JOC*Note*

Palladium-Catalyzed Intramolecular *C*-Arylation of Benzylic Carbon: Synthesis of 3-Benzoxazolylisoindolinones by a Sequence of Ugi-4CR/Postfunctionalization

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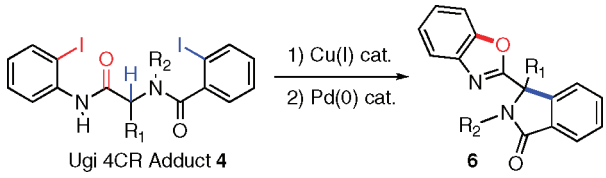
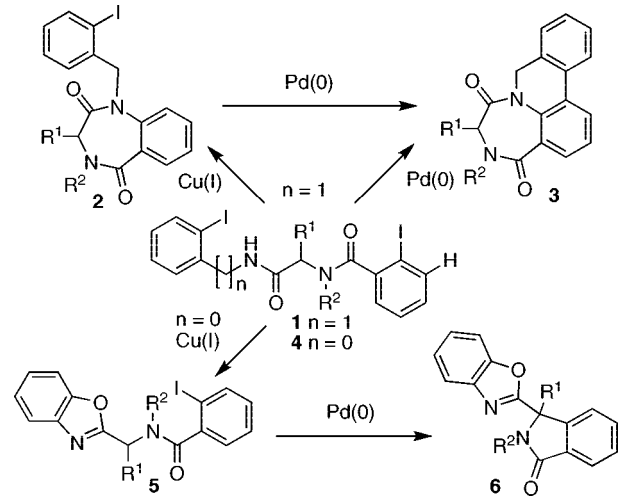


Submitting Ugi-adduct **4** to two consecutive metal-catalyzed intramolecular reactions, namely copper-catalyzed *O*-arylation and palladium-catalyzed *C*-arylation of benzylic carbon developed in the course of this study, affords the benzoxazolylisoindolinones in good to excellent yields.

Multicomponent reactions (MCR) offer a unique way to generate libraries of complex molecules efficiently with a high degree of diversity[1,2] Among them, the Ugi four-component reaction (Ugi-4CR)[3] is without doubt one of the most powerful transformations that has been extensively investigated for the past 20 years. Mainly two strategies have been developed around this reaction to further increase its versatility and the complexity-generating power: (a) tethering principle, by linking two of the four reactants together, a number of three-component syntheses of heterocycles have been developed;[1] and (b) postfunctionalization, by applying an efficient intramolecular reaction on the properly functionalized Ugi adducts, a variety of medicinally relevant heterocycles have been synthesized in only two operations.[4] Using this latter strategy, we have developed a two-step synthesis of a number of macrocycles including cyclophanes and cyclodepsipeptides.[5–7] We have also reported the elaboration

SCHEME 1. From Linear Ugi-Adducts to Heterocycles



of Ugi-adduct **1** ($n = 1$) containing two aryl halide functions and synthesized 1,4-benzodiazepine-2,5-diones **2** and its tetracyclic derivatives **3**[8] by using copper and palladium-catalyzed cyclization reactions (Scheme 1).[9] As a continuation of this research program, we became interested in the structural elaboration of the Ugi-adduct **4** ($n = 0$, Scheme 1) and have uncovered a direct intramolecular arylation of benzylic C_{sp^3} carbon (**5** to **6**). Parallel to this work, Yorimitsu and Oshima have independently developed a palladium-catalyzed arylation of aryl(azaaryl)methanes, including the α-arylation of 2-benzylbenzoxazole.[10] We report herein a two-step conversion of the Ugi adduct **4** to benzoxazolylisoindolinones **6**. The salient

