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Facile Access to Functionalized Spiro[indoline-3,2′-pyrrole]-2,5′-diones via Post-Ugi Domino Buchwald−Hartwig/Michael Reaction

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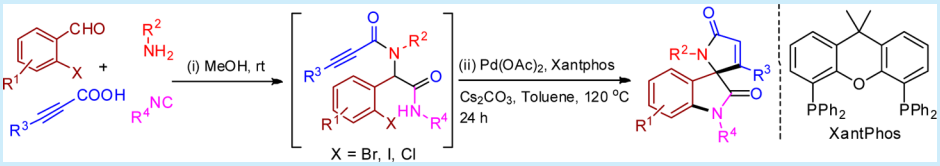
Supporting Information



ABSTRACT: A novel access to spiro[indoline-3,2′-pyrrole]-2,5′-diones is presented via a palladium-catalyzed post-Ugi cascade cyclization approach involving a Buchwald−Hartwig/Michael reaction sequence. The method allows the easy construction of a library of spirooxindoles in moderate to good yields starting from readily available precursors. In addition, alkynoic acids are replaced with *α,β*-unsaturated acids leading to variably substituted spirooxindoles.

Isocyanide based multicomponent reactions (IMCR) with subsequent post-transformations have been extensively demonstrated as a powerful method to access new and privileged heterocyclic scaffolds.[1] These reactions are particularly appealing in terms of molecular diversity, simplicity, and atom economy along with the ease of using readily available starting materials. However, the post-IMCR transformations are generally restricted to a single chemical reaction, thus limiting the challenge of achieving a high level of structural complexity. In this context, efforts to develop novel and selective post-MCR transformations in a domino fashion will significantly contribute to the advancement of diversity-oriented synthesis as well as heterocyclic chemistry.[2]

The ability to access spirocyclic nitrogen-containing heterocycles has always remained a great inspiration for organic chemists because of their widespread prevalence in nature.[3] In particular, the pyrrolidinyl-spirooxindole framework is present in a large number of bioactive, naturally occurring alkaloids such as spiro-tryprostatin B, horsefiline, as well as various medicinally relevant compounds (Figure 1).[4] As a consequence, efforts have been made to design and develop new methods for the construction of novel synthetic spirooxindole-fused-heterocycles.[5] So far, domino or multicomponent reactions based on the versatile reactivity of isatin derivatives[5,6] have remained the most prevalent methods for the synthesis of the spirooxindole framework, while very few methods construct the indole unit itself.[7]

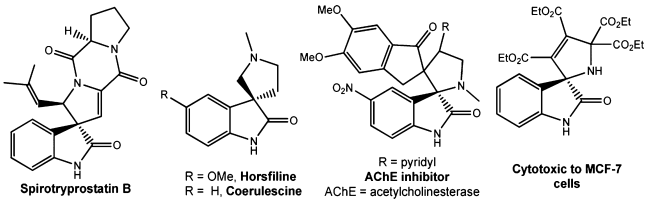
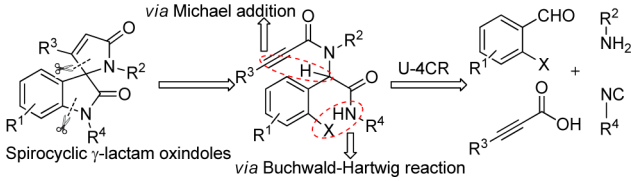


Figure 1. Bioactive compounds containing a spirooxindole framework.

Despite these remarkable advances, finding cost-effective and sustainable synthetic methods to reproduce the structural diversity and complexity of natural molecules would always be a welcome addition. Encouraged by the numerous bioactivities of spiro-oxindoles and in continuation of our endeavor toward the diversity-oriented synthesis of bioactive heterocyclic molecules using MCR reactions,[2m−o,8] we were interested in designing a new post-MCR strategy for the synthesis of novel spirooxindoles from readily available starting materials. We envisioned that an efficient and concise one-pot post-Ugi modification comprising a domino Buchwald−Hartwig/Michael reaction sequence to obtain spiro[indoline-3,2′-pyrrole]-2,5′-diones would be highly appealing (Scheme 1).

