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SHORT COMMUNICATION

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Regio- and Chemoselective Formation of Spiroindolinone–Isoindolinone by a Palladium-Catalyzed Buchwald–Hartwig Addition–Elimination Sequence

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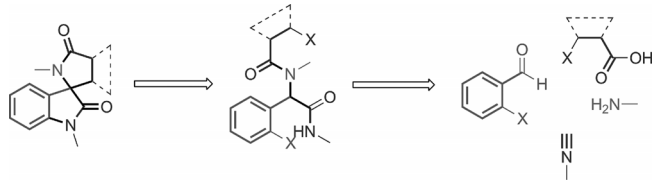
Keywords: Post-Ugi cascade cyclizations / Multicomponent reactions / Heterocycles / Palladium / Spiroindolinones

The usual way to synthesize spiroindolinones is the application of isatin derivatives. Here, we report the first Pd-catalyzed Buchwald–Hartwig addition–elimination strategy for the formation of the spiroindolinone–isoindolinone architecture. The application of the Ugi-4-component reaction (Ugi-4CR) allows the facile introduction of diversity and increases the practicality of this protocol.

Introduction

Indoles, especially spiroindolinones, are widespread in nature's kingdom. They remain a topic of interest for the synthetic organic chemist because of their omnipresence in pharmaceuticals and biologically important alkaloids (Figure 1).[1] As a consequence, in the past few years, important efforts have been made for the construction, modification, and decoration of this privileged architecture.[2,3] However, most strategies start with (derivatives of) isatins,[1h] which may be considered as a severe limitation of the existing protocols. As a result, improved methodologies in terms of substrate scope and starting material availability are always welcomed. Nowadays, metal-catalyzed cascade cyclizations are rising to prominence, as they provide direct access to polycyclic frameworks in a single step.[4] Moreover, multicomponent reactions (MCR) are a powerful tool to introduce diversity in an atom-economical fashion.[5] Hence, we envisioned that the combination of these two strategies may deliver a concise route to spiroindolinones (Scheme 1).



Scheme 1. Retrosynthetic approach for the formation of spiroindolinones.

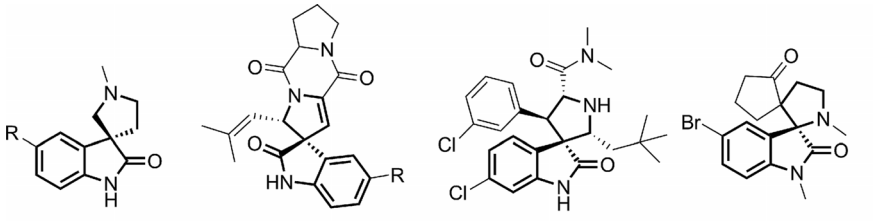


Figure 1. Examples of some natural products and pharmaceutically important compounds containing the spiroindolinone core.

With this core approach in mind and as a result of our ongoing interest in MCR[6] and cascade cyclizations,[7] we designed a complementary disconnection strategy for the formation of spiroindolinones (Scheme 1). Here we report a palladium-catalyzed post-Ugi cascade cyclization approach towards the spiroindolinone–isoindolinone framework.

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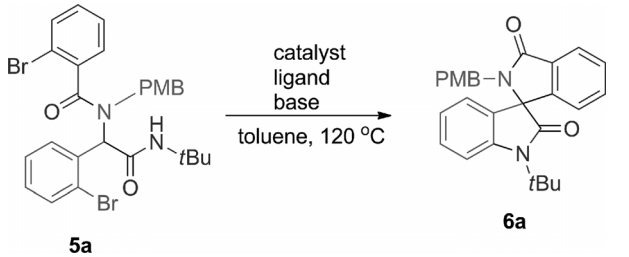
Results and Discussion