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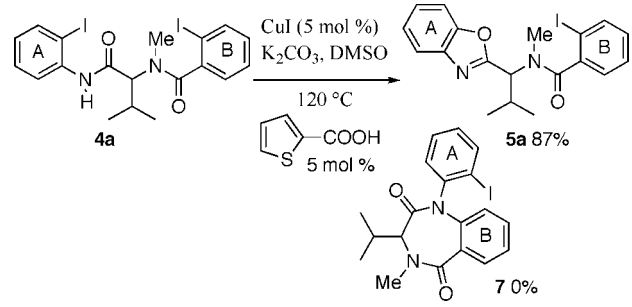
feature of the present work is the differentiation of two tethered aryl iodides for the construction of two different heterocycles. Both benzoxazole and isoindolinone are considered to be privileged structures in medicinal chemistry[11,12] and a compound combining these two units has been recently patented.[13]

The amide **4a** was initially chosen to investigate its reactivity under copper catalysis.[14] Due to the presence of two aryl halide functions, two possible reaction pathways leading to benzodiazepinedione **7** or benzoxazole **5a**[15] could be expected. Interestingly, treatment of compound **4** under conditions previously optimized for the cyclization of amide **1** (CuI, thiophene-2-carboxylic acid,[16] DMSO, K_2CO_3, 110 °C) afforded exclusively the benzoxazole **5a** in 87% yield via an intramolecular *O*-arylation process (Scheme 2).[17] The alternative intramolecular *N*-arylation leading to benzodiazepinedione was not observed. This result implied that the oxidative addition of ring A aryl iodide to Cu(I) occurred preferentially over the ring B counterpart, although ring B is electronically poorer than A and should thus be more prone to oxidative addition.[18] This regioselectivity is opposite to that observed in the cyclization of **1**. This selective formation of benzoxazole turned out to be quite general and a range of amides **4** with different R^1 and R^2 groups, including aliphatic and aromatic ones, readily cyclized to benzoxazoles **5** in good to excellent yields (Table 1). However, a low yield of benzoxazole was obtained when R^2 = H and Ph (**5b**, **5f**). Except for **5b** and **5d**, all other precursors were prepared by Ugi-4CR from readily accessible aldehydes, anilines, isocyanides, and carboxylic acids.

SCHEME 2. Copper-Catalyzed Cyclization of Amide 4a



The NMR spectra of compounds **5** were rather difficult to interpret. For example, compound **5a** exhibited three different sets of signals in its ^1H NMR spectrum. Variable-temperature NMR experiments revealed the coalescence of two of them at 348 K. However, a full coalescence was not observed even at 372 K. The presence of rotamers and atropisomers, resulting from a hindered rotation around the N−CO (a) and $C_{aromatic}$−CO bond (b),[19] respectively, can be advanced to explain the observed phenomena.[20] Indeed, compound **5**, having two rotationally restricted C−C bonds and one chiral sp^3 center, can exist as a mixture of up to four observable diastereomers on the NMR time scale (Figure 1).

The presence of an aryl iodide function in **5** provided a handle for further structural elaboration. One possible transformation—offered by structure **5**—is the direct intramolecular *C*-arylation of the benzylic C_{sp^3} carbon. This transformation was therefore investigated.

To our delight, treatment of a DMSO solution of compound **5a** in the presence of $Pd(OAc)_2$ (5 mol %) and KOAc (2 equiv) at 120 °C afforded benzoxazolylisoindolinones **6a** in 35% yield. Although palladium-catalyzed arylation of C_{sp^3} α to a carbonyl group is well-established,[21] direct arylations of methylenebenzoxazoles have, to the best of our knowledge, not been documented previously.[10]

Encouraged by this result, we set out to optimize the reaction conditions by varying the ligand, the base, the solvent, and the temperature. The results are summarized in Table 2. As expected, the ligand structure has a dramatic effect on the reaction efficiency, with PCy_3 and ligand **L1** (Figure 2) being the most efficient (entry 5 and 11). The ideal temperature for this transformation was found to be 90 °C. At lower temperatures (50–90 °C), the reaction became sluggish (entry 2–4). DMSO proved to be a better solvent than DMF, whereas dioxane

