Ugi/Palladium-Catalysed Intramolecular Cyclopropyl Direct Alkenylation Cascade Reaction Providing Access to Azacycles

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Abstract. A novel example of Ugi/Palladium-catalyzed intramolecular cyclopropyl direct alkenylation cascade reaction providing access to novel azacycles in one pot has been developed. Palladium-catalysed direct alkenylation of cyclopropyl C−H bonds proceeds in high efficiency with easy work-up. This transformation was adjusted by 2-substituent on cyclopropyl providing alternative access to cyclopropyl-fused azacycles or ring-expending products.

1. Introduction

Cyclopropanes are prevalent structural motifs in currently marketed drugs or candidates, often in conjunction with a group of amides in close vicinity (Fig. 1). [1-6] this prevalence can be attributed to their strategic use aiming at increasing metabolic stability without a large increase in molecular weight or installation of fluorine atoms. In its own right, cyclopropane is an attractive scaffold providing opportunities to arrange pendant groups in a rigid and specific three-dimensional orientation in space.

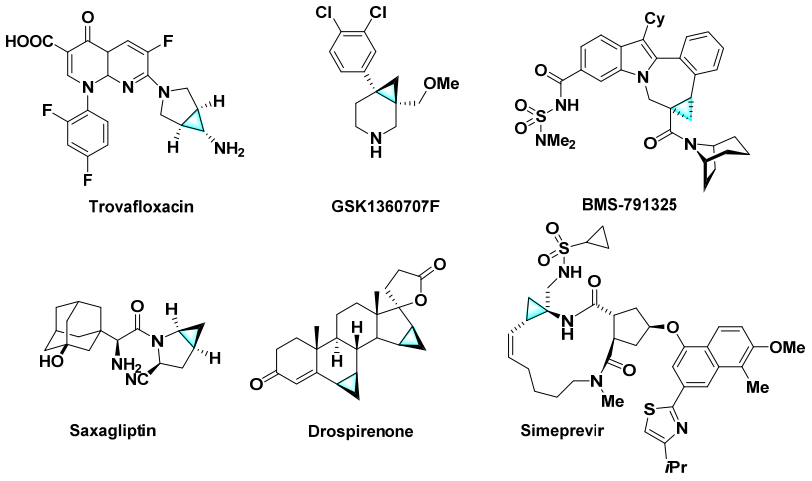
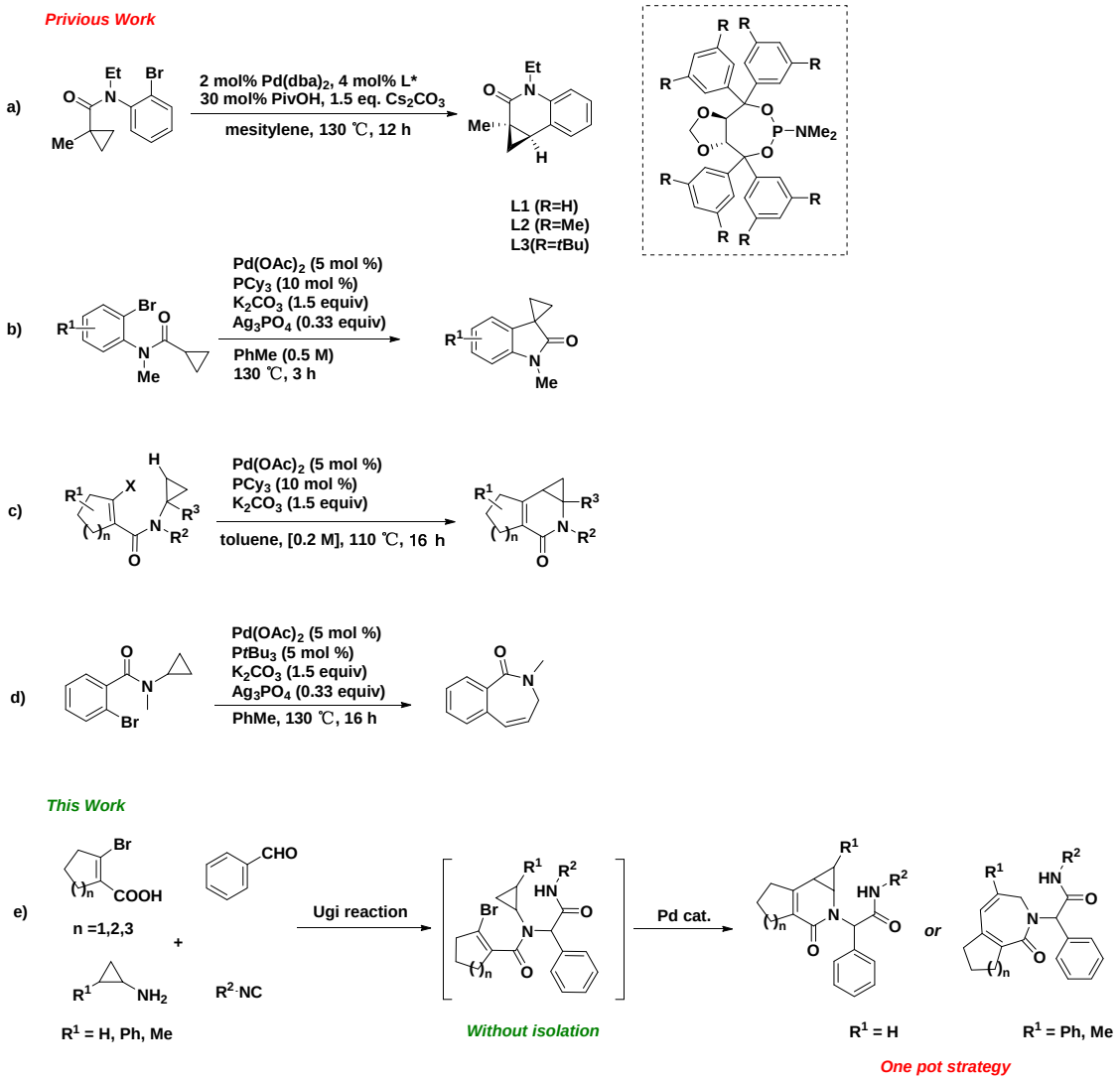


