Cl, Br, or I) have been reported (Scheme 1a).[10,11] In contrast, a widely used activation method without C–X bond is the use of a directing group.[13] Hydrazones have been used for various C–H functionaliza-



Scheme 1 Pd-catalyzed C–C or C–H bond activation of amine derivatives.

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ob00349g

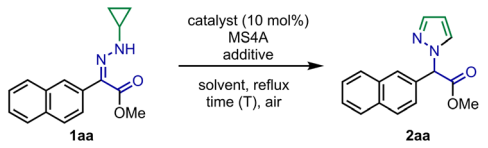
tions,[14] first reported on C(sp^2)–H functionalization by Inamoto's group in 2007 (Scheme 1b).[14a] More recently, C(sp^3)–H functionalization using 2,6-dimethoxyphenyl groups as a substituent on the hydrazone carbon has also been reported by Dong's group.[14b] However, C–C bond cleavage of cyclopropanes utilizing hydrazones has not been explored. Thus, as part of our continuous research into the reactivity of hydrazones and the synthesis of nitrogen-containing heterocycles,[15] we expected that the C–C bond cleavage reaction of *N*-cyclopropyl hydrazones would lead a development of new methodology in the field of organic synthetic chemistry. Herein, we report palladium-catalyzed sequential reaction involved in C–C bond cleavage of cyclopropanes followed by cycloisomerization, along with the elucidation of the reaction pathway by a series of control experiments and DFT calculations. The protocol enables the synthesis of α-pyrazole carbonyl compounds, which have a potential of biological activity.[16,17]

Results and discussion

At the beginning of this study, the reaction conditions were optimized using cyclopropylhydrazone **1aa** in xylene, expecting C–C bond cleavage *via* C(sp^3)–H activation (Table 1).[11] The use of Rh(III) or Ni(II) catalysts, which were reported in directing group-accelerated C(sp^2)–H activation or C(sp^3)–H activation, did not yield pyrazole **2aa** efficiently (entries 1 and 2).[18,19] In contrast, the yield improved to 49% when $Pd(OAc)_2$ was used (entry 3). To accelerate the reaction, $Pd(TFA)_2$ was examined; however, the yield decreased (entry 4). Subsequently, additives were examined. The addition of AgOAc, which was expected to act as a promoter for the regeneration of $Pd(OAc)_2$, did not improve the yield (entry 5).[20] When hexafluoro-2-propanol (HFIP) was added to promote C–C bond cleavage *via* C–H activation,[21] a higher yield was observed to produce the desired pyrazole (entry 6). In contrast, the use of HFIP as a solvent was not effective for the sequential reaction (entry 7). Finally, when *tert*-amyl alcohol was used as a solvent, the yield improved to 80% (entry 8).[22]

