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Ugi-Post Functionalization, from a Single Set of Ugi-Adducts to Two Distinct Heterocycles by Microwave-Assisted Palladium-Catalyzed Cyclizations: Tuning the Reaction Pathways by Ligand Switch

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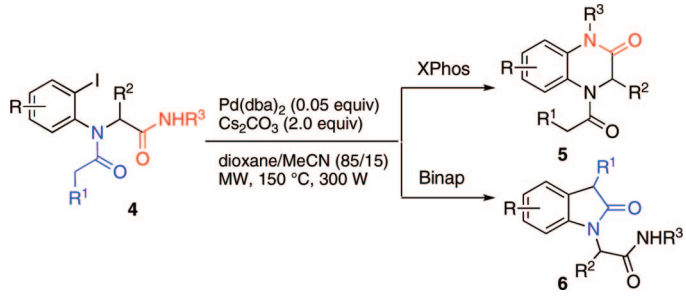

Linear amides **4**, prepared in one step by the Ugi four-component reaction, were converted to 3,4-dihydroquinoxalin-3-ones (**5**) or to 2-(2-oxoindolin-1-yl)acetamides (**6**) dependent on the catalytic conditions. While microwave irradiation was found to be determinant on the reaction efficiency, the choice of ligand diverged the reaction pathways. Heating a solution of **4** in dioxane/MeCN (v/v = 85/15) under microwave irradiation conditions in the presence of $Pd(dba)_2$ (0.05 equiv) and Cs_2CO_3 (2 equiv), using XPhos as a supporting ligand, afforded the 3,4-dihydroquinoxalin-3-ones (**5**) via an intramolecular N-arylation of the secondary amide. On the other hand, using BINAP as ligand under otherwise identical conditions, intramolecular α-CH arylation of tertiary amide occurred to furnish the oxindoles (**6**).

Introduction

The postfunctionalization of multicomponent reaction (MCR)[1] adducts has received considerable attention in recent years.[2] Indeed, MCR is not only a valuable tool for rapidly creating molecular complexity and diversity suitable for biological evaluation but is also capable of providing scaffolds with appropriate functionalities paired for further transformations, expanding consequently the chemical space accessible by this enabling technology.[3]

Isonitrile-based MCRs, represented by the Passerini three-component reaction[4] and Ugi four-component reaction,[5] are among the most powerful transformations that have been extensively investigated for the past 20 years.[6] Because of the mildness of reaction conditions, the wide application scope, and the high variability (four diversity points for U-4CR), they provided perfect tools for generating multifunctional adducts.

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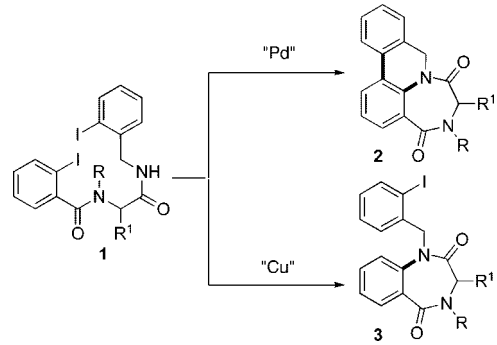
Naturally, these reactions have been associated with a number of post-transformations such as cyclocondensation,[7] ring-closure metathesis,[8] cycloaddition,[9] macrolactonization,[10] S_NAr,[11] S_N2 reaction,[12] radical cyclization[13] etc. for the synthesis of various cyclic scaffolds. The association of rich and diverse palladium-catalyzed chemistry[14] with the Ugi reaction has also been investigated. Indeed, performing the Heck reactions,[15] the N-arylations,[16] the C-arylation of benzylic carbon,[17] the C−H funcationalization,[18] the Suzuki−Miyaura reaction,[19] and the Sonogashira couplings[20] on the properly functionalized Ugi-adducts allowed the facile access to a number of medicinally relevant heterocycles.[21]

SCHEME 1. From Single Ugi Adduct to Different Set of Heterocycles by Metal Switch



Notwithstanding the effiency of these reaction sequences, the functionalized Ugi-adducts in most of these processes were designed and synthesized for participation in a single defined chemical process. Therefore, each of these two-step sequences generally led to a single set of heterocyclic system. The power of the MCR/postfunctionalization would be reinforced if the same MCR-adduct could be diverged to different heterocyclic scaffolds by exploiting its multifunctionalities.[22] Toward this end, we have recently reported that the linear Ugi-adduct **1** can be converted to tetracyclic compound **2** or benzodiazepinedione **3** at will by simply switching the metal catalysts (Scheme 1).[23,24] As a continuation of this work, we reasoned that it should be conceivable to assemble a single subset of molecules bearing multiple reaction sites, which could then undergo, in a selective manner, different palladium-catalyzed transformations by simply changing one or two reaction parameters.[25] In view of the recent spectacular advances on the palladium-catalyzed N-arylation of amides[26] and C-arylation of acidic methylene groups,[27] we were interested in the Ugi-adduct **4** and hypothesized that by judicious choice of the base we would be able to orient the reaction pathways toward the formation of either dihydroquinoxalinones **5** or oxindoles **6** (Scheme 2). While a divergent synthesis of