We began our study with **5a**, synthesized by the Ugi-4-component reaction (U-4CR)[8] of 2-bromobenzaldehyde (**1a**), 4-methoxybenzylamine (**2a**), 2-bromobenzoic acid (**3a**), and *t*Bu isocyanide (**4a**), by using $Pd(OAc)_2$ (5 mol-%), PPh_3 (10 mol-%), and Cs_2CO_3 (2 equiv.) in toluene at 120 °C for 20 h. To our delight, the formation of 58% of the desired product **6a** was observed by ^1H NMR spectroscopy (Table 1, entry 1). Changing the ligand from PPh_3 to DPPE or Me-Phos resulted in lower yields (Table 1, entries 2 and 3). Xantphos substantially enhanced the performance of the reaction and led to 87% of the desired product **6a** (Table 1, entry 4). Among the bases screened, Cs_2CO_3 proved to be the best (Table 1, entries 4–7). While xylene was found to be as good as toluene, other solvents revealed a global failure for this cascade cyclization (Table 1, entries 8 and 9). No amelioration was observed upon switching the Pd catalysts (entries 10–12). Reducing the reaction time to 15 h gave a cleaner reaction profile and provided the highest yield of **6a**, while further reduction led to incomplete reaction (Table 1, entries 13 and 14). To our delight, ligand loading could be reduced to 5 mol-% without compromising the yield (Table 1, entry 16), However, lowering the catalyst loading led to failure in achieving completion of the reaction (Table 1, entry 17). Finally, a control experiment established the requirement for the Pd catalyst (entry 18).

With the optimized conditions on hand (Table 1, entry 16), we investigated the influence of different halides on the efficiency of our Pd-catalyzed cascade cyclization. Almost identical results were observed upon switching the halide from bromine to chlorine or even to fluorine in the acid-derived part (Table 2, entries 1–3). However, a significant drop of the yield was observed when we employed Ugi adduct **5a**^{iv}, which was synthesized by using 2-iodobenzoic acid (Table 2, entry 4). When experiments were carried out at low temperature (80 °C), only **5a**^{iii}, bearing fluorine, gave some detectable amount of spiro compound **6a**. Compound **5a**^{v}, derived from 2-iodobenzaldehyde, was successfully converted into **6a** (Table 2, entry 5). Because of the low cost and availability of the starting benzaldehyde, we proceeded with 2-bromobenzaldehyde.

Table 1. Optimization of the Pd-catalyzed cascade cyclization.[a]

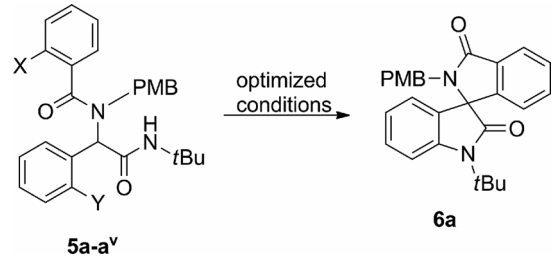


5a **6a**

Entry	Catalyst	Ligand	Base	Time [h]	Yield [%][b]
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	20	58
2	$Pd(OAc)_2$	DPPE	Cs_2CO_3	20	21
3	$Pd(OAc)_2$	Me-Phos	Cs_2CO_3	20	41
4	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	20	87
5	$Pd(OAc)_2$	Xantphos	K_2CO_3	20	51
6	$Pd(OAc)_2$	Xantphos	Na_2CO_3	20	52
7	$Pd(OAc)_2$	Xantphos	KOAc	20	traces
8	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	20	traces[c]
9	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	20	82[d]
10	$Pd(dba)_2$	–	Cs_2CO_3	20	n.d.[e]
11	$Pd(PPh_3)_2Cl_2$	–	Cs_2CO_3	20	70
12	$Pd_2(dba)_3$	–	Cs_2CO_3	20	35
13	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	15	97
14	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	10	80
15	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	15	82[f]
16	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	15	96[g] (92)[h]
17	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	15	56[i]
18	–	–	Cs_2CO_3	20	n.d.[e,j]
19	$Pd(OAc)_2$	Xantphos	–	15	n.d.[e]