Figure 1. Marketed drugs and development candidates having an annulated cyclopropyl ring system.

Although a broad range of methods for the construction of cyclopropane rings have been reported, the direct functionalization of an existing cyclopropane group as a complementary strategy remains

underdeveloped and highly desired. Over the past decade, Palladium-catalyzed intramolecular cyclopropane C-H functionalization has attracted considerable attention (Scheme 1a-d). [7-11] This initial proof of feasibility prompted us to exploit this reaction principle further with the aim to develop a rapid access to synthetically versatile building blocks containing the skeleton of cyclopropane.



Scheme 1. Palladium-catalyzed intramolecular cyclopropane C-H functionalization.

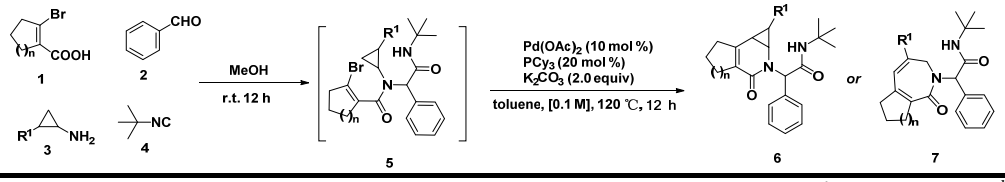
As our continuous interests in multiple component reaction (MCR) [12-15] for diversity-oriented synthesis highly functionalized structures in a facile and rapid manner, we envisaged that the proper union of MCR with Palladium-catalyzed intramolecular cyclopropane C-H functionalization in one pot reaction will extremely expand its application as a novel strategy. The inherent ring strain and orbital rehybridization found within cyclopropane ring systems may facilitate the desired cascade transformation towards ring expension. Because the carbon atoms in cyclopropane rings exhibit sp^2-like properties, which may provide the advantage of greater catalyst–substrate interactions and, therefore, promote C–H bond cleavage towards the formation of larger rings in one pot.

