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A concise route to indoloazocines *via* a sequential Ugi–gold-catalyzed intramolecular hydroarylation†

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A diversity oriented approach for the synthesis of indoloazocines is reported employing an Ugi reaction followed by a gold-catalyzed intramolecular hydroarylation.

Indoloazocines are important members of the indole containing alkaloid family and challenging synthetic targets. Some members are deoxyisoaustamide,[1] okaramine N[2] and balasubramide[3] (Fig. 1). Despite its importance, this framework is scarcely investigated, and reports generally deal with multistep processes, which limits the scope and diversity.[4] Addressing this issue, Echavarren and co-workers have recently reported a gold-catalyzed intramolecular hydroarylation procedure giving access to a short route to the indoloazocine framework.[5a,b] We have recently developed an intramolecular carbocyclization for the construction of azocino[*b*]-indoles and an intramolecular reductive Heck reaction for the generation of azocino[*cd*]indoles.[6] Although such transition-metal-catalyzed transformations[7] are rising to prominence, the synthesis of the starting materials *via* an elaborate multi-step sequence is mostly required, thereby hampering the introduction of much diversity.

Through the years, multicomponent reactions (MCRs)[8] have received increasing attention due to their simplicity, efficiency, atom economy, shortened reaction times, and diversity oriented synthesis. The combination of MCRs with transition-metal-catalysis gives access to complex molecules in few steps as compared to traditional multistep processes. As a result of our recent endeavours regarding the chemistry of the indole core,[6,9] multicomponent reactions[10] and transition-metal-catalysis,[11] a concise diversity oriented approach towards indoloazocines was developed. Compound **5a** was synthesized by Ugi reaction[8] of tryptamine with *p*-methoxy benzaldehyde, ^{t}Bu-isonitrile and 2-butynoic acid in methanol at rt. This readily formed compound **5a** was used for investigating the intramolecular hydroarylation to furnish indoloazocine **6a**. When 5 mol% of $Hg(OTf)_2$ was used as catalyst[6a] in $CDCl_3$, only 30% conversion was observed after 20 h at rt. The conversion was improved to 50% when 5 mol% of AgOTf was employed (Table 1, entries 1 and 2). No amelioration was observed with AuCl, $AuCl_3$, $Au(PPh_3)Cl$, $FeCl_3$, *p*-tolylsulfonic acid and $Yb(OTf)_3$ (Table 1, entries 3–8).[7p]

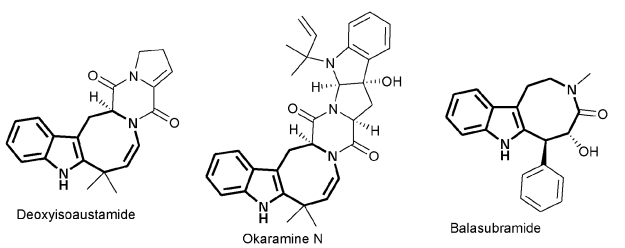
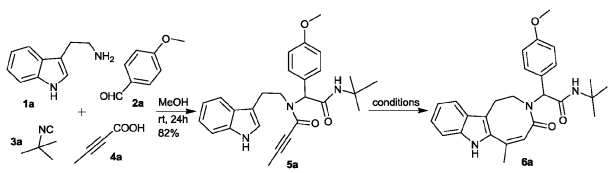


Fig. 1 Alkaloids containing the indoloazocine core.

Table 1 Optimization of the intramolecular hydroarylation[a]



Entry	Catalyst (mol%)	Solvent	Time/h	Temp/°C	Conversion (%) (Yield (%))[b]
1	$Hg(OTf)_2$ (5)	$CDCl_3$	20	rt	30 (20)
2	AgOTf (5)	$CDCl_3$	20	rt	50 (35)
3	AuCl (5)	$CDCl_3$	20	rt	Traces
4	$AuCl_3$ (5)	$CDCl_3$	20	rt	0
5	$Au(PPh_3)Cl$ (5)	$CDCl_3$	20	rt	0
6	$FeCl_3$ (5)	$CDCl_3$	20	rt	0
7	*p*-tolylsulfonic acid (5)	$CDCl_3$	20	rt	0
8	$Yb(OTf)_3$ (5)	$CDCl_3$	20	rt	0
9	**$Au(PPh_3)OTf$ (5)**	**$CDCl_3$**	**8**	**rt**	**100 (85)**
10	$Au(PPh_3)OTf$ (5)	$CDCl_3$	4	50	40
11	$Au(PPh_3)OTf$ (5)	$CDCl_3$	4	80	25
12	$Au(PPh_3)OTf$ (5)	DCM-d_2	8	rt	100 (82)
13	$Au(PPh_3)OTf$ (5)	ACN-d_3	20	rt	0
14	$Au(PPh_3)OTf$ (5)	THF-d_8	20	rt	Traces
15	$Au(PPh_3)OTf$ (5)	MeOH	20	rt	—[c]
16	$Au(PPh_3)OTf$ (3)	$CDCl_3$	20	rt	80

[a] All reactions were run on a 0.1 mmol scale of **5a**. [b] Conversion based on ^{1}H NMR analysis; yields (in parentheses) are isolated yields. [c] Addition of methanol on triple bond was observed.