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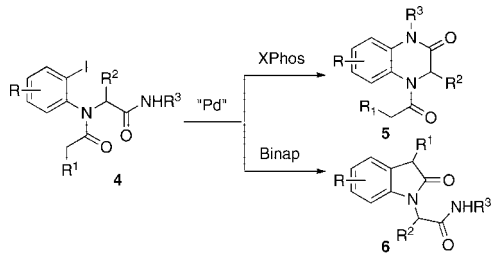
SCHEME 2. From Single Ugi Adduct to Different Set of Heterocycles by Ligand Switch



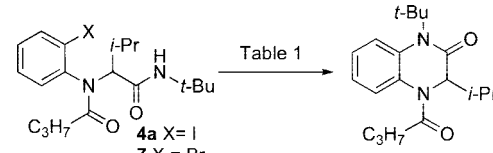
these two heterocycles from the same linear amide **4** was indeed achieved, we observed that it was not the base, but the structure of ligand that determined the reaction manifold. Thus under microwave irradiation conditions, palladium-catalyzed intramolecular N-arylation of amide **4** in the presence of Xphos ligand afforded the 3,4-dihydroquinoxalin-3-ones (**5**).[28] On the other hand, when BINAP was used as ligand under otherwise identical conditions, amide **4** was converted to 2-(2-oxoindolin-1-yl)acetamides (**6**) by an intramolecular arylation of enolate.[29]

Results and Discussion

Synthesis of 3,4-Dihydroquinoxalin-2-ones. 3,4-Dihydroquinoxalin-2-ones (benzopiperazinones) are attractive synthetic targets in medicinal chemistry. These compounds have been reported to present antidiabetic[30] or antiviral activities,[31] to act as multiple drug resistance antagonists,[32] and to be inhibitors of aldose reductase,[33] agonists of the γ-aminobutyric acid (GABA)/benzodiazepine receptor complex,[34] and antagonists of the AMPA and angiotensin II receptors.[35] Because of their significant biological activities, they are considered as priviledged scaffolds in medicinal chemistry.[36]

Recently, Kalinski and co-workers reported an Ugi/Pd-catalyzed amidation sequence for the synthesis of such heterocycles.[16a] Whereas the viability of the sequence was demonstrated, the reported process suffered from the poor yield obtained in the Pd-catalyzed amidation reaction (3−50%) and the limited number of examples investigated (5 examples). This prompted us to re-evaluate the sequence using amide **4a** (R^1 = C_2H_5, R^2 = *i*-Pr, R^3= *t*-Bu, X = I) as a model compound, and the results are summarized in Table 1.

TABLE 1. Palladium-Catalyzed Intramolecular *N*-Arylation: Survey of Reaction Conditions[a]



entry	Pd	ligand	solvent	*T* (°C)	yield[b] (%)
1	$Pd(dba)_2$	XPhos	dioxane	reflux	40
2	$Pd(dba)_2$	Xantphos	dioxane	reflux	55
3	$Pd(dba)_2$	XPhos	dioxane	MW[c]	44
4	$Pd(dba)_2$	XPhos	DMF	MW[c]	77
5	$Pd(dba)_2$	XPhos	dioxane/CH_3CN[d]	MW[c]	91
6[e]	$Pd(dba)_2$	XPhos	dioxane/CH_3CN[d]	MW[c]	28
7	$Pd(OAc)_2$	XPhos	dioxane/CH_3CN[d]	MW[c]	67
8	$PdCl_2$(dppf)		dioxane/CH_3CN[d]	MW[c]	58
9	$Pd(dba)_2$		dioxane/CH_3CN[d]	MW[c]	87
10	$Pd(dba)_2$	Me-Phos	dioxane/CH_3CN[d]	MW[c]	78
11	$Pd(dba)_2$	Xantphos	dioxane/CH_3CN[d]	MW[c]	60
12	$Pd(dba)_2$	Rac BINAP	dioxane/CH_3CN[d]	MW[c]	0
13[f]	$Pd(dba)_2$	XPhos	dioxane/CH_3CN[d]	MW[c]	81
14[g]	$Pd(dba)_2$	XPhos	dioxane/CH_3CN[d]	MW[c]	34

[a] General conditions: **4a** (1.0 equiv), palladium (0.05 equiv), ligand (0.05 equiv), and Cs_2CO_3 (2.0 equiv), C = 0.015 M. [b] Referred to chromatographically pure product. [c] Microwave irradiation power: 300 W, 150 °C. Microwave experiments were conducted using a Discover microwave reactor from CEM. All experiments were performed in sealed tubes (capacity 10 mL) under argon atmosphere. Microwave irradiation of 300 W was used, the temperature being ramped from room temperature to 150 °C in 1 min. Once this temperature was reached, the reaction mixture was held at 150 °C for 2 h. The temperature in the MW experiments was measured by an external IR sensor. [d] v/v = 85/15. [e] K_2CO_3 was used as a base. [f] Bromide **7** was used as starting material. [g] Chloride **8** was used as starting material.