[a] Unless otherwise stated, all reactions were run with Ugi adduct **5a** (0.1 mmol), catalyst (5 mol-%), ligand (10 mol-%), and base (2 equiv.) in toluene (2 mL) under a N_2 atmosphere at 120 °C. [b] Yields were determined by ^1H NMR spectroscopy by using 2,4,6-trimethoxybenzaldehyde as an internal standard. [c] 1,4-Dioxane or acetonitrile or DMF were used as solvents. [d] Xylene was used as solvent. [e] Not detected. [f] The reaction was carried out at 100 °C. [g] A ligand concentration of 5 mol-% was used. [h] Isolated yield. [i] Concentrations used: catalyst 3 mol-%; ligand 5 mol-%. [j] Only unreacted starting material was observed by TLC and MS analysis.

Table 2. Effect of the type of halide on the Pd-catalyzed cascade cyclization.



5a-a^{v} **6a**

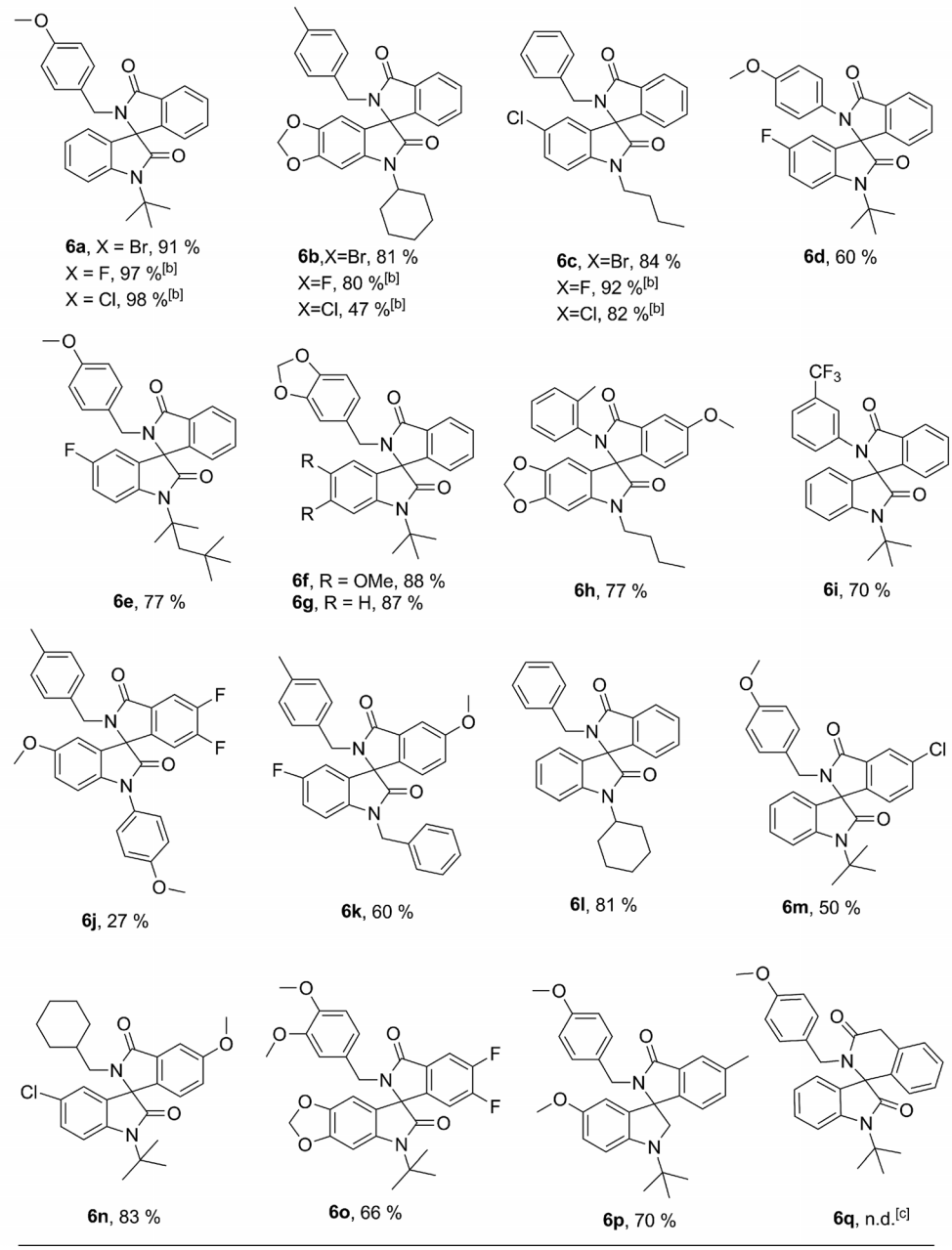
Entry	Ugi adduct **5a**	X	Y	Yield [%][a]
1	**5a**	Br	Br	96 (traces)[b]
2	**5a**^{ii}	Cl	Br	98 (traces)[b]
3	**5a**^{iii}	F	Br	97 (18)[b]
4	**5a**^{iv}	I	Br	53 (n.d.)[b]
5	**5a**^{v}	Br	I	95