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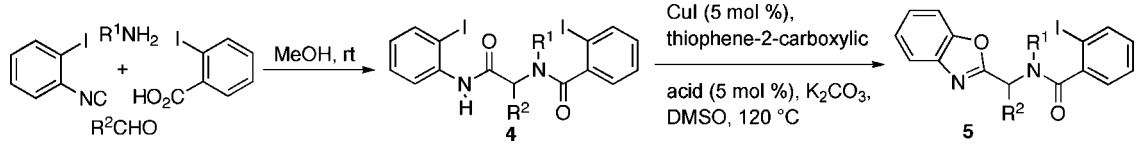
TABLE 1. Synthesis of Benzoxazoles by a Sequence of the Ugi-4CR/Copper-Catalyzed *O*-Arylation



entry	R^1	R^2	yield of linear amide	yield of benzoxazole
1	CH_3	*i*-Pr	**4a**, 83%	**5a**, 83%
2	CH_3	H	**4b**, (−)[a]	**5b**, 26%
3	$PhCH_2$	*i*-Pr	**4c**, 48%	**5c**, 77%
4	$CH_2CH_2CH_2$		**4d**, (−)[a]	**5d**, 63%
5	*i*-Pr	*n*-C_3H_7	**4e**, 58%	**5e**, 66%
6	*n*-C_4H_9	Ph	**4f**, 60%	**5f**, 15%
7	*n*-C_4H_{19}	*n*-C_6H_{13}	**4g**, 65%	**5g**, 71%
8	*n*-C_4H_9	*i*-Pr	**4h**, 94%	**5h**, 68%
9	*p*-$MeOPhCH_2$	*i*-Pr	**4b**, 48%	**5i**, 96%

[a] Synthesized by peptide coupling.

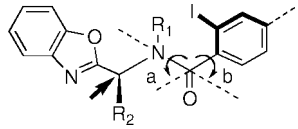
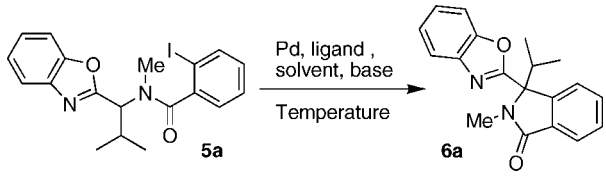


FIGURE 1. Stereochemical elements of benzoxazole **5**.

TABLE 2. Palladium-Catalyzed *C*-Arylation, Survey of Reaction Conditions[a]



entry	ligand	solvent	base	temp (°C)	yield (%)
1		DMSO	KOAc	120	35
2	PCy_3	Dioxane	NaO*t*Bu	50–90	14
3	PCy_3	THF	NaO*t*Bu	50–90	11
4	PCy_3	DMF	NaO*t*Bu	50–90	48
5	PCy_3	DMSO	NaO*t*Bu	90	62
6	L1	DMSO	NaO*t*Bu	110	60
7	PCy_3	DMSO	KOAc	110	53
8	PCy_3	DMSO	LiO*t*Bu	90	43
9	PCy_3	DMSO	KO*t*Bu	90	45
10[b]	PCy_3	DMSO	NaO*t*Bu	90	degradation
11	L1	DMSO	NaO*t*Bu	90	66
12	L2	DMSO	NaO*t*Bu	90	41
13	L3	DMSO	NaO*t*Bu	90	29
14	L4	DMSO	NaO*t*Bu	90	52
15	L5	DMSO	NaO*t*Bu	90	24
16	L6	DMSO	NaO*t*Bu	90	45
17[c]	PCy_3	DMSO	NaO*t*Bu	90	no reaction

[a] All reactions were carried out under an argon atmosphere with 0.05 equiv of $Pd(OAc)_2$, 1.5 equiv of base, *C* 0.2 M. [b] 3.0 equiv of base. [c] 0.05 equiv of $Pd(dba)_2$.

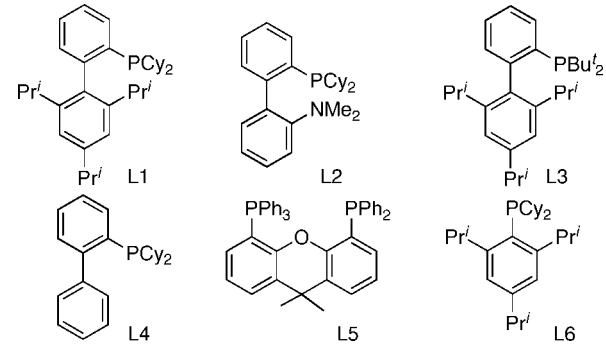


FIGURE 2. Ligand structure.