A bidentate ligand, Xantphos,[37] and a monodentate biaryl monophosphine, Xphos,[38] were initially used in combination with $Pd(dba)_2$ (5% equiv) and Cs_2CO_3 (2.0 equiv) in refluxing dioxane for the cyclization of **4a**. Indeed, both ligands were found to be effective to afford cyclized product in moderate yield (entries 1, 2). Since microwave heating was known to be beneficial to the palladium-catalyzed intramolecular *N*-arylation reaction,[26,39] we next carried out the reaction under microwave irradiation using XPhos as ligand.[40] In dioxane, performing the reaction under microwave irradiation did not have significant impact on the reaction outcome (entry 3). However, when DMF or a mixture of solvent dioxane/acetonitrile (v/v = 85/15) was used, the reaction proceeded more efficiently to provide **5a** in yields of 77% and 91%, respectively (entries 4 and 5). Variation of the base (entry 6), the palladium sources (entries 7, 8), and ligands (entries 9−12) invariably reduced the yield of cyclic product. It should be noted that under microwave irradiation cyclization of **4a** took place under ligandless conditions using $Pd(dba)_2$ as catalyst to afford **5a** in 87% (entry 9). These latter

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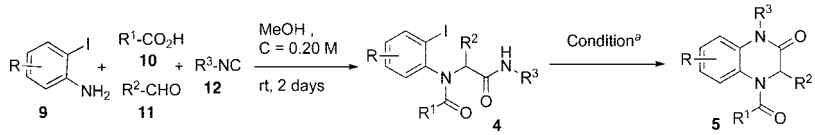
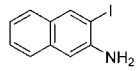
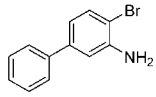
TABLE 2. UGI-4CR/Palladium-Catalyzed Intramolecular N-Arylation: Synthesis of Benzopiperazinones



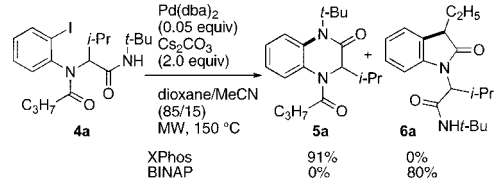
entry	R (Aniline)	R^1	R^2	R^3	Yield of **4**[b]	Yield of **5**[b]
1	H	*n*-C_3H_7	*i*-Pr	*t*-Bu	**4a**, 85%	**5a**, 86%
2	H	*n*-C_3H_7	$BnCH_2$	*t*-Bu	**4b**, 75%	**5b**, 90%
3	H	*n*-C_3H_7	Me	*t*-Bu	**4c**, 70%	**5c**, 66%
4	H	$MeOCH_2$	*i*-Pr	*t*-Bu	**4d**, 90%	**5d**, 88%
5	H	*n*-C_3H_7	Me	*c*-C_6H_{11}	**4e**, 69%	**5e**, 90%
6	H	*n*-C_2H_5	*i*-Pr	Bn	**4f**, 87%	**5f**, 84%
7		*n*-C_3H_7	*i*-Pr	*t*-Bu	**4g**, 67%	**5g**, 95%
8	4-F	*n*-C_2H_5	*i*-Pr	*t*-Bu	**4h**, 42%	**5h**, 83%
9	4-Me	*n*-C_2H_5	Me	*t*-Bu	**4i**, 80%	**5i**, 92%
10	4-MeO	(*S*)-$PhCH(CH_3)CH_2$	Me	*t*-Bu	**4j-4j'**,[c] 64%	**5j**,[d] 74%
11		*n*-C_2H_5	*i*-Pr	*t*-Bu	**4k**, 54%	**5k**, 78%
12	H	*t*-Bu	Me	*t*-Bu	**4l**, 87%	**5l**, 65%
13	H	*i*-Pr	Me	*t*-Bu	**4m**, 82%	**5m**, 79%
14	3-MeO	*n*-C_2H_5	*i*-Pr	*t*-Bu	**4n**, 71%	**5n**, 0%
15	H	CH_3	*i*-Pr	*t*-Bu	**4o**, 87%	**5o**, 25%

[a] General conditions: **4** (1.0 equiv), palladium (0.05 equiv), XPhos (0.05 equiv), and Cs_2CO_3 (2.0 equiv) in dioxane/MeCN = 85/15 (v/v), *C* = 0.015M, MW (300 W, 150 °C). [b] Referred to chromatographically pure product. [c] Two separable diastereoisomers. [d] Pure diastereomer **4j** was used for the cyclization.

conditions were subsequently found to be substrate dependent and have only limited application scope. Overall, the optimized conditions for this cyclization were as follows: $Pd(dba)_2$ (0.05 equiv), XPhos (0.05 equiv), and Cs_2CO_3 (2.0 equiv) in dioxane/CH_3CN (v/v = 85/15) under microwave irradiation (entry 5). The aryl bromide **7** participated in the reaction efficiently to afford the desired product **5a** in 81% yield (entry 13). On the other hand, the aryl chloride **8** was much less reactive under these conditions providing the benzopiperazinone **5a** in only 34% yield together with unreacted starting materials (54% recovered) (entry 14).

