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Switching the regioselectivity *via* indium(III) and gold(I) catalysis: a post-Ugi intramolecular hydroarylation to azepino- and azocino-[*c*,*d*]indolones†

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A post-Ugi indium(III)- and gold(I)-mediated regioselective intramolecular hydroarylation for the synthesis of azepino- and azocino-[*c*,*d*]indolones is described.

Indium- and gold-mediated carbocyclization and heteroannulation reactions have recently been reported[1] as mild and efficient procedures imparting high regioselectivity.[2] Many elegant approaches involving gold-catalyzed carbocyclizations have also been reported for the generation of structurally cumbersome heterocycles.[3] Indole-based natural products that contain a tricyclic azepino- or azocino-[*c*,*d*]indolone core[4] have emerged as interesting targets due to their intriguing biological activities and molecular architectures. They are exemplified by the indole alkaloids clavicipitic acid,[5a] (−)-aurantioclavine,[5b] decursivine,[5c] and serotobenine[5d] (