Scheme 1. Retrosynthetic Analysis for Spirooxindoles



To test our hypothesis, optimization efforts were initiated by using the easily accessible *N*-(1-(2-bromophenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-(4-methoxybenzyl)but-2-ynamide (**1a**), obtained via Ugi reaction of *o*-bromobenzaldehyde, 4-methoxybenzylamine, *tert*-butyl isocyanide, and 2-butynoic

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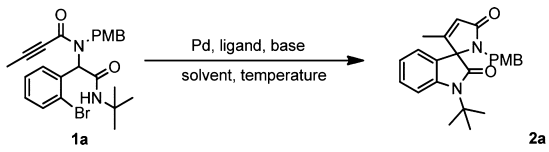
acid, as a substrate in the presence of a Pd catalyst under various conditions (Table 1). A systematic study revealed that

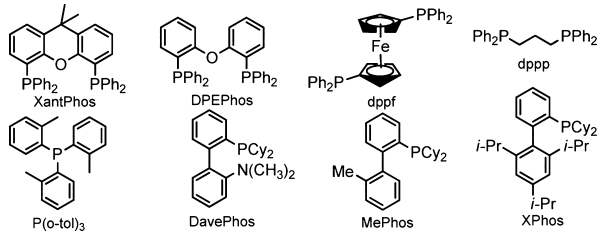
Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	catalyst	ligand	base	solvent	t °C	yield (%)[b]
1	$Pd(OAc)_2$	Xantphos	K_2CO_3	Toluene	120	21
2	$Pd(OAc)_2$	Xantphos	K_3PO_4	Toluene	120	27
3	**$Pd(OAc)_2$**	**Xantphos**	**Cs_2CO_3**	**Toluene**	**120**	**81 (75)**
4	$Pd(OAc)_2$	Xantphos	*t*-BuOLi	Toluene	120	nd
5	$Pd(OAc)_2$	Xantphos	*t*-BuONa	Toluene	120	nd
6	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	DMF	120	8
7	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	MeCN	120	38
8	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	DME	120	40
9	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Xylene	120	68
10	$PdCl_2$	Xantphos	Cs_2CO_3	Toluene	120	45
11	$Pd(TFA)_3$	Xantphos	Cs_2CO_3	Toluene	120	67
12	$PdCl_2(PPh_3)_2$	-	Cs_2CO_3	Toluene	120	nd
13	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	Toluene	120	55
14	$Pd(OAc)_2$	DPEPhos	Cs_2CO_3	Toluene	120	nd
15	$Pd(OAc)_2$	X-Phos	Cs_2CO_3	Toluene	120	17
16	$Pd(OAc)_2$	Dave-Phos	Cs_2CO_3	Toluene	120	13
17	$Pd(OAc)_2$	dppf	Cs_2CO_3	Toluene	120	nd
18	$Pd(OAc)_2$	dppp	Cs_2CO_3	Toluene	120	nd
19	$Pd(OAc)_2$	P(*o*-tol)$_3$	Cs_2CO_3	Toluene	120	23
20	$Pd(OAc)_2$	Me-Phos	Cs_2CO_3	Toluene	120	15
21	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Toluene	120, 36 h	81 (74)
22	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Toluene	120, 18 h	69
23	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Toluene	140, 18 h	67