With the appropriate conditions in hand, the scope of this two-step synthesis of 3,4-dihydroquinoxalin-3-ones was explored by combined use of Ugi-4CR and Pd-catalyzed intramolecular amidation. The results are summarized in Table 2. As expected, the Ugi reaction proceeded uneventfully under standard conditions (MeOH, rt) with a wide range of substrates. From three aldehydes, seven anilines, six carboxylic acids, and three isonitriles, 15 amides were synthesized in yields ranging from 42 to 90%. The low yield obtained with 4-fluoroaniline (entry 8) is understandable considering the reduced nucleophilicity of the nitrogen and the low basicity of the resulting imine.[41] The intramolecular palladium-catalyzed amidation worked well with most of the substrates examined. The benzyl amide, cyclohexyl amide, and *tert*-butyl amide cyclized efficiently, indicating that the reaction was insensititve to the steric hindrance around the secondary amide unit. The electronic properties of the aromatic ring have no significant impact on the reaction outcome as the presence of methyl, methoxy, and fluorine substituents were well tolerated. The reaction was, however, found to be sensitive to steric hindrance *ortho* to the iodide as a Ugi-adduct derived from 3-methoxy-2-iodo aniline (**4n**) failed to cyclize under standard conditions (entry 14). Amides synthesized from linear and α-branched aliphatic aldehydes and carboxylic acid all cyclized without event. Surprisingly, in the cyclization of acetyl derivative **4o**, the desired 3,4-dihydroquinoxalin-2-one (**5o**) was isolated in only 25% yield together with oxindole **6d** in 54% yield (vide infra). The aryl bromide **4k**, as demonstrated in the optimization phase, is reactive enough to afford compound **5k** in 78% yield.

SCHEME 3. Ligand-Directed Reaction Divergency

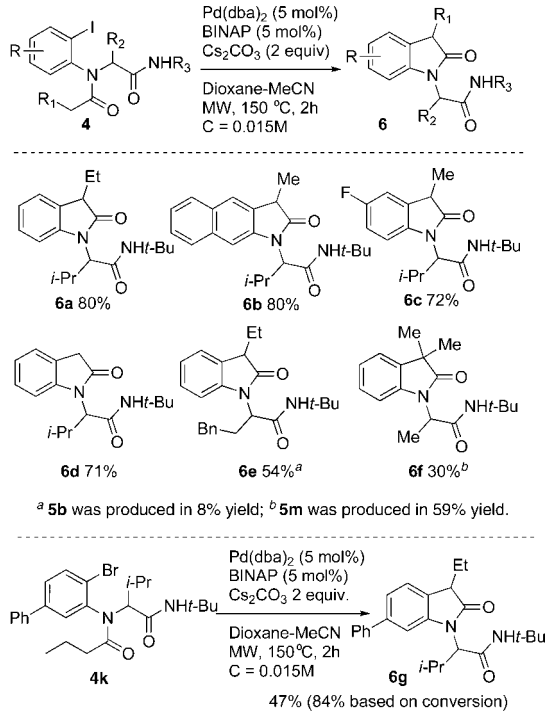


Synthesis of Indolin-2-ones. During the optimization of the Pd-catalyzed N-arylation reaction (Table 1), we frequently observed the formation of oxindole **6** as a side product when ligands other than XPhos were used. This product was very likely derived from competitive intramolecular palladium-catalyzed α-arylation of the tertiary amide.[27,29,42] While use of XPhos as a supporting ligand suppressed completely the oxindole formation, we found that cyclization of **4a** in the presence of Binap *completely reversed the benzopiperazinones/oxindole selectivity* leading to the formation of oxindole **6a** as a mixture of two diastereoisomers (Scheme 3). The optimal conditions found consisted of using $Pd(dba)_2$ (0.05 equiv) as a palladium source, rac-Binap (0.05 equiv) as a ligand, and

(41) Marcaccini, S.; Torroba, T. *Nature Protocols* **2007**, *2*, 632–639.

(42) (a) Marsden, S. P.; Watson, E. L.; Raw, S. A. *Org. Lett.* **2008**, *10*, 2905–2908. (b) Jia, X. Y.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040–4042. (c) J. Hillgren, M.; Marsden, S. P. *J. Org. Chem.* **2008**, *73*, 6459–6461.

SCHEME 4. Synthesis of Oxindoles through α-Arylation

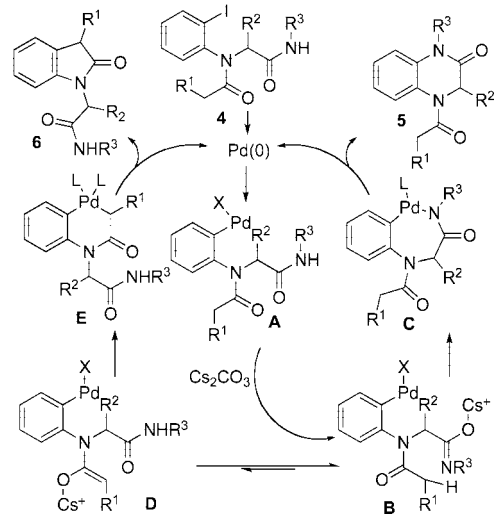


Cs_2CO_3 (2 equiv) as a base in dioxane−CH_3CN (v/v = 85/15) under microwave irradiation. The conditions turned out to be generally applicable to amides with different susbsituent patterns. It can be applied to the synthesis of 3-unsubstituted, 3-substituted, and 3,3-disubstituted oxindoles. However, in the latter case, the intramolecular N-arylation became competitive probably due to the increased steric hindrance associated with the creation of the quaternary carbon center. Using bulky *tert*-butylamide derived from *tert*-butyl isocyanide was important in order to ensure the occurrence of the α-arylation. Indeed, submitting the benzyl amide **4f** to the above conditions afforded the dihydroquinoxalinone **5f** as the only isolable product in 78% yield. Finally, aryl bromide **4k** also proved to be reactive, leading to the formation of oxindole **6g** in 47% yield together with recoved starting materials (44%).

