Palladium-Catalyzed Ring Opening of Aminocyclopropyl Ugi Adducts

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Abstract: The ring opening of aminocyclopropanes triggered by activation with an intramolecular arylpalladium(II) iodide complex is an interesting strategy for the synthesis of nitrogen heterocycles and a valuable Ugi postcondensation-type transformation. Six- and seven-membered-ring cyclic enamines may be obtained.

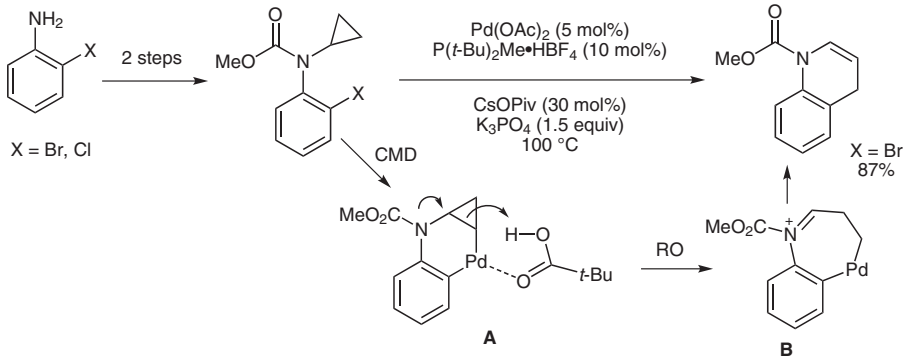
Key words: aminocyclopropanes, ring opening, palladium, Ugi, Ugi–Smiles

Cyclopropanes represent a unique class of compounds in organic chemistry. The carbon–carbon σ-bonds of these strained compounds display reactivities closer to π-bonds leading to their usual treatment as bent bonds or Walsh orbitals. This property has motivated a great number of cyclopropane ring-opening studies under transition-metal catalysis.[1] In these reactions, the cyclopropyl moiety interacts as an alkene with a carbon–metal bond generated in the vicinity of the strained cycle. Thus, cyclopropyl equivalents of π-allyl complex may be involved in various palladium-catalyzed cascades starting with vinyl or alkylidene cyclopropyl derivatives and leading to intermediate palladacycles.[2] Oxa analogues of these palladacycles have been reported as well in various oxidative or reductive rearrangements of hydroxy or ketocyclopropane derivatives.[3] In comparison, the ring opening of aminocyclopropanes is less documented. Under thermal or acidic conditions, aminocyclopropanes are known to rearrange into enamine derivatives which may be further transformed (for instance by oxidation to pyridines or acylation).[4] Following our study on the palladium ring opening of furan-substituted Ugi adducts,[5] we envisaged that Ugi reactions[6] involving cyclopropylamines could serve as a platform to study the potential intramolecular arylpalladium(II) interaction with the cyclopropyl moiety. The recent report by Rousseaux et al. suggesting that cyclopropylamine derivatives may ring open via a palladium-triggered concerted metalation–deprotonation (CMD) process[7] prompted us to disclose our results obtained with both different catalytic system and starting materials.

Due to our ongoing interest in multicomponent reactions (MCR), we decided to assemble a cyclopropyl moiety and an aryl iodide precursor of the arylpalladium species via Ugi-type coupling.

In order to test the feasibility of the ring opening, the Ugi–Smiles[8] reaction was carried out using an iodinated hydroxypyridine as the acidic partner. As such, the four-component adduct was obtained in one step. The ring-opening reaction was then evaluated under the conditions previously developed for the furan cleavage. Thus, an acetonitrile solution of the Ugi–Smiles adduct **1a** was submitted to microwave irradiation after addition of 5 mol% of $PdCl_2(PPh_3)_2$ and 1.5 equivalents of diisopropylethylamine. After heating the mixture at 130 °C for 20 minutes the desired dihydropyridopyridine **2a** was obtained in quantitative yield (Scheme 2).

The aminocyclopropane ring opening turned out to be quite general as several Ugi–Smiles adducts **1** were prepared and submitted successfully to the palladium-catalyzed reaction. Indeed, the reaction carried out with an aryliode (Table 1, entry 1) or with an iodinated heterocycle (Table 1, entries 2–6) affords the desired dihydropyri-



Scheme 1 Ring opening reported by Rousseaux et al.