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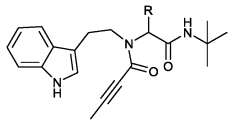
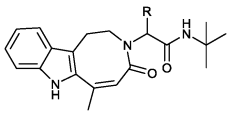
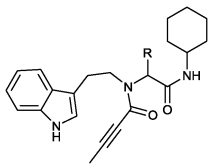
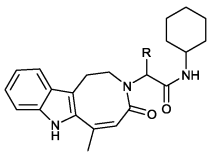
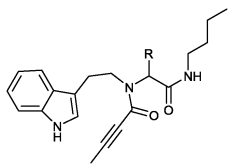
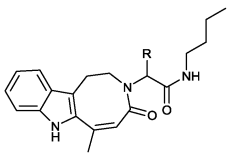
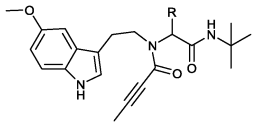
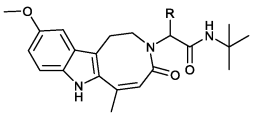
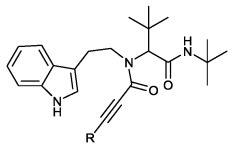
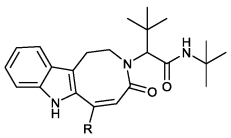
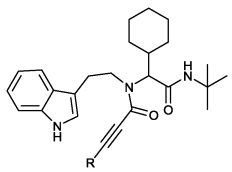
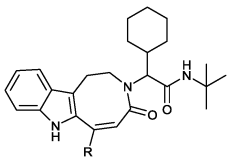
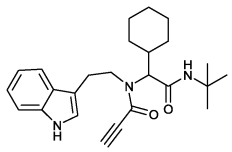
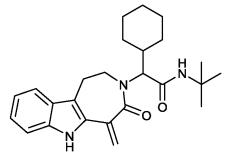
Table 2 Scope of the hydroarylation process

Entry	Ugi adduct **5** (yield)	Indoloazocine **6** (yield)
		
1	**5a**, R = 4-MeOC$_6$H$_4$, (82%)	**6a**, R = 4-MeOC$_6$H$_4$, (85%)
2	**5b**, R = Cy, (95%)	**6b**, R = Cy, (84%)
3	**5c**, R = *t*-Bu, (89%)	**6c**, R = *t*-Bu, (90%)
4	**5d**, R = 2,6-diClC$_6$H$_4$, (76%)	**6d**, R = 2,6-diClC$_6$H$_4$, (91%)
5	**5e**, R = Phenethyl, (75%)	**6e**, R = Phenethyl, (85%)
6	**5f**, R = furan-2-yl, (43%)	**6f**, R = furan-2-yl, (72%)
		
7	**5g**, R = Cy, (84%)	**6g**, R = Cy, (88%)
8	**5h**, R = 2,6-diClC$_6$H$_4$, (84%)	**6h**, R = 2,6-diClC$_6$H$_4$, (89%)
		
9	**5i**, R = Cy, (88%)	**6i**, R = Cy, (89%)
10	**5j**, R = 2,6-diClC$_6$H$_4$, (91%)	**6j**, R = 2,6-diClC$_6$H$_4$, (80%)
		
11	**5k**, R = *n*-pentyl, (34%)	**6k**, R = *n*-pentyl, (85%)
12	**5l**, R = Cy, (48%)	**6l**, R = Cy, (65%)
		
13	**5m**, R = Et, (82%)	**6m**, R = Et, (85%)
14	**5n**, R = Ph, (75%)	**6n**, R = Ph, (0%)
		
15	**5o**, R = *i*-Pr (86%)	**6o**, R = *i*-Pr (81%)
16	**5p**, R = *t*-Bu (84%)	**6p**, R = *t*-Bu (0%)
		
17	**5q**, (92%)	**6q**, (56%)

A cationic gold complex,[7i] formed *in situ* by mixing 5 mol% of Au(PPh$_3$)Cl and AgOTf, turned out to be the best catalyst giving 100% conversion in 8 h at rt (Table 1, entry 9). To reduce the reaction time the cyclization was performed at elevated temperature, however, the conversion dropped significantly (Table 1, entries 10 and 11). While changing the solvent to dichloromethane resulted in similar results, no conversion was observed in acetonitrile and only traces of product were formed in tetrahydrofuran (Table 1, entries 12–14). The reaction was also tried in methanol, aiming at the possibility of developing a one-pot two-step process. However, addition of methanol to the triple bond[12] occurred (Table 1, entry 15). Reducing the catalyst loading to 3 mol% resulted in 80% conversion in 20 h (Table 1, entry 16).