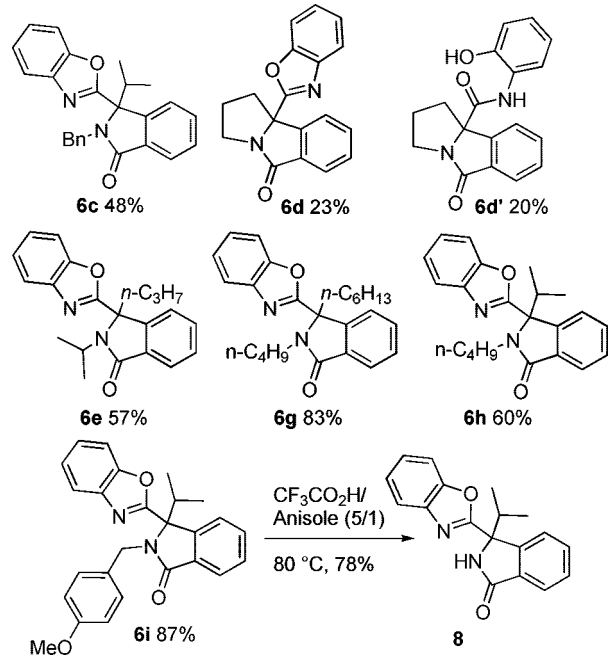


FIGURE 3. Synthesis of isoindolinone by an intramolecular palladium-catalyzed C_{sp^3}-arylation.

or THF were rather poor reaction media (entry 2,3). Sodium *tert*-butoxide stood out as a base, and a counterion effect was observed since lithium and potassium *tert*-butoxide provided inferior results under otherwise identical conditions (entries 5, 8, and 9). Using excess base was detrimental to the reaction (entry 10) and 1.5 equiv was found to be optimal (entry 10).

To probe the scope and limitation of this direct *C*-arylation process, a range of substituted benzoxazole amides were next submitted to the optimized cyclization condition. Results are shown in Figure 3. In most cases, cyclization proceeded smoothly to afford the desired compounds in moderate to good yields. However, compounds **5b** (R^2 = H) and curiously **5f** (R^2 = Ph), having a more acidic proton, led only to the destruction of the starting materials. In the case of proline-derived benzoxazole, partial hydrolysis of the benzoxazole occurred, leading to **6d** and **6d′** in yields of 23% and 20%, respectively. Both

structures have been confirmed by X-ray analysis (cf. Supporting Information).

Finally, the *N*-(4-methoxybenzyl) group in **6i** was readily removed under mild acidic conditions (CF_3CO_2H-anisole, 80 °C) to afford the unprotected isoindolinone **8** in 78% yield.

In conclusion, we documented a direct intramolecular *C*-arylation of methylenebenzoxazole. Starting from an Ugi-adduct having two aryl iodide units, regiospecific sequential intramolecular *O*- and *C*-arylation reactions led to an efficient synthesis of 3-substituted 3-benzoxazolylisoindolinones. In combination with the versatile Ugi four-component reaction, highly functionalized heterocycles can thus be easily prepared in three steps from readily accessible starting materials.