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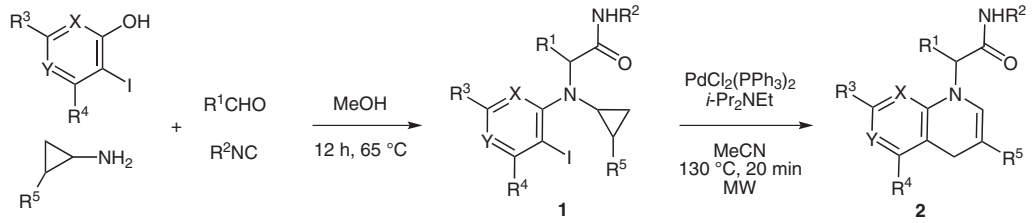
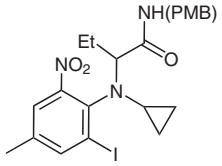
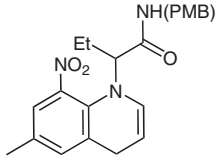
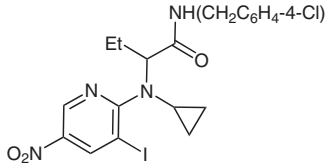
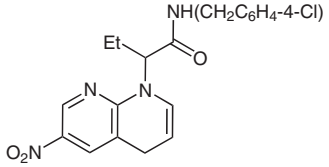
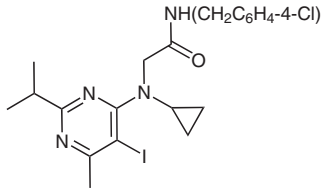
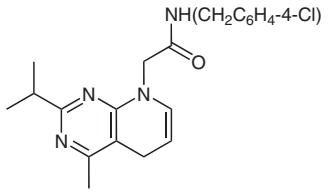
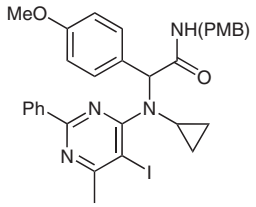
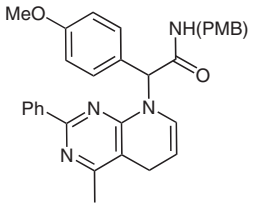
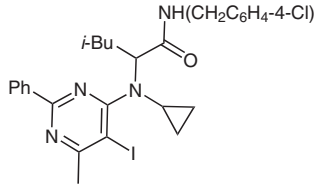
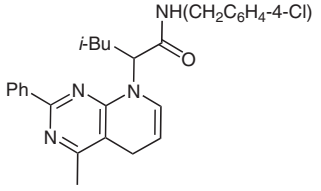
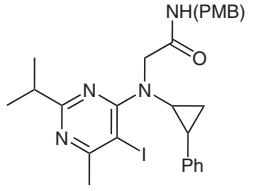
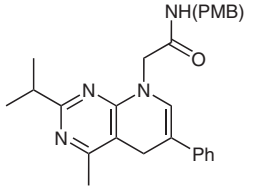
dine derivatives **2** in moderate to good yields. In the case of Ugi–Smiles adducts resulting from the coupling of an aromatic aldehyde (Table 1, entry 4), the reaction is less efficient probably due to competitive fragmentation as previously reported.[9]

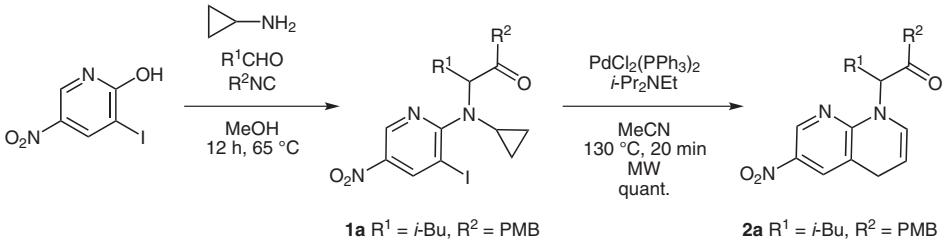
The reaction was then extended to Ugi adducts **3** by replacing the phenol with 2-iodobenzoic acid. The behavior of these adducts towards the palladium catalyst is interesting as both the functional environment of the cyclic nitrogen and size of the resulting cycle are different from the former examples. As compiled in Table 2, the ring opening of the four-component adducts proceeded smoothly under palladium catalysis, and the corresponding benzoazepinones **4** were isolated in good yields.