[a] Yields were determined by ^1H NMR spectroscopy. [b] The reaction was carried out at 80 °C, and the yield was determined by ^1H NMR spectroscopy.

The applicability of this unprecedented Pd-catalyzed cascade cyclization protocol for the preparation of spiroindolinones is shown in Table 3. A variety of electron-donating and electron-withdrawing functional groups on either the aldehyde or the acid part of the Ugi adduct are compatible with this transformation. It is worth noting that aromatic amines, and even highly deficient aniline, are well tolerated in this protocol (compounds **6d**, **6h**, **6i**). Although the use of an aromatic isocyanide resulted in a poor yield (compound **6j**), aliphatic isonitriles nominated themselves as effective substrates. To our surprise, an attempt to expand the size of isoindolinone ring met with complete failure (compound **6q**).

To get some mechanistic insight, competitive experiments between different halides were carried out, and fluorine was

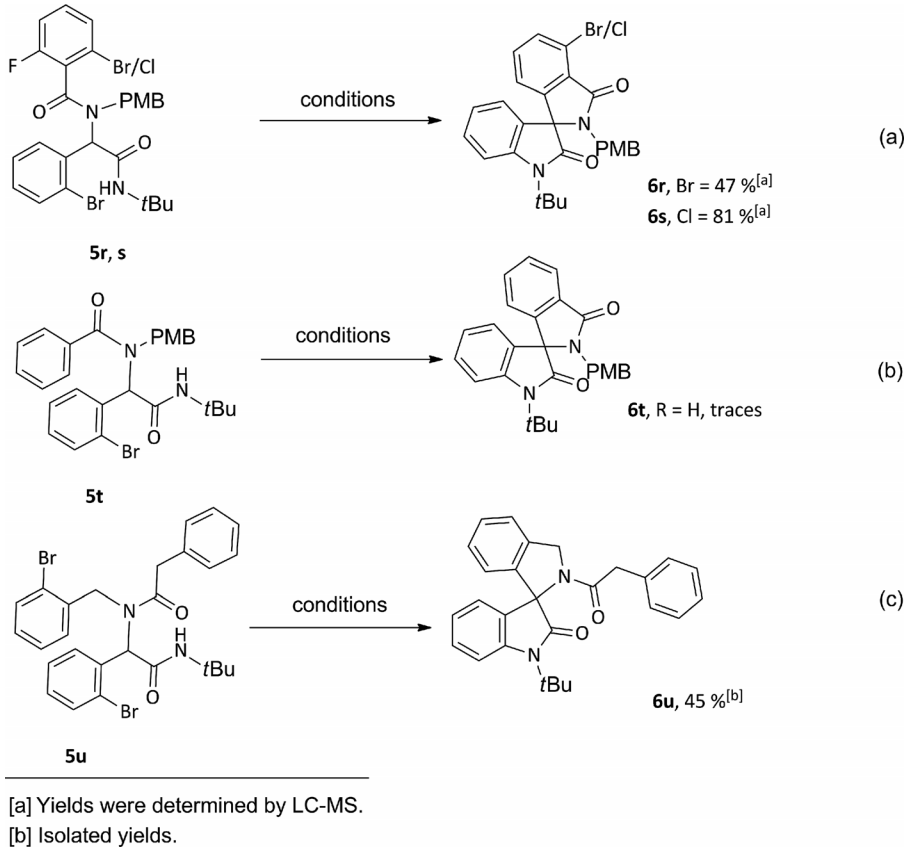
Table 3. Scope of the Pd-catalyzed cascade cyclization.[a]