Effect of Ligand on the Reaction Divergence: Mechanistic Implication. The palladium-catalyzed cross-coupling reaction is initiated by oxidative addition of haloarene to Pd(0) species, followed by transmetalation and reductive elimination to afford the coupled product with concurrent regeneration of Pd catalyst. A classic mechanism accounting for the formation of products **5** and **6** from **4** is illustrated in Scheme 5. The α-arylation of tertiary amides usually required strong bases like NaO-*t*-Bu and LiHMDS. Indeed, under thermal conditions, Cs_2CO_3 is known to be inefficient for promotion of oxindole formation through α-arylation of tertiary amide.[29a] The key questions we asked with regard to the reaction divergency were as follows: (a) How can ligand switch modulate so efficiently the two different reaction pathways? (b) How can the enolate of tertiary amide be formed?

The oxidative addition of aryl iodide to Pd(0) species leading to **A** is a common step for both the N-arylation and the α-C-arylation reactions and should thus have no consequence on the subsequent reaction pathways. With regard to the reductive elimination step of N-arylation, it is known that this step is faster from Pd complexes with bidentate ligands than from those with

SCHEME 5. Ligand-Dependent Reaction Divergence: Mechanistic Hypothesis



monodentate ligands.[43] Thus, if complex **C** was formed in the case where BINAP was used as a ligand, the reductive elimination should occurr to deliver the *N*-arylamide. This is, however, not the case, and we concluded that the role of supporting ligand on the partition of reaction pathways cannot be explained on this step either. Overall, we hypothesized that it is the transmetalation step that determined the reaction outcome.[44] It is reasonable to assume that the N−H of the secondary amide would be deprotonated first in the presence of a weak base (Cs_2CO_3) leading to the intermediate **B**. When XPhos was used as a ligand, the availability of a vacant coordination site of metal would facilitate the coordination of amidate to Pd, thus accelerating the transmetalation step (from **B** to **C**). Reductive elimination from **C** would then afford the benzopiperizinone **5**. It has to be noted that formation of a k^2-amidate palladium complex, often associated with the monodentate ligand, is known to inhibit the reductive elimination in an intermolecular amidation reaction.[43,44] However, we assumed that in the intramolecular version leading to the formation of a six-membered ring, the formation of such complex may not be so pronunced due to the geometry constraint.[45] In addition, the anilide nitrogen atom can also serve as a ligating site for Pd(II) species[46] to favor the formation of k^1-amidate palladium complex even with a monodentate ligand. On the other hand with sterically hindered secondary amide (*tert*-butyl amide) in the presence of a bidentate BINAP, the coordination of the secondary amide or the attack of the amidate on the tetracoordinated Pd(II) species **B** leading to **C** would be slowed down for steric reasons. Consequently, intramolecular proton shift from complex **B** could become competitive leading to the formation of enolate **D**. Transmetalation would subsequently take place to afford palladacycle **E**, which upon reductive elimination would produce oxindole **6**.

Conclusions

In conclusion, we have demonstrated that ligand can not only influence the reaction efficiency of a given palladium-catalyzed

(43) Fujita, K.-I.; Yamashita, M.; Puschmann, F.; Alvarez-Falcon, M. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044–9045.
(44) (a) Ikawara, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007.
(45) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35–37.
(46) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardiá, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587–1594.

transformation, but also completely switch the reaction manifolds with multifunctional substrates. Thus, from a single set of Ugi-adducts, two different heterocycles were readily synthesized by palladium-catalyzed intramolecular N-arylation and C-arylation processes. While microwave irradiation was important to the reaction efficiency, the choice of ligand determined the reaction pathways. Using monodentate XPhos as a supporting ligand, cyclization of **4** afforded the 3,4-dihydroquinoxalin-3-ones (**5**) via an intramolecular N-arylation of the secondary amide. On the other hand, in the presence of BINAP under otherwise identical conditions, intramolecular α-CH arylation of tertiary amide occurred to furnish the oxindole **6**. Combining with the versatile Ugi four-component reaction, these two medicinally relevant heterocycles can now be prepared in only two steps from the same, readily accessible starting materials. We assumed that high responsiveness of palladium chemistry to reaction parameters could be taken for granted for the similar reactivity switches with other substrates having more than one set of paired functional groups.

Experimental Section

General Procedure for the Preparation of Ugi Adducts 4. Iodoaniline (0.34 mmol, 1.2 equiv) and aldehyde (0.34 mmol, 1.2 equiv) were mixed together in dry methanol (0.2 M) under argon and stirred for 45 min. Isocyanide (0.285 mmol, 1.0 equiv) and carboxylic acid (0.34 mmol, 1.2 equiv) were then added, and the mixture was stirred for 2 days at room temperature. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted three times with EtOAc, and the organic layers were combined, backwashed with saturated aqueous $NaHCO_3$ solution and brine, dried over sodium sulfate, and evaporated under reduced pressure. Purification by preparative TLC (eluent: EtOAc/heptane) afforded the desired Ugi aduct.