These results must be analyzed in the light of the recent study of Rousseaux et al. (Scheme 1). Their reported structures are close to the ones we obtained with Ugi–Smiles adducts, but their work is limited to the reactivity of bromo and chloro derivatives together with the use of a catalytic system [$Pd(OAc)_2$, PivOH, PR_3] prone to trigger

Table 1 Synthesis of Dihydropyridine Derivatives **2**



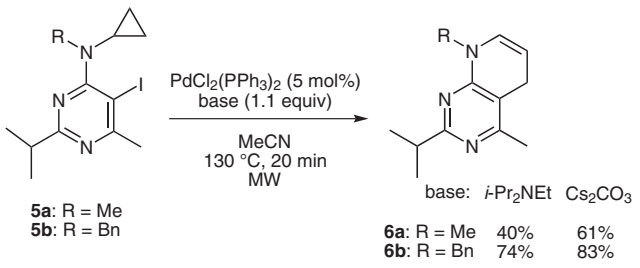
Entry	**1**	Yield (%)	**2**	Yield (%)
1		72		86
2		30		85
3		92		100
4		38		25
5		77		64
6		37		45[10]



Scheme 2 First aminocyclopropane ring opening (ACRO)

CH-activation processes. Under these conditions, it is not surprising that their mechanistic study led them to conclude that the aminocyclopropane ring opening requires a prior CMD step to form an azapalladabicyclo[4.1.0]heptane intermediate **A** followed by the cyclopropyl ring opening to form palladacycle **B** (Scheme 1). Their conclusion is supported by the absence of reaction without pivalic acid.[11]

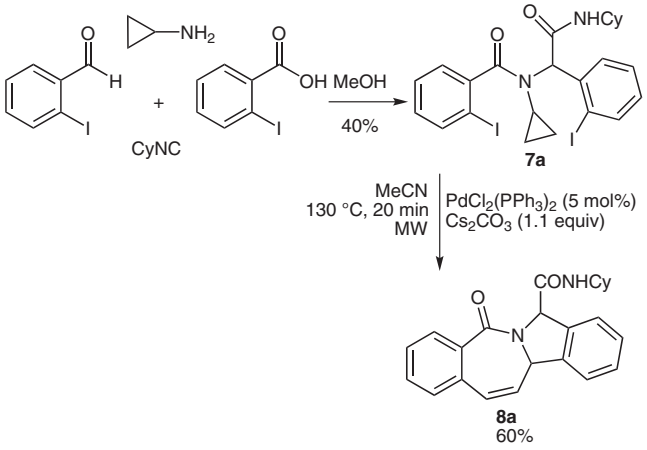
Herein, the productive cyclization and ring opening with a palladium catalyst traditionally used in standard cross-coupling reactions indicates that an alternative mechanism may be operating at least with aryl iodides. To address whether this behavior could be attributed to the more complex nature of the Ugi adducts, we decided to prepare less complex starting aryliodocyclopropyl derivatives using standard synthetic pathways (Scheme 3). When **5a** and **5b** were treated with palladium under our conditions, the expected fused dihydroquinolines were isolated in moderate 40% and 74% yields. The latter could be increased by replacing diisopropylethylamine with cesium carbonate.



Scheme 3 Quinolines from standard starting materials

The mechanism involving a CMD or a direct ring opening of the cyclopropyl through interaction with a cationic palladium intermediate species merits further consideration. Such a mechanistic discussion could obviously be extended to the reported palladium-catalyzed ring opening of hydroxycyclopropanes such as the Fujiwara–Nakamura intermolecular arylation[3b,c] or the more recent report of Orellana.[3h] In the first case, the use of a starting triflate together with the lack of a suitably positioned directing group to form a palladacycle intermediate through a CMD is more in favor of a direct ring opening.