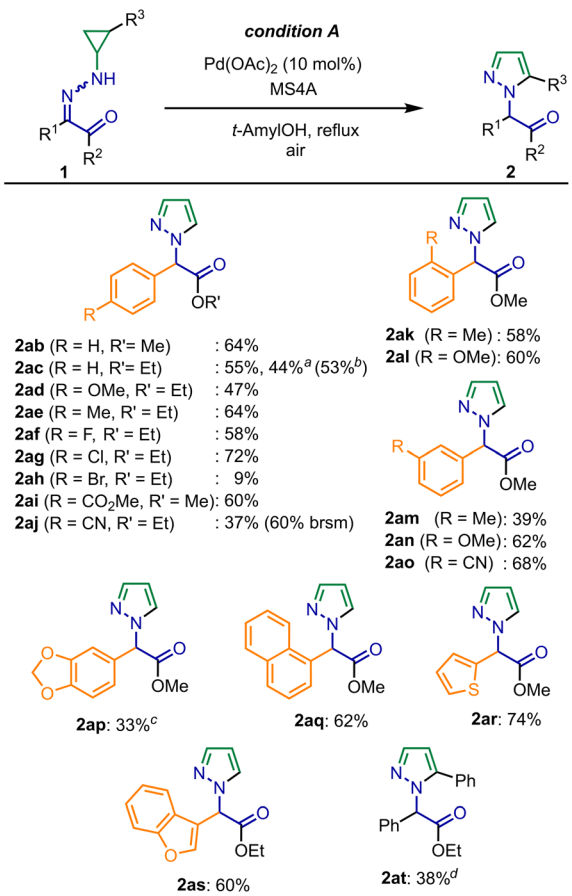
With the optimized conditions established, the substrate scope was investigated (Scheme 2). First, a substrate bearing aryl groups on the hydrazone carbon was examined. When various 4-substituted aryl groups were examined, pyrazoles were obtained with good yields except for the hydrazone **1ah** bearing bromo arene moiety (**2ab–2aj**). It is noted that although the synthesis of **2ab** has been reported by N–H insertion with pyrazole,[17b–d] an alternative reliable synthetic method was provided. Moreover, we confirmed that the *E*/*Z* geometry of hydrazones did not affect the yield (**2ac**), which suggests that *E*/*Z* isomerization through azo-hydrazone tautomerism driven by acyl group occurs during the reaction.[23] To confirm the steric effect of the substituents, substrates having a methyl or methoxy group at the 2-position on the benzene ring were tested. This resulted in pyrazoles **2ak** and **2al** exhibiting nearly identical yields as the *para*-substituted substrates.

Table 1 Reaction optimization[a]



Entry	Catalyst	Additive (equiv.)	Solvent	*T* (h)	Yield (%)
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (1.0) K_2CO_3 (1.0)	Xylene	16	13[b]
2	$Ni(OTf)_2$	PivOH (1.0)	xylene	16	N.D.
3	$Pd(OAc)_2$	—	xylene	14	49[b]
4	$Pd(TFA)_2$	—	xylene	16	42[b]
5	$Pd(OAc)_2$	AgOAc (2.0)	xylene	16	39[b]
6	$Pd(OAc)_2$	HFIP (2.0)	xylene	15	69
7	$Pd(OAc)_2$	—	HFIP	21	N.D.
8	$Pd(OAc)_2$	—	*t*-AmylOH	4	80

[a] Conditions: **1aa** (0.09–0.17 mmol), catalyst (10 mol%), MS4A (79–100 mg) in solvent (0.10 M) at reflux. [b] Yields were determined by ^1H NMR using triphenylmethane as an internal standard.