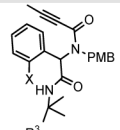
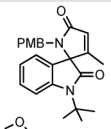
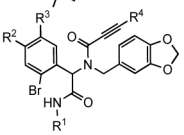
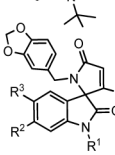
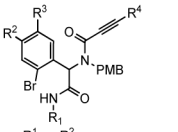
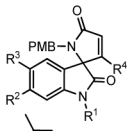
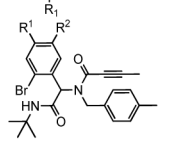
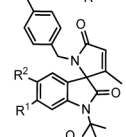
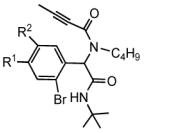
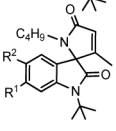
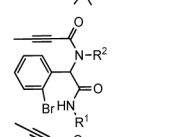
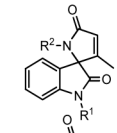
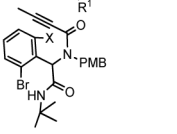
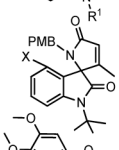
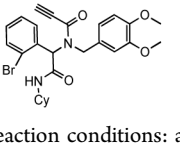
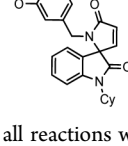
[a]Reaction conditions: all reactions were performed with **1a** (0.2 mmol), catalyst (5 mol %), ligand (7.5 mol %), and base (0.4 mmol) in solvent (2.0 mL) at different temperatures for 24 h. [b]Yields based on ^{1}H NMR. isolated yield in parentheses. nd = not detected.



the catalyst, the ligand, the base, and the temperature exerted a remarkable influence on the yield of the products (Table 1). Lower yields were obtained with K_2CO_3 and K_3PO_4 (entries 1 and 2) as compared to Cs_2CO_3 (entry 3), while replacement with stronger bases such as *t*-BuONa or *t*-BuOLi resulted in no reaction (entries 4 and 5). Also replacement of toluene with more polar solvents displayed a diminished activity in terms of yield (entries 6–9). Among the different Pd-catalyst tested, $Pd(OAc)_2$ was found to be the best (entries 3 and 10–13). The choice of ligand is critical since only Xantphos was effective for the aforementioned domino transformation, whereas well-reported ligands for Buchwald–Hartwig amidation[9] or *N*-arylation of Ugi adducts like Me-Phos[10a] or P(*o*-tol)$_3$[10b] were found to be ineffective (entries 19 and 20). Moreover, both DPEphos and dppf, which are also bidentate ligands and have similar bite angles as Xantphos, did not turn out to be that active. This emphasizes the importance of the flexible coordination environment of the Xantphos backbone to promote this domino sequence effectively.[11] It was also observed that the reaction was occurring in a cascade manner and in the absence of catalyst or ligand or base resulted in no product yield (Table S2, Supporting Information).

Further efforts to increase the yield by varying the reaction time or temperature were not successful (entries 21–23). We concluded that the best conditions are $Pd(OAc)_2$ (5 mol %), Xantphos (7.5 mol %), and Cs_2CO_3 (2 equiv) in toluene at 120 °C for 24 h, allowing the above domino reaction to occur smoothly providing the spirooxindole **2a** in 75% isolated yield (Table 1, entry 3). With the optimized reaction conditions in hand, we evaluated the scope and limitations of the process (Table 2). Initially, the influence of the haloaldehyde subunit

Table 2. Scope of the Developed Domino Buchwald–Hartwig/Michael Process[a]