Besides the mechanistic challenge highlighted by these results, one must not forget the synthetic interest of these transformations. Indeed, the enamine formation associated with the use of a multicomponent process to obtain the starting cyclopropylamine may lead to interesting cascades. Thus, the Ugi coupling of iodobenzaldehyde, iodobenzoic acid, and cyclopropyl amine affords in one step a suitable adduct for a palladium-triggered aminocyclopropane ring opening–Heck cascade (Scheme 4). In this case, the regioselectivity issues raised by the presence of two different iodides may be controlled by the different electronic nature of the aryl moiety; the more electrophilic iodobenzamide being expected to react first with the palladium(0) catalyst. The final tetracycle **8a** was obtained as a single diastereomer in a 60% isolated yield.



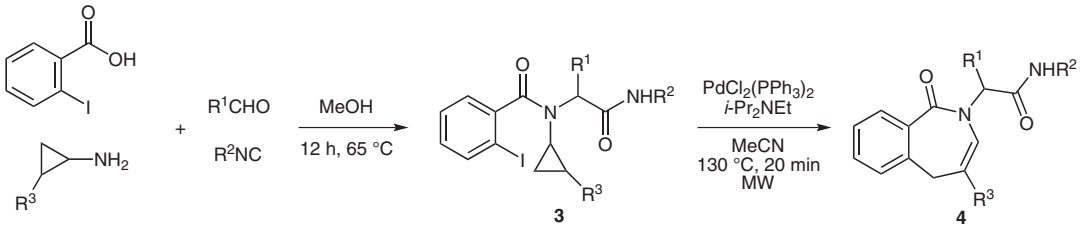
Scheme 4 Palladium-triggered cascade of Ugi adducts

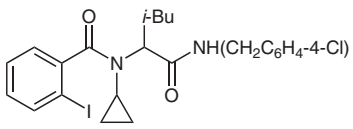
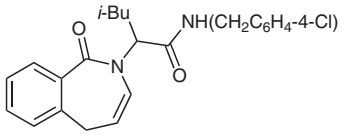
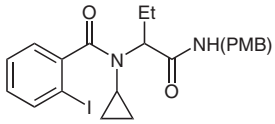
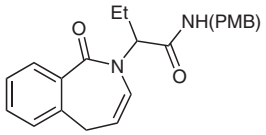
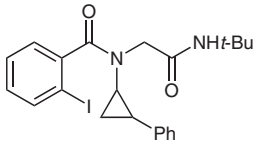
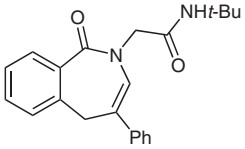
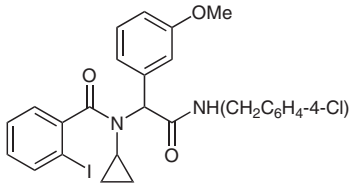
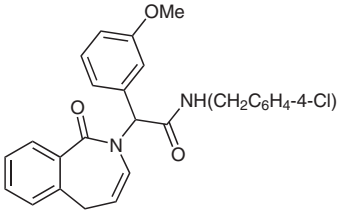
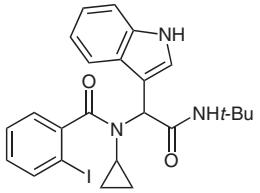
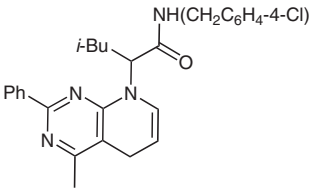
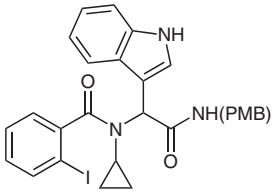
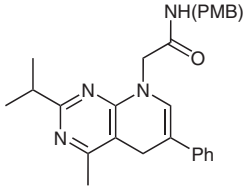
To conclude, we have extended the scope of the palladium-triggered ring opening of amino cyclopropanes. Six- and seven-membered-ring heterocycles may be easily formed under palladium catalysis. The use of $PdCl_2(PPh_3)_2$ as catalyst indicates that the previously suggested CMD mechanism may not be operative in this case. The synthetic potential of this reaction has been demonstrated in a palladium-triggered aminocyclopropane ring opening–Heck cascade. We are currently studying the mechanism of these ring openings as well as their integration in various cascades.