***N-tert*-Butyl-2-(*N*-(2-iodophenyl)butyramido)-3-methylbutanamide (4a):** white solid; R_f = 0.53 (7:3 hexanes/EtOAc); mp 122−124 °C; IR (neat, cm^{-1}) ν 3339, 2961, 1641, 1536, 1466, 1388, 1362, 1243, 1225, 1017, 737, 720; ^1H NMR ($CDCl_3$, 300 MHz) rotamers δ 7.89−7.82 (2dd, J = 7.9, 1.5 Hz, 1H), 7.60 and 7.18 (dd, J = 7.9, 1.5 Hz, 1H), 7.42 and 6.36 (broad s, 1H, NH), 7.40−7.30 (m, 1H), 7.04−6.94 (2td, J = 7.9, 1.5 Hz, 1H), 4.36 and 3.59 (d, J = 10.8 Hz, 1H), 2.60−2.30 (m, 1H), 2,09−1.93 (m, 1H), 1.93−1.77 (m, 1H), 1.66−1.45 (m, 2H), 1.34 and 1.28 (s, 9H), 1.09 and 0.99 (d, J = 6.6 Hz, 3H), 0.90 and 0.83 (d, J = 6.6 Hz, 3H), 0.82−0.74 (2t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) rotamers 174.9 and 174.7, 170.2 and 168.7, 145.7 and 143.5, 140.6 and 140.5, 130.7 and 129.8, 130.1, 129.9 and 129.6, 103.3 and 102.9, 75.8 and 69.3, 51.6 and 51.3, 38.3 and 38.1, 30.4, 29.0, 29.0, 28.0, 22.2, 20.9, 19.9, 19.8, 19.1, 19.0, 14.2, 14.2; HRMS (*m*/*z*, ES^+) calcd for $C_{19}H_{29}IN_2O_2$ ($[M + Na]^+$) 467.1165, found 467.1177.

***N-tert*-Butyl-2-(*N*-(2-bromophenyl)butyramido)-3-methylbutanamide (7):** light brown solid; R_f = 0.60 (3:2 hexanes/EtOAc); mp 106−108 °C; IR (neat, cm^{-1}) ν 3339, 2964, 1676, 1642, 1537, 1473, 1395, 1245, 1065, 738; ^1H NMR ($CDCl_3$, 500 MHz) rotamers δ 7.60 (2d, J = 7.8 Hz, 1H), 7.56 and 7.21 (d, J = 7.8 Hz, 1H), 7.52 and 6.37 (broad s, 1H, NH), 7.38−7.30 (m, 1H), 7.25−7.13 (m, 1H), 4.33 and 3.53 (d, J = 10.4 Hz, 1H), 2.58 and 2.42 (m, 1H), 2.10−1.97 and 1.94−1.84 (m, 2H), 1.63−1.47 (m, 2H), 1.34 and 1.28 (s, 9H), 1.09 and 0.99 (d, J = 6.7 Hz, 3H), 0.90 (m, 3H), 0.79 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) rotamers 174.9 and 174.5, 170.0 and 168.3, 142.3 and 139.9, 133.8 and 133.7, 130.5 and 129.7, 130,0 and 129.5, 128.9 and 128.4, 125.4 and 124.8, 76.3 and 69.0, 51.2 and 50.8, 37.3 and 37.0, 29.6 and 28.7, 28.5 and 27.5, 21.2 and 20.0, 19.6 and 19.4, 18.7 and 18.6, 13.8 and 13.7; HRMS (*m*/*z*, ES^+) calcd for $C_{19}H_{29}{}^{79}BrN_2O_2$ ($[M + Na]^+$) 419.1310, found 419.1325, $C_{19}H_{29}{}^{81}BrN_2O_2$ 421.1290, found 421.1310.

***N-tert*-Butyl-2-(*N*-(2-chlorophenyl)butyramido)-3-methylbutanamide (8):** light brown solid; R_f = 0.59 (3:2 hexanes/EtOAc); mp 95−97 °C; IR (neat, cm^{-1}) ν 3335, 2964, 1668, 1641, 1541, 1481, 1385, 1245, 1217, 769; ^1H NMR ($CDCl_3$, 500 MHz) rotamers δ 7.60−7.46 (d, J = 7.9 Hz, 1H), 7.52 and 6.38 (broad s, 1H, NH), 7.43−7.37 (m, 1H), 7.33−7.18 (m, 2H), 4.30 and 3.55 (d, J = 10.5 Hz, 1H), 2.58 and 2.41 (m, 1H), 2.10−1.95 (m, 1H), 1.93−1.83 (m, 1H), 1.61−1.47 (m, 2H), 1.33 and 1.27 (s, 9H), 1.07 and 0.97 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.79−0.77 (2t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) rotamers 174.9 and 174.5, 170.1 and 168.4, 140.7 and 138.4, 134.3 and 133.8, 130.4 and 130.3, 130.4 and 129.5, 129.9 and 129.3, 128.2 and 127.8, 76.2 and 69.2, 51.1 and 50.7, 36.9 and 36.6, 29.2 and 28.6, 28.4 and 27.4, 20.8 and 19.81, 19.7 and 19.4, 18.6 and 15.8, 13.8 and 13.7; MS (*m*/*z*, ESI^+) 729 and 727 (2 M + Na), 377 and 375 (M + Na). Anal. Calcd for $C_{19}H_{29}ClN_2O_2$: C, 64.67; H, 8.28; N 7.84. Found: C, 64.61; H, 8.45; N 7.83.