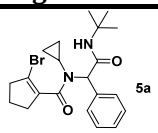
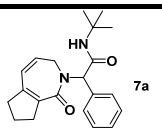
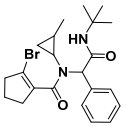
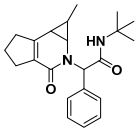
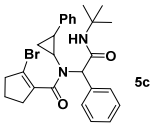
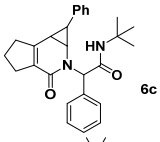
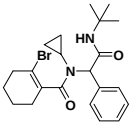
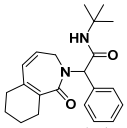
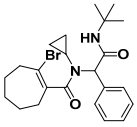
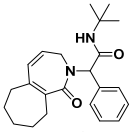
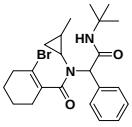
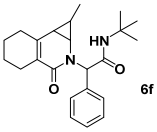
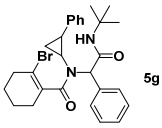
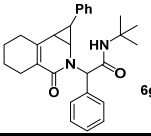
Among named MCRs, the Ugi four-component reaction (Ugi-4CR) is, with no doubt, one of the most powerful synthetic tools due to its advantages of saving synthetic operations as well as maximizing the buildup of structural diversity. [6-20] so, we decided to assemble a cyclopropyl

moiety and an alkenyl bromide precursor in Ugi addicts followed by Palladium-catalyzed intramolecular cyclopropane C-H functionalization. Herein, we describe the a novel reaction cascade of Ugi/Palladium-catalyzed intramolecular alkenylation of cyclopropane methylene C–H in one pot to achieve the synthesis seven or five membered azacycle backbones via adjusting the 2-substituents on cyclopropane to trigger *in situ* ring opening (Scheme 1e).

2. Results and discussion

Table 1. Palladium-catalyzed intramolecular cyclopropane C-H functionalization accessing azacycles.[a]



Entry	Ugi adduct	Product	R^1	Yield[b] (%)
1	 5a	 7a	H	55
2	 5b	 6b	Me	37
3	 5c	 6c	Ph	33
4	 5d	 7d	H	58
5	 5e	 7e	H	42
6	 5f	 6f	Me	33
7	 5g	 6g	Ph	28

[a]Reaction conditions: To a solution of **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol) in 5 mL MeOH were added **4** (0.5 mmol), and the mixture was allowed to stirred at room temperature for 12 h. Then, the solvent was removed under reduced pressure. To a 10 mL Schlenk tube The residue without further purification was added to a solution of $Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %), K_2CO_3 (2.0 equiv) in 5 mL toluene under N_2 atmosphere. The mixture was allowed to stir at 120°C for 12h. [b]Isolated yield.

First of all, the optimized conditions were established (Table 1): To a solution of **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol) in 5 mL MeOH were added **4** (0.5 mmol), and the mixture was allowed to

stirred at room temperature for 12 h. Then, the solvent was removed under reduced pressure. To a 10 mL Schlenk tube, without further purification, the residue was added to a solution of Pd $(OAc)_2$ (10 mol%), PCy_3 (20 mol%), K_2CO_3 (2.0 equiv) in 5 mL toluene under N_2 atmosphere. The mixture was allowed to stir at 120 °C for 12 h. With the optimized conditions in hand, the substrate scan was investigated as shown in Table 1. To our delight, the Ugi adducts **5** gave moderate to good conversion to product **6** or **7**. We also explored the effect of 2-substitution on cyclopropane group. Substitution me- and Ph- impeded reactivity of ring opening only to give cyclopropyl-fused product **6** (Entry 2, 3, 6 and 7). While without 2-substitution, ring opening occurred, providing access to ring-expending product **7** (Entry 1, 4 and 5). We also tested different ring sizes in the component of aldehyde. Notably, this reaction can be compatible with cyclopentyl, cyclohexyl and cycloheptyl (Entry 1, 5 and 7).