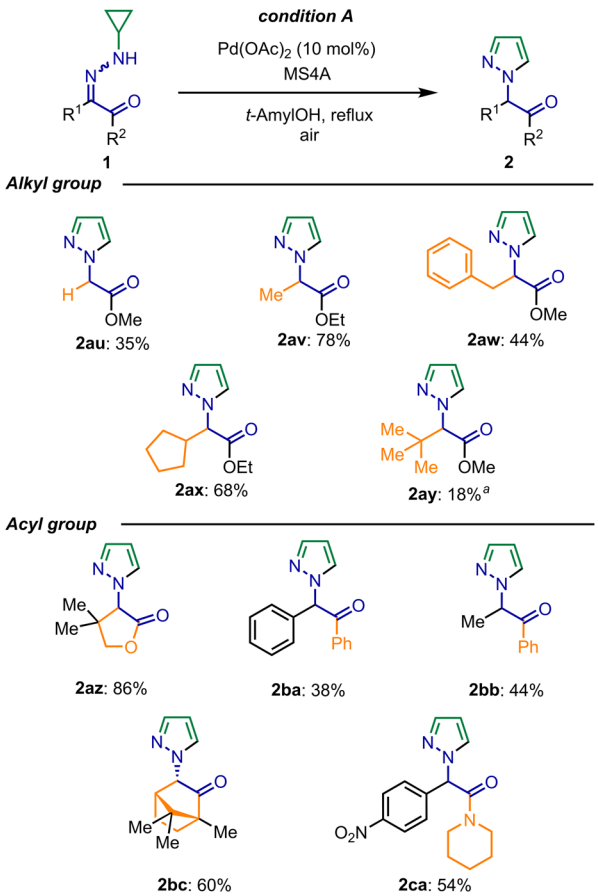


Scheme 2 Scope for aryl groups of *N*-cyclopropy acylhydrazones. Conditions: **1** (0.067–0.20 mmol), $Pd(OAc)_2$ (10 mol%), MS4A (60–168 mg) in *t*-AmylOH (0.10 M) at reflux for 5–28 h. [a] **1ac** (2.8 mmol) was used. [b] (*E*)-Isomer was used. [c] After 19 h, stirred at 150 °C in a sealed tube for 9 h. [d] After stirred at 140 °C in a sealed tube for 21 h, $Pd(OAc)_2$ (10 mol%) was added and stirred for 4 h.

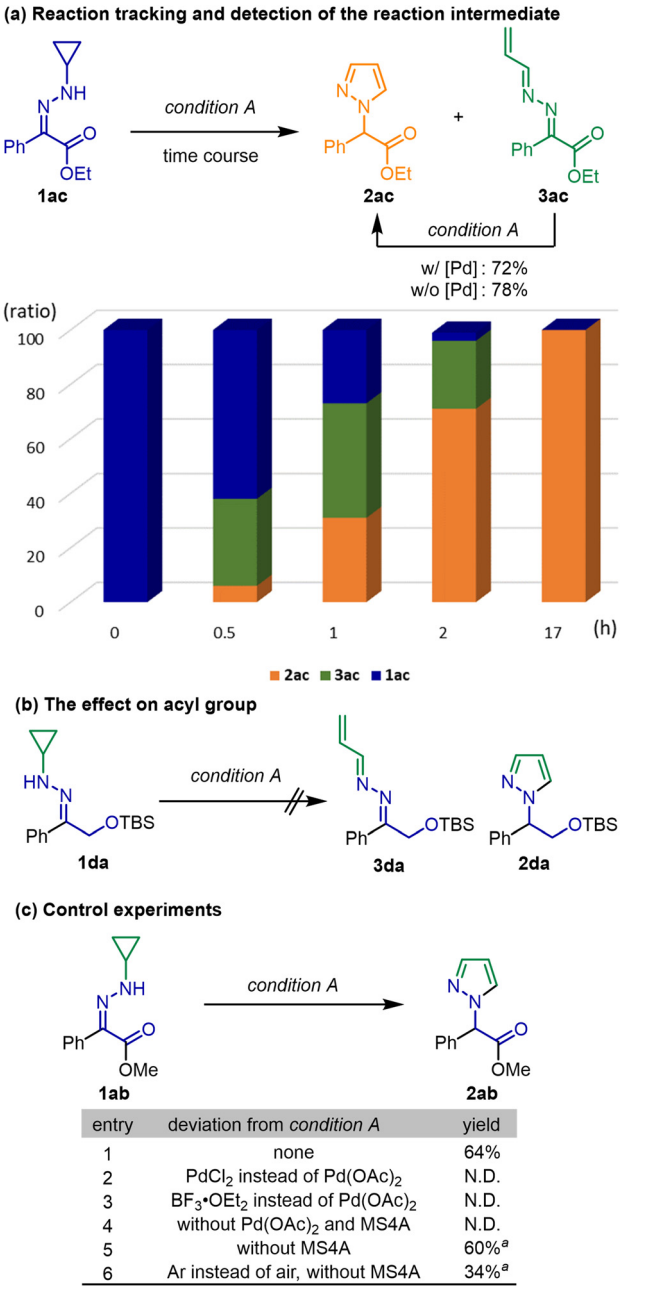
The yield of pyrazole **2am** having a methyl group at the 3-position on the benzene ring decreased, while a methoxy or cyano group was not affected, giving pyrazole **2an** or **2ao** a good yield. A substrate **1ap** bearing a methylenedioxy group at the 3- and 4-positions could also be applied to the reaction; however, a higher reaction temperature was required. When 1-naphtylhydrazone **1aq** was used, the reaction proceeded smoothly. The substrates linked to a heterocycle, such as thiophene and benzofuran, were applicable to the reaction (**2ar**, **2as**). Subsequently, the reaction of substrate **1at** bearing a phenyl group at the cyclopropane moiety produced 5-aryl pyrazole in moderate yield although the reaction necessitated an elevated temperature and more catalyst.[24]