entry	substate	product		yield (%)[b]
1			**2a**; X= I	80
2			**2a**; X = Cl	30
3			**2d**; R^1 = Cy-hexyl, R^2 = R^3 = H, R^4 = CH_3	97
4			**2e**; R^1 = *t*-Bu; R^2 = R^3 = H, R^4 = CH_2CH_3	78
5			**2f**; R^1 = *t*-Bu, R^2 = R^3 = OCH_3, R^4 = CH_3	46
6			**2g**; R^1 = *t*-Bu, R^2 = H, R^3 = Cl, R^4 = Ph	41
7			**2h**; R^1 = Cy-hexyl, R^2 = R^3 = OCH_3, R^4 = Et	92
8			**2i**; R^1 = *t*-Bu, R^2 = H, R^3 = Cl,R^4 = CH_3	58
9			**2j**; R^1 = Cy-hexyl, R^2 = H, R^3 = Cl, R^4 = CH_3	51
10			**2k**; R^1 = Cy-hexyl, R^2 = H, R^3 = F, R^4 = CH_3	93
11			**2l**; R^1 = *t*-Bu, R^2 = R^3 = H, R^4 = Ph	77
12			**2m**; R^1 = *p*-tolyl; R^2 = H; R^3 = Cl; R^4 = Ph	15
13			**2n**; R^1 = R^2 = OCH_3	51
14			**2o**; R^1 = F, R^2 = H	50
15			**2p**; R^1 = R^2 = H	80
16			**2q**; R^1 = R^2 = OCH_3	45
17			**2r**; R^1 = n-Bu; R^2 = 3,4-dimethoxy benzyl	85
18			**2s**; R^1 = *t*-Bu; R^2 = Cy-propyl	80
19			**2t**; X = F	53
			2u; X = Br	74
20			**2v**	nd

[a]Reaction conditions: all reactions were performed with Ugi substrate (0.2 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (7.5 mol %) and Cs_2CO_3 (0.4 mmol) in toluene (2.0 mL) at 120 °C for 24 h. [b]Isolated yield; nd = not detected. PMB = *p*-methoxybenzyl.

on the reaction outcome was examined. Whereas the *o*-iodobenzaldehyde afforded **2a** in 80% yield, the *o*-chlorobenzaldehyde led to a significant decrease in the reaction yield (entries 1 and 2). As illustrated in Table 2, electron-donating or electron-withdrawing groups on the aryl ring were well tolerated. Also, substrates bearing ortho, meta, or para substituents provided the corresponding products in moder-

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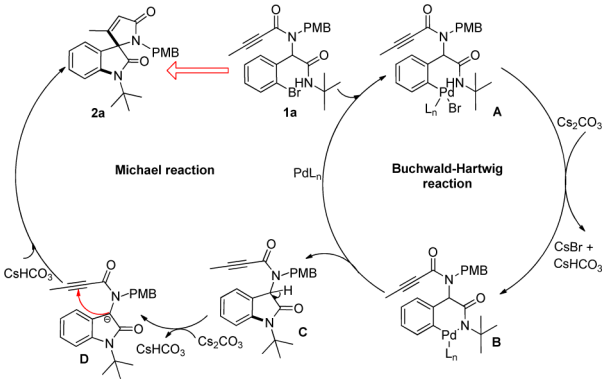
ate-to-good yields. The reaction worked well with aliphatic but not with aromatic isonitriles (entry 12). In addition, the Ugi adduct derived from propiolic acid failed to give the desired spirocycle (entry 20).

Mechanistically, two new chemical bonds are formed in the present process, involving a Buchwald−Hartwig amidation (C−N bond) and Michael addition (C−C bond) sequence. Although it was reasonable to assume that two bonds were formed sequentially and the aryl-amidation preceded the base-catalyzed Michael addition, more convincing support was sought. Our attempts to carry out the reactions in a sequential manner, i.e., first the base-catalyzed Michael addition from the active methine[12] and then a Buchwald−Hartwig amidation or reverse proved to be futile. Thus, the involvement of a palladacycle in the intramolecular Michael addition[13] could not be ruled out with certainty. Moreover, our attempts to stop the reaction after intermolecular *N*-arylation failed. Our assumption that the second step of the reaction is simply a base-catalyzed nucleophilic addition reaction was ascertained when 2-alkynoic acid was replaced with benzoic acid or 2-fluorobenzoic acid, resulting in the desired product in traces and 90% yield, respectively (see the Supporting Information, Scheme S1).