*N-(tert-butyl)-2-(1-oxo-3, 6, 7, 8-tetrahydrocyclopenta [c] azepin-2 (1H)-yl)-2-phenylacetamide (**7a**)*: White solid (93.2 mg, 55% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.46 (m, 2H), 7.40 – 7.29 (m, 3H), 6.75 (s, 1H), 6.17 – 6.15 (m, 1H), 5.85 – 5.82 (m, 1H), 5.62 (t, *J* = 1.0 Hz, 1H), 3.69 – 3.67 (m, 2H), 2.44 – 2.30 (m, 4H), 1.52 (d, *J* = 5.6 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.9, 170.4, 153.8, 136.6, 129.0, 128.3, 127.8, 123.5, 115.6, 61.9, 53.0, 44.3, 32.8, 29.6, 28.6, 23.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{27}N_2O_2$ 339.2067, found 339.2064.

*N-(tert-butyl)-2-(1-methyl-3-oxo-1a, 3, 4, 5, 6, 6b-hexahydrocyclopenta [d] cyclopropa [b] pyridin-2 (1H)-yl)-2-phenylacetamide (**6b**)*: White solid (65.3 mg, 37% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.54 (m, 2H), 7.41 – 7.28 (m, 3H), 6.72 (s, 1H), 5.66 (t, *J* = 1.0 Hz, 1H), 3.48 (t, *J* = 7.0 Hz, 1H), 2.61 – 2.59 (m, 1H), 2.52 – 2.50 (m, 2H), 2.32 – 2.30 (m, 2H), 2.16 – 2.02 (m, 1H), 1.48 (d, *J* = 5.5 Hz, 2H), 1.34 (s, 9H), 0.92 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1, 168.2, 148.3, 136.7, 129.0, 129.0, 128.9, 127.8, 62.1, 53.0, 44.2, 33.5, 28.9, 28.6, 25.0, 24.0, 20.2, 14.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{29}N_2O_2$ 353.2224, found 353.2229.

*N-(tert-butyl)-2-(3-oxo-1-phenyl-1a, 3, 4, 5, 6, 6b-hexahydrocyclopenta [d] cyclopropa [b] pyridin-2 (1H)-yl)-2-phenylacetamide (**6c**)*: White solid (68.5 mg, 33% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.50 (m, 2H), 7.41 – 7.26 (m, 5H), 7.24 – 2.22 (m, 1H), 6.99 – 6.90 (m, 2H), 6.76 (s, 1H), 5.71 (t, *J* = 1.0 Hz, 1H), 3.98 (dd, *J* = 7.2, 6.4 Hz, 1H), 3.27 (m, 1H), 3.05 (m, 1H), 2.52 – 2.50 (m, 2H), 2.35 – 2.32 (m, 2H), 1.49 (d, *J* = 5.5 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1, 168.1, 146.8, 139.6, 136.8, 133.7, 129.1, 129.0, 128.8, 127.9, 127.80, 127.5, 62.1, 52.5, 47.8, 33.5, 30.2, 30.1, 28.9, 28.6, 24.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{31}N_2O_2$ 415.2380, found 415.2387.

*N-(tert-butyl)-2-(1-oxo-1, 3, 6, 7, 8, 9-hexahydro-2H-benzo [c] azepin-2-yl)-2-phenylacetamide (**7d**):* White solid (102.4 mg, 58% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (m, 2H), 7.41 – 7.28 (m, 3H), 6.75 (s, 1H), 6.11 (m, 1H), 5.84 (m, 1H), 5.65 (t, *J* = 1.0 Hz, 1H), 3.68 (dd, *J* = 3.9, 1.0 Hz, 2H), 2.45 (m, 2H), 2.32 (m, 2H), 1.71 – 1.58 (m, 5H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.0, 169.40, 149.0, 136.6, 129.0, 129.0, 128.8, 127.8, 123.9, 117.9, 61.9, 53.0, 44.3, 28.8, 28.6, 25.6, 22.6, 22.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{29}N_2O_2$ 353.2224, found 353.2221.