Experimental Section

General Procedure for the Ugi-Reaction. To a solution of methylamine hydrochloride (75.5 mg, 1.12 mmol) in methanol (0.2M) was added triethylamine (160 μL, 1.14 mmol). The mixture was stirred for 15 min, then isobutyraldehyde (78.5 mg, 1.09 mmol) was added and the stirring was continued for 15 min. 2-Iodobenzoic acid (277.8 mg, 1.12 mmol) was added followed by 1-iodo-2-isocyanobenzene (258.8 mg, 1.13 mmol). After being stirred at room temperature for 8 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, heptane/AcOEt = 3/1) to give the product **4a** (508 mg, 83%) as a yellow solid. Mp 160–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) (ppm) δ 1.13 (m, 6H), 1.25–1.27 (m, 1H), 2.84 (s, 3H), 4.96 (d, J = 9.8 Hz, 1H), 6.85 (br s, 1H), 7.08 (td, J = 7.9 and 1.5 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.33 (t, J = 6.9 Hz, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.81 (m, 2H), 8.19–8.28 (m, 1H), 8.39 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K) (ppm) δ 19.8, 19.9, 25.5, 32.1, 57.2, 90.1, 94.5, 122.0, 122.4, 122.6, 126.1, 128.4, 128.9, 130.4, 138.6, 139.3, 139.4, 171.9, 172.0 (C=O). IR ν 3250, 2920, 2850, 1697, 1628, 1583, 1518, 1465, 1432, 1398, 1177, 1073, 1014 cm^{-1}. HRMS for $C_{19}H_{20}I_2N_2O_2$ [M + Na] calcd 584.9508, found 584.9527.

General Procedure for Formation of Benzoxazoles. To a solution of compound **4a** (120 mg, 0.21 mmol) in DMSO (10 mL, 0.02M) was added CuI (4 mg, 0.02 mmol), K_2CO_3 (58 mg, 0.42 mmol), and thiophene-2-carboxylic acid (5.4 mg, 0.04 mmol). After being stirred overnight at 110 °C, the reaction mixture was diluted with water and extracted with AcOEt. The organic phase was washed with NH_4Cl, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, heptane/AcOEt = 3/1) to give the product **5a** (81 mg, 87%) as a yellow solid. Multiple isomers. Mp 126–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) (ppm) δ 0.69, 074 (d, J = 6.0 Hz, 3H), 1.04, 1.10 (d, J = 6.4 Hz, 3H, H18), 2.54–2.65 (m, 1H), 2.69 (s, 3H), 4.34, 5.84 (d, J = 11.5 Hz, 1H), 6.95–7.19 (m, 2H), 7.27–7.37 (m, 3H), 7.47–7.48 (m, 1H), 7.66–7.69 (m, 2H). IR ν 3051, 2962, 2924, 2872, 1642, 1610, 1584, 1562, 1468, 1453, 1394, 1328, 1314, 1241, 1153, 1070, 1014, 863, 742 cm^{-1}. HRMS for $C_{19}H_{19}IN_2O_2$ [M + Na] calcd 457.0385, found 457.0389.

General Procedure for Formation of Isoindol-1-ones. To a solution of **5a** (100 mg, 0.23 mmol) in DMSO (5 mL, 0.05 M) was added $Pd(OAc)_2$ (2.5 mg, 0.01 mmol), XPhos (14 mg, 0.03 mmol), and NaO^{t}Bu (33 mg, 0.35 mmol). The mixture was stirred overnight at 90 °C. The reaction mixture was washed with water, then extracted with AcOEt. The organic extracts were washed with brine, dried over Na_2SO_4, and evaporate to dryness. The residue was purified by flash chromatography (SiO_2, heptane/AcOEt = 3/1) to give the product **6a** (47 mg, 66%) as a yellow solid. Mp 126–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) (ppm) δ 0.77 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H), 3.16 (s, 3H), 3.20 (m, 1H), 7.31–7.37 (m, 2H), 7.42–7.47 (m, 1H), 7.51–7.60 (m, 3H), 7.73–7.76 (m, 1H), 7.90–7.94 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K) (ppm) δ 16.5, 17.4, 26.8, 33.0, 70.9, 110.8, 120.4, 123.7, 123.8, 124.6, 125.5, 129.1, 131.5, 132.5, 140.6, 143.0, 150.5, 163.5, 168.4. IR ν 2961, 2921, 2849, 1784, 1698, 1454, 1384, 1240, 1103, 1015, 730 cm^{-1}. HRMS for $C_{19}H_{18}N_2O_2$ [M + Na] calcd 329.1262, found 329.1256.

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Supporting Information Available: Data and copies of ^{1}H spectra for compounds **5**, **6**, and **8**, copies of ^{13}C NMR spectra for **6**, and X-ray ORTEP for **6d** and **6d′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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