Next, substrates bearing an alkyl group on the hydrazone carbon were studied. When methyl, benzyl, and cyclopentyl groups, as well as a non-substituted substrate (R^1 = H), were examined, the reaction proceeded smoothly (Scheme 3, **2au**–**2ax**). Hydrazone bearing a *tert*-butyl group required a higher temperature and more catalyst, producing pyrazole **2ay** in low yield. Finally, different acyl groups on the hydrazone carbon were examined. Pyrazole **2az** was obtained in high yield from lactone having an α-dimethyl group, which might fix orientation of the carbonyl group accelerated the C–C bond cleavage process. In addition to phenyl ketones **1ba** and **1bb**, the desired products were also obtained from hydrazone **1bc**, which was derived from camphorquinone. Furthermore, amide **1ca** was also applicable to the reaction.

Subsequently, we conducted several studies to obtain knowledge of the reaction mechanism. To identify the reaction intermediate, hydrazone **1ac** was treated under condition A, and its transformation was observed at any particular time (Fig. 1a). As a result, the formation of conjugated azine **3ac**



Scheme 3 Scope for alkyl and acyl groups of *N*-cyclopropyl acylhydrazones. Conditions: **1** (0.068–0.18 mmol), $Pd(OAc)_2$ (10 mol%), MS4A (60–118 mg) in *t*-AmylOH (0.10 M) at reflux for 5–32 h. [a] After stirred at 130 °C in a sealed tube for 13 h, $Pd(OAc)_2$ (10 mol%) was added and stirred for 11 h.



entry	deviation from *condition A*	yield
1	none	64%
2	$PdCl_2$ instead of $Pd(OAc)_2$	N.D.
3	$BF_3{\cdot}OEt_2$ instead of $Pd(OAc)_2$	N.D.
4	without $Pd(OAc)_2$ and MS4A	N.D.
5	without MS4A	60%[a]
6	Ar instead of air, without MS4A	34%[a]

Fig. 1 Mechanistic studies. [a] Yields were determined by ^1H NMR using triphenylmethane as an internal standard.

was observed before the disappearance of the starting material, while the existence of **3ac** was not confirmed at 17 h. Furthermore, when azine **3ac** was subjected to condition A, pyrazole **2ac** was obtained in high yield. These results suggest that conjugated azine is the reaction intermediate. In addition, pyrazole **2ac** was obtained in a slightly higher yield when the reaction was conducted without a palladium catalyst, supporting the notion that a palladium catalyst is not involved in the transformation from azine to pyrazole. When α-siloxyhydrazone **1da** was employed under the optimized condition, conjugated azine and pyrazole were not formed (Fig. 1b). The result suggests that the acyl group is essential for the C–C bond cleavage and implies that it works as a directing group for the palladium complex. Finally, control experiments were performed under optimized conditions using hydrazone **1ab** (Fig. 1c). First, regarding the palladium catalyst, the exchange from $Pd(OAc)_2$ to $PdCl_2$ did not produce pyrazole (entries 1 and 2). In addition, pyrazole was not obtained with $BF_3{\cdot}OEt_2$ or without a catalyst (entries 3 and 4). These results suggest that the C–C bond cleavage reaction occurs rather than vinylcyclopropane rearrangement.[25] The yield decreased without MS4A a little (entry 5). Finally, an argon atmosphere decreased the yield, which suggests that the Pd(0) species formed *in situ* are regenerated into Pd(II) species by oxygen molecules (entry 6).