_N_-(4-Chlorobenzyl)-2-[cyclopropyl(5-iodo-2-isopropyl-6-methylpyrimidin-4-yl)amino]acetamide (1d)

To a solution of 5-iodo-2-isopropyl-6-methylpyrimidin-4-ol (278 mg, 1.0 mmol) in MeOH under argon atmosphere were added formaldehyde (75 μL, 1.0 mmol), cyclopropylamine (70 μL, 1.0 mmol), and *p*-chlorobenzylisocyanide (150 μL, 1.0 mmol). The reaction

Table 2 Synthesis of Benzoazepinones **4**



Entry	3	Yield (%)	4	Yield (%)
1		95		79
2		65		70
3		59		65[10]
4		60		78
5		80		55
6		66		69

mixture was stirred for 3 d at 60 °C. The solvent was removed under reduced pressure and purification by flash column chromatography on silica with a PE–Et_2O mixture (75:25) gave the adduct **1d** as a white solid (461 mg, 92%); mp 121–122 °C. R_f = 0.1 (PE–Et_2O, 5:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (br s, 1 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 7.05 (d, *J* = 8.1 Hz, 2 H), 4.33 (d, *J* = 5.8 Hz, 2 H), 4.23 (s, 2 H), 3.14–3.12 (m, 1 H), 2.80 (sept, *J* = 6.8 Hz, 1 H), 2.59 (s, 3 H), 1.09 (d, *J* = 6.8 Hz, 6 H), 0.76–0.74 (m, 2 H), 0.50–0.48 (m, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.5, 170.9, 170.8, 165.1, 136.6, 133.2, 129.1, 128.7, 81.3, 55.8, 42.7, 36.4, 35.7, 30.3, 21.5, 11.2. HRMS: *m/z* calcd for $C_{20}H_{24}ClIN_4O$: 498.0683; found: 498.0683. IR: ν = 1666, 1536, 1436, 1356, 1264, 1231, 1091, 1015 cm^{-1}.

***N*-(4-Chlorobenzyl)-2-{2-isopropyl-4-methylpyrido[2,3-*d*]pyrimidin-8(5*H*)-yl}acetamide (2d)**

To a solution of **1d** (100 mg, 0.200 mmol) in MeCN (0.1 M) were added a catalytic amount of $PdCl_2(PPh_3)_2$ (7 mg, 0.010 mmol) and DIPEA (34 μL, 0.200 mmol). The mixture was stirred for 20 min at 130 °C under MW irradiation (100 W, 13 bar). The solvent was removed under reduced pressure and purification by flash column chromatography on silica, eluting with a PE–Et_2O mixture (30:70), gave **2d** as a white solid (74 mg, quant.); mp 168–169 °C. R_f = 0.1 (100% Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.3 Hz, 2 H), 7.07 (d, *J* = 8.3 Hz, 2 H), 6.71 (br s, 1 H), 5.93 (d, *J* = 7.6 Hz, 1 H), 4.73 (dt, *J* = 7.6, 4.0 Hz, 1 H), 4.33 (d, *J* = 5.8 Hz, 2 H), 4.20 (s, 2 H), 3.41 (s, 2 H), 2.80 (sept, *J* = 6.8 Hz, 1 H), 2.16 (s, 3 H), 1.08

(d, J = 6.8 Hz, 6 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.0, 169.4, 163.6, 156.5, 136.5, 133.2, 130.3, 128.9, 128.7, 108.2, 101.7, 52.0, 42.6, 37.0, 24.2, 21.6, 21.3. HRMS: *m/z* calcd for $C_{20}H_{23}ClN_4O$: 370.1560; found: 370.1557. IR: ν = 1649, 1559, 1538, 1459, 1396, 1263, 1220, 1091 cm^{-1}.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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