General Procedure for the Preparation of 3,4-Dihydroquinoxalin-3-ones 5. To a solution of Ugi adduct **4** (0.034 mmol, 1.0 equiv) in dioxane/acetonitrile (v/v = 85/15; 0.015 M) were added Cs_2CO_3 (0.068 mmol, 2.0 equiv), $Pd(dba)_2$ (0.0017 mmol, 0.05 equiv), and Xphos (0.0017 mmol, 0.05 equiv) in a Teflon-capped vial. The vial was degazed under vacuum, refilled with argon, and subjected to microwave heating (300 W, 150 °C) for 2 h. After the reaction mixture was cooled to room temperature, the reaction mixture was concentrated to dryness and purified by preparative TLC (eluent: EtOAc/heptane) to give 3,4-dihydroquinoxalin-3-ones.

1-*tert*-Butyl-4-butyryl-3-isopropyl-3,4-dihydroquinoxalin-2(1*H*)-one (5a): light brown solid; R_f = 0.40 (7:3 hexanes/EtOAc); mp 81−83 °C; IR (neat, cm^{-1}) ν 2961, 2933, 2871, 1665, 1652, 1495, 1463, 1395, 1330, 1287, 1218, 1190, 1001, 960; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.17−7.19 (m, 3H), 7.13 (t, J = 7.2 Hz, 1H), 5.03 (d, J = 9.4 Hz, 1H), 2.54 (t, J = 7.3 Hz, 2H), 1.65 (m, 2H), 1.60 (s, 9H), 1.44 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H), 0.69 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.7, 171.9, 134.8, 131.8, 125.8, 125.6, 123.9, 122.7, 64.7, 58.6, 35.4, 29.9, 28.2, 19.2, 19.1 (2C), 13.7; MS (*m*/*z*, ESI^+) 339 (M + Na). Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.11; H, 9.00; N, 8.81.

1-*tert*-Butyl-4-butyryl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one (5b): colorless oil; R_f = 0.30 (9:1 hexanes/EtOAc); IR (neat, cm^{-1}) ν 2963, 1672, 1493, 1454, 1385, 1366, 1325, 1285, 1215, 754, 698; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31−7.20 (m, 4H), 7.20−7.09 (m, 3H), 7.09−7.02 (m, 2H), 5.46 (dd, J = 11.0, 4.1 Hz, 1H), 2.75−2.63 (m, 1H), 2.61−2.54 (m, 1H), 2.54−2.46 (m, 2H), 1.98−1.86 (m, 1H), 1.72−1.64 (m, 2H), 1.61 (s, 9H), 1.40−1.32 (m, 1H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 175.6, 172.4, 141.5, 135.3, 131.2, 128.8 (2C), 128.6, 126.6, 126.3, 124.3, 122.8, 60.0, 58.9, 35.9, 32.6, 30.9, 30.2, 19.4, 14.1; HRMS (*m*/*z*, ESI^+) calcd for $C_{24}H_{30}N_2O_2$ ($[M + Na]^+$) 401.2205, found 401.2202.

1-*tert*-Butyl-4-butyryl-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (5c): white solid; R_f = 0.39 (4:1 hexanes/EtOAc); mp 107−109 °C; IR (neat, cm^{-1}) ν 2965, 1664, 1496, 1389, 1365, 1328, 1263, 1210, 1189, 1030, 771, 761, 740, 663; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 7.8 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 5.47 (q, J = 7.0 Hz, 1H), 2.53 (m, 2H), 1.73−1.64 (m, 2H), 1.62 (s, 9H), 1.05 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 175.9, 171.4, 134.8, 130.9, 126.2, 125.8, 123.9, 122.4, 58.4, 55.4, 35.5, 29.7, 19.1, 14.7, 13.7; HRMS (*m*/*z*, ESI^+) calcd for $C_{17}H_{24}N_2O_2$ ($[M + Na]^+$) 311.1735, found 311. 1730.

General Procedures for the Preparation of 2-(2-Oxoindolin-1-yl)acetamides 6. To a solution of Ugi adduct **4** (0.034 mmol, 1.0 equiv) in dioxane/acetonitrile (v/v = 85/15; 0.015 M) were added Cs_2CO_3 (0.068 mmol, 2.0 equiv), $Pd(dba)_2$ (0.0017 mmol, 0.05 equiv), and rac-BINAP (0.0017 mmol, 0.05 equiv) in a Teflon-capped vial. The vial was degassed under vacuum, refilled with argon, and subjected to microwave heating (300 W, 150 °C) for

2 h. After the reaction mixture was cooled to room temperature, the reaction mixture was concentrated to dryness and purified by preparative TLC (eluent: EtOAc/heptane) to give 2-(2-oxoindolin-1-yl)acetamides.