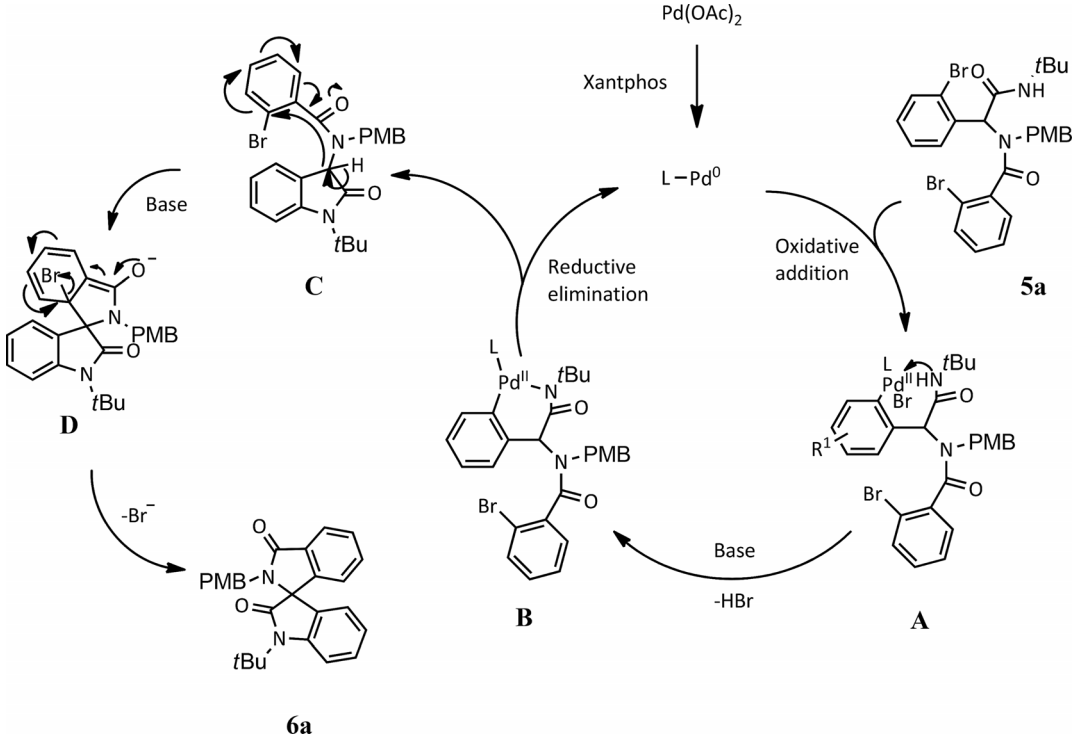
[a] The reactions were run by using the optimized conditions with 0.2 mmol of **5**. [b] Yields were determined by ^{1}H NMR spectroscopy. [c] Not detected.

found to be the most reactive, pointing to an addition–elimination reaction (Scheme 2a). To further support this hypothesis, an experiment without halide in the "upper" aromatic ring was carried out. Employment of **5t**, resulting from unsubstituted benzoic acid, gave only traces of the cyclized compound (Scheme 2b).[9] Finally, the experiment with **5u**, derived from 2-bromobenzylamine, resulted in a moderate yield (Scheme 2c). This confirms the necessity of a carbonyl group for the efficient "upper" ring closure.