*N-(tert-butyl)-2-(1-oxo-3, 6, 7, 8, 9, 10-hexahydrocyclohepta [c] azepin-2 (1H)-yl)-2-phenylacetamide (**7e**):* White solid (77.1 g, 42% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.46 (m, 2H), 7.41 – 7.28 (m, 3H), 6.75 (s, 1H), 6.05 – 6.03 (m, 1H), 5.84 (m, 1H), 5.64 (t, *J* = 0.9 Hz, 1H), 3.70 – 3.68 (m, H), 2.43 – 2.25 (m, 4H), 1.71 – 1.61 (m, 2H), 1.61 – 1.53 (m, 3H), 1.53 – 1.45 (m, 1H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1, 170.6, 151.4, 136.60, 129.0, 129.0, 128.4, 127.7, 124.0, 116.2, 61.9, 52.8, 44.3, 30.9, 28.6, 28.0, 27.9, 27.3, 26.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{31}N_2O_2$ 367.2380, found 367.2371.

*N-(tert-butyl)-2-(1-methyl-3-oxo-1, 1a, 3, 4, 5, 6, 7, 7b-octahydro-2H-cyclopropa [c] isoquinolin-2-yl)-2-phenylacetamide (**6f**):* White solid (60.1 g, 33% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.57 (m, 2H), 7.41 – 7.28 (m, 3H), 6.72 (s, 1H), 5.65 (t, *J* = 1.0 Hz, 1H), 3.48 (t, *J* = 7.0 Hz, 1H), 2.62-2.58 (m, 1H), 2.26 (m, 2H), 2.22 – 2.11 (m, 2H), 2.11 – 2.02 (m, 1H), 1.75 – 1.65 (m, 2H), 1.65 – 1.46 (m, 2H), 1.33 (s, 9H), 0.93 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ

171.1, 168.91, 145.0, 136.7, 131.4, 129.0, 127.7, 62.10, 52.8, 44.2, 29.5, 28.6, 25.4, 24.3, 23.17, 22.6, 20.2, 15.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{31}N_2O_2$ 367.2380, found 367.2386.

*N-(tert-butyl)-2-(3-oxo-1-phenyl-1, 1a, 3, 4, 5, 6, 7, 7b-octahydro-2H-cyclopropa [c] isoquinolin-2-yl)-2-phenylacetamide (**6g**):* White solid (60.0 g, 28% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.50 (m, 2H), 7.41 – 7.26 (m, 5H), 7.26 – 7.20 (m, 1H), 6.97 – 6.89 (m, 2H), 6.63 (s, 1H), 5.71 (t, *J* = 1.0 Hz, 1H), 3.98 (dd, *J* = 7.2, 6.4 Hz, 1H), 3.30 – 2.24 (m, 1H), 3.15 – 2.95 (m, 1H), 2.31 – 2.21 (m, 2H), 2.20 – 2.18 (m, 2H), 1.77 – 1.61 (m, 2H), 1.67 – 1.47 (m, 2H), 1.33 (s, 7H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1, 168.8, 139.6, 138.5, 136.8, 130.9, 129.1, 128.8, 127.9, 127.7, 127.3, 62.1, 52.5, 47.8, 30.1, 29.5, 29.3, 28.6, 25.4, 23.2, 22.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{33}N_2O_2$ 429.2537, found 429.2542.

3. Conclusion

In conclusion we have developed a novel example of Ugi/Palladium-catalyzed intramolecular cyclopropyl direct alkenylation cascade reaction providing access to novel azacycles in one pot. Palladium-catalyzed direct alkenylation of cyclopropyl C−H bonds proceeds in high efficiency with easy work-up. This transformation was adjusted by 2-substituent on cyclopropyl providing alternative access to cyclopropyl-fused azacycles or ring-expending products.

Acknowledgments

This work was financially supported by 2017 Research Fund of Xinyang Agriculture and Forestry University for Young Teachers.

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