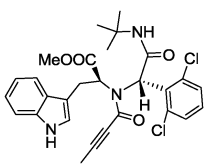
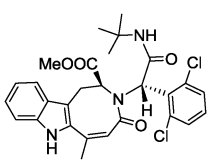
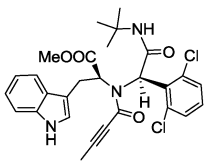
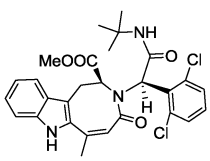
The optimized conditions (Table 1, entry 9) were applied on the diversely substituted Ugi adducts **5a–q**. In most of the cases the indoloazocines could be obtained in good to excellent yields (Table 2). In the case of compounds **5n** and **5p**, no cyclized product formed possibly due to steric hindrance of the bulky phenyl and *t*-butyl substituents on the alkyne fragment (Table 2, entries 14 and 16). Surprisingly the terminal alkyne **5q** gave the 7-*exo*-dig product **6q** (Table 2, entry 17), possibly due to a metal carbene intermediate stage as described by Echavarren and co-workers.[5]

Having investigated the scope and limitations of the optimized protocol on tryptamine derivatives, we investigated L-tryptophan methylester as the starting material. After Ugi reaction a mixture of two diastereoisomers was obtained, which was separated by column chromatography. Both diastereoisomers could be cyclized resulting in the formation of pure diastereoisomeric indoloazocines in good yields (Table 3). Structures of these diastereoisomers were unambiguously assigned as being **6r** (*S*,*S*) and **6s** (*S*,*R*) by X-ray crystallography (Scheme 1).

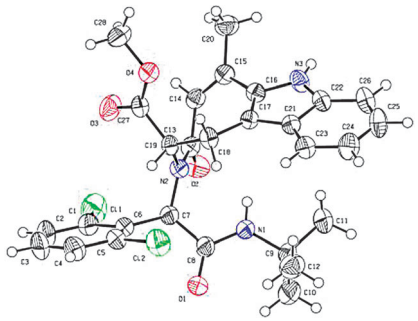
A plausible mechanism[5,13] is depicted in Scheme 2. Nucleophilic attack of the 3-position of the indole core on the activated alkyne could give spiro intermediate **B**.[14] This on 1,2-shift produces intermediate **C** which on deprotonation and protodeauration forms indoloazocine **6**.

In summary, we have developed a concise diversity oriented approach to indoloazocines. The merits of this method are mild reaction conditions, good to excellent yields, the introduction of four points of diversity due to the Ugi 4CR, and selectivity for

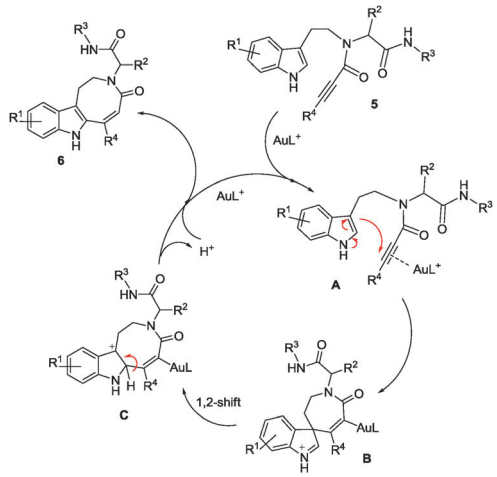
Table 3 Expanding the scope of the hydroarylation process

Entry	Ugi adduct **5** (yield)	Indoloazocine **6** (yield)
1		
	5r, (14%)[a]	**6r**, (62%)
2		
	5s, (29%)[a]	**6s**, (49%)

[a] Yield of pure isolated diastereoisomer. Combined yield for the Ugi reaction is 92% with a 65 : 35 diastereomeric ratio.



Scheme 1 Crystal structure of compound **6s**. Thermal ellipsoids are drawn at the 50% probability level.†



Scheme 2 Plausible mechanism for the intramolecular hydroarylation.

the 8-*endo*-dig cyclization using a cationic gold complex. This is a very facile method in terms of starting material availability, scope and diversity. Further expansion of this method for the synthesis of alkaloid like structures is under current investigation.

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