On the basis of these observations and previous reports,[10] a plausible mechanism for this Pd-catalyzed cascade cyclization is proposed in Scheme 3. Oxidative addition of Pd^0 to **5a** results in intermediate **A**. Subsequent attack of amide followed by reductive elimination gives **C**. This can undergo an addition–elimination reaction in the presence of a base to deliver spiroindolinone **6a**. However, the possibility for the reverse order, that is the addition–elimination reaction followed by Pd-catalyzed Buchwald–Hartwig coupling, could not be eliminated.



Scheme 2. Control experiments for the Pd-catalyzed cascade cyclization. Reactions were run by using the optimized conditions with 0.2 mmol of **5**.



Scheme 3. Plausible mechanism for the cascade cyclization.

Conclusions

In summary, we have demonstrated an efficient Pd-catalyzed Buchwald–Hartwig addition–elimination sequence for the construction of the spiroindolinone–isoindolinone framework. The reaction occurred under relatively mild conditions with a broad substrate scope and good to excellent yields. The control experiments provide support for the proposed mechanism. Further, application of this protocol for cascade cyclization by using dehydrogenative coupling is under investigation (Scheme 2b).[9]

Experimental Section

General Procedure for the Pd-Catalyzed Cascade Cyclization: To a screw-cap vial were added Ugi product **5a**–**v** (0.2 mmol), $Pd(OAc)_2$ (5 mol-%), Xantphos (5 mol-%), and Cs_2CO_3 (2 equiv.), along with dry toluene (3 mL). The reaction vial was then evacuated and back-filled with N_2 (five times), and the reaction mixture was stirred at 120 °C for 15–20 h. After completion of the reaction, the mixture was diluted with EtOAc (100 mL) and extracted with water (50 mL). The organic layer was washed with brine (50 mL), dried with magnesium sulfate, and concentrated under reduced pressure to obtain a residue, which was subjected to silica gel column chromatography (20–40% ethyl acetate in heptane) to afford the desired product **6a**–**v**.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic data, and copies of the ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

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[9] Employment of the Ugi adduct **5v**, derived from the electron deficient 4-nitrobenzoic acid, yielded 15% of the desired product **6v**. This might point to a Pd-catalyzed ring closure employing C-H activation for the upper spiro ring. This work is under current investigation.

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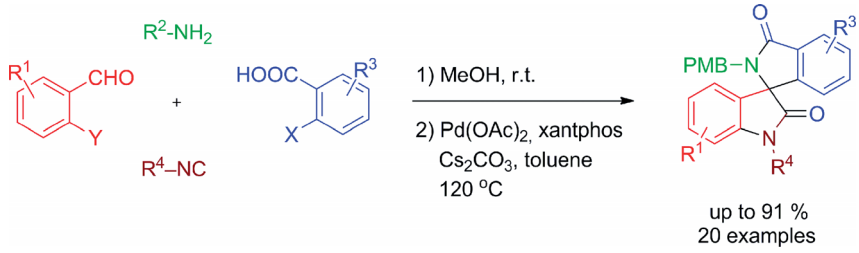

A Pd-catalyzed cascade cyclization strategy has been documented for expedient access to the spiroindolinone–isoindolinone architecture. The Ugi-4-component reaction (Ugi-4CR) generates diversity, while Pd catalysis ensures regioselective ring closure.

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