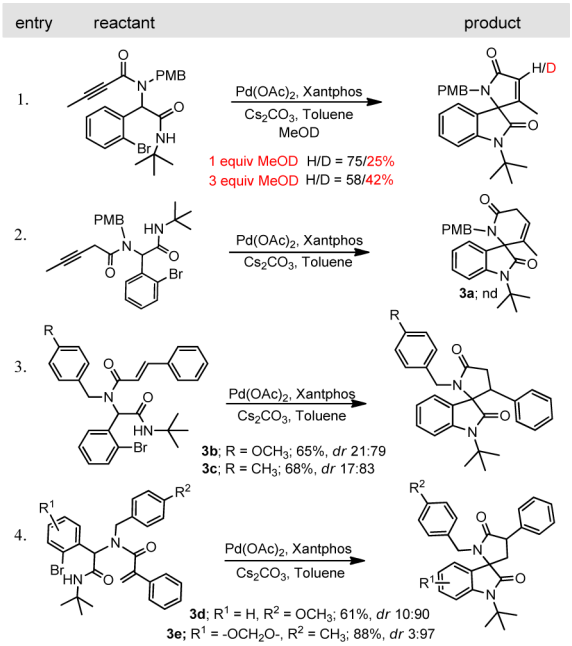
Based on these observations and previous reports,[10,12] we hypothesized a reaction mechanism which is outlined in Scheme 2. The first step is the oxidative addition of the Pd(0)

Scheme 2. Plausible Mechanism for the Domino Cyclization



catalyst to **1a** leading to palladium complex **A**. Thereafter, the base-catalyzed deprotonation of the amide and its co-ordination to the Pd(II) species results in the formation of a six-membered palladacycle **B.** This is followed by reductive elimination giving intermediate **C**. The next step involves the base-catalyzed Michael addition leading to the final product **2a**. The activation of this Csp^3−H proton by base is well documented in the literature regarding C-arylations.[12a] To further shed light on the reaction mechanism, we performed a deuterium-labeling experiment on the tandem Buchwald−Hartwig/Michael addition sequence of the Ugi adduct **1a** in the presence of $Pd(OAc)_2$, Xantphos, and Cs_2CO_3 with up to 3 equiv of deuterated methanol in toluene. According to the NMR spectra, the deuterium was located on the endocyclic double bond of the pyrrole ring (Table 3, entry 1). Further, it was ascertained that the use of 2-alkynoic acids was necessary to ensure the occurrence of this domino reaction as substitution with 3-alkynoic acid (Table 3, entry 2) failed to produce the desired spirocycle. Furthermore, use of *α,β*-unsaturated acids instead of 2-alkynoic acids resulted in good yields with adequate diastereoselectivity (Table 3, entries 3 and 4).

Table 3. Control Experiments and Extended Scope[a]



[a]Reaction conditions: all reactions were performed with Ugi substrate (0.2 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (7.5 mol %), and Cs_2CO_3 (0.4 mmol) in toluene (2.0 mL) at 120 °C for 24 h, dr ratio determined on the basis of LC−MS analysis.

In summary, we have devised a highly efficient methodology for the synthesis of the spiro[indoline-3,2′-pyrrole]-2,5′-dione framework via a Pd(0)-catalyzed domino Buchwald−Hartwig/Michael reaction sequence. The protocol works equally well when alkynoic acids are replaced with *α,β*-unsaturated acids (such as cinnamic acids or atropic acid) leading to diversely substituted spirooxindoles. The operational simplicity together with the synthetic efficiency of the protocol will be beneficial for academic and industrial research toward the synthesis of druglike small molecules with enhanced structural diversity and molecular complexity. Further studies on the reaction scope and the expansion of the synthetic applications of the above methodology are under current investigation.

■ ASSOCIATED CONTENT

Supporting Information

Details of the experimental procedure as well as characterization data (^1H and ^{13}C NMR and HRMS) of Ugi adducts as well as spirooxindoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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‡N.S. and Z.L. contributed equally.

Notes

The authors declare no competing financial interest.

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