***N-tert*-Butyl-2-(3-ethyl-2-oxoindolin-1-yl)-3-methylbutanamide (6a) (mixture of two diastereoisomers):** white solid; R_f = 0.40 (4:1 hexanes/EtOAc); mp 93−95 °C; IR (neat, cm^{-1}) ν 3346, 2960, 2929, 1697, 1609, 1537, 1484, 1460, 1357, 1212, 1097, 1025, 745, 628; ^{1}H NMR ($CDCl_3$, 500 MHz) two diastereoisomers, δ 7.38−7.20 (m, 3H), 7.07 (dd, J = 7.2, 7.1 Hz, 1H), 6.76−5.89 (broad s, 1H, NH), 4,28 and 4.23 (d, J = 7.9 Hz, 1H), 3.53 (m, 1H), 2.90 (m, 1H), 2.19−1.99 (m, 2H), 1.30 and 1.27 (2s, 9H), 1.12 (m, 3H), 0.91−0.74 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) two diastereoisomers, 178.9 and, 178.8, 168.3 and 168.0, 143.1 and 142.9, 128.2 and 128.1, 128.0, 123.6, 123.6, 122.6 and 122.6, 110.9, 64.6 and 63.7, 51.3, 46.5 and 46.2, 29.7, 28.6 and 28.6, 26.2 and 25.9, 23.7 and 23.6, 20.2 and 20.1, 19.0 and 18.7, 9.7 and 9.5; HRMS (*m*/*z*, ESI^+) calcd for $C_{19}H_{28}N_2O_2$ ($[M + Na]^+$) 339.2042, found 339.2037.

***N-tert*-Butyl-2-(3-ethyl-2-oxo-2,3-dihydro-1*H*-benzo[*f*]indol-1-yl)-3-methylbutanamide (6b) (mixture of two diastereoisomers):** light brown solid; R_f = 0.55 (7:3 hexanes/EtOAc); mp 129−131 °C; IR (neat, cm^{-1}) ν 3348, 2965, 2929, 1697, 1677, 1640, 1536, 1531, 1454, 1357, 1219, 1203, 868, 746, 607; ^{1}H NMR ($CDCl_3$, 500 MHz) two diastereoisomers, δ 7.83 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 6.80−5.81 (broad s, 1H, NH), 4.38 and 4.34 (d, J = 9.3 Hz, 1H), 3.68 (m, 1H), 2.96−2.13 (m, 1H), 2.26−2.09 (m, 2H), 1.30−1.27 (2s, 9H), 1.17 (t, J = 6.0 Hz, 3H), 0.90 and 0.85 (2t, J = 7.4 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) two diastereoisomers, 178.5 and 178.4, 168.1 and 167.9, 133.6, 130.2, 129.0, 128.9, 127.7, 127.6, 126.3, 124.5, 122.9 and 122.9, 106.8 and 106.7, 63.9, 51.4, 45.9 and 45.5, 28.6 and 28.6, 26.0 and 25.7, 24.1, 20.3 and 20.1, 19.0 and 18.7, 9.7 and 9.5; HRMS (*m*/*z*, ESI^+) calcd for $C_{23}H_{30}N_2O_2$ ($[M + Na]^+$) 389.2198, found 389.2190.

***N-tert*-Butyl-2-(5-fluoro-3-methyl-2-oxoindolin-1-yl)-3-methylbutanamide (6c) (mixture of two diastereoisomers)L.** light yellow solid; R_f = 0.69 (7:3 hexanes/EtOAc); mp 107−109 °C; IR (neat, cm^{-1}) ν 2963, 1703, 1698, 1482, 1338, 1220, 1190, 919, 859, 667; ^{1}H NMR ($CDCl_3$, 500 MHz) two diastereoisomers, δ 7.41−7.26 (m, 1H), 7.01−6.91 (m, 2H), 6.41−5.88 (broad s, 1H, NH), 4.22 (m, 1H,), 3.49 (q, J = 7.9 Hz, 1H), 2.85 (m, 1H), 1.49 (d, J = 7.9 Hz, 3H), 1.31 (2s, 9H), 1.10 (m, 3H), 0.75 (2d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) two diastereoisomeres, 179.3 and 179.2, 168.0, 158.7 (d, J = 241 Hz), 138.1 and 137.9, 131.7 (d, J = 8 Hz), 114.1 (d, J = 23 Hz), 112.3 (d, J = 8 Hz), 112.0 (d, J = 8 Hz), 111.3 (d, J = 23 Hz), 64.3, 51.5 and 51.4, 40.7 and 40.6, 28.6, 26.0, 20.0, 18.7 and 18.5, 16.1 and 15.7; HRMS (*m*/*z*, ESI^+) calcd for $C_{18}H_{25}FN_2O_2$ ($[M + Na]^+$) 343.1792, found 343.1782.

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Supporting Information Available: Physical and spectroscopic data of compounds **4b**−**o**, **5d**−**o**, and **6d**−**g**. Copies of ^{1}H and ^{13}C NMR spectra for compounds **4a**−**o**, **5a**−**o**, **6a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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