Control experiments could not determine definitively whether C–C bond cleavage proceeds directly[8a] or is mediated by C–H activation.[11] Therefore, to elucidate further detail process in the sequential reaction, an energy profile of the C–C bond cleavage/cycloisomerization reaction was estimated by DFT studies (Fig. 2). The calculations were first performed at the B97D/Lanl2DZ (for Pd) and B97D/6-31G+(d,p)-def2TZV (for the other atoms) level. Then, single-point energy calculations in the presence of solvent (chlorobenzene) were performed. Initially, hydrazone **1** is transformed to 6-membered chelate palladium complex **A**, which is more stable than 5-membered complex **A′**. Subsequently, β-carbon elimination of **A** proceeds in 19.6 kcal mol^{-1} of activation energy to produce imino-palladacycle **B** along with enamino-tautomer **B′** in equilibrium. Next, conjugated azine **C** is formed from enamine **B′** through the elimination of palladium hydride species. Then, the palladium hydride species undergo reductive elimination without any energy barriers. Pd(0) species are oxidized to $Pd(OAc)_2$ by oxygen molecules to complete the catalytic cycle.[26,27] Finally, cycloisomerization proceeds under heating conditions to produce pyrazole **2**.[28] The possibility of C–C bond cleavage *via* C–H activation is ruled out due to the high energy level of 5-membered chelate palladium complex **A′** and the subsequent transition state in **A′** to palladacycle **D**.[11]

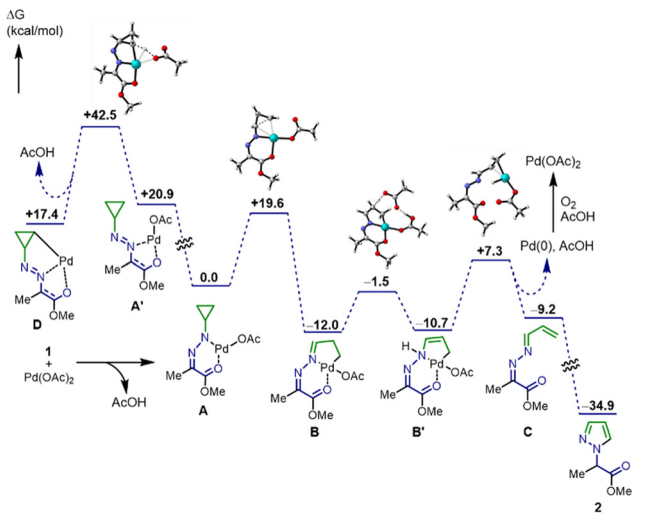


Fig. 2 Gibbs free energy profile.

Conclusions

In conclusion, we have developed Pd-catalyzed C–C bond cleavage of *N*-cyclopropyl acylhydrazones through β-carbon elimination of cyclopropane, followed by cycloisomerization to produce pyrazoles. Regarding substrate scope, various aryl and alkyl groups on hydrazone carbons can be utilized. Furthermore, various carbonyl functional groups such as esters, lactones, ketones, and amides can also be applied to the sequential reaction. A series of control experiments and DFT calculations suggest that C–C bond cleavage proceeds *via* β-carbon elimination followed by tautomerization/depalladation, resulting in the formation of conjugated azines. We expect the protocol leads to atom-economical skeletal editing, including C–H bond and C–C bond scissions as well as incorporating directing groups. This synthetic strategy can introduce sterically hindered secondary and tertiary alkyl groups under weakly acidic conditions. In addition, it enables the synthesis of 1-alkyl-5-aryl pyrazole, which is difficult to obtain with chemo/regioselectivity, as a single product.[29,30] These α-pyrazole carbonyl compounds have a potential of biological activity. Therefore, this synthetic strategy might be one way to enrich compound library in medicinal chemistry. A more efficient synthetic method for 1,5-disubstituted pyrazoles using cyclopropyl hydrazones through the deconstructive strategy is currently under development.

Author contributions

HF and KF conducted the experiments. HF wrote the original draft. MY conceptualized and managed the work, and were involved in review and editing. SH and YK conducted the computational study. NT and TF reviewed the work. MU supervised and review the work.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This study was supported by a Grant-in-Aid from JSPS KAKENHI, the MEXT Leading Initiative for Excellent Young Researchers grant, and Nagai Memorial Research Scholarship from the Pharmaceutical Society of Japan (N-235304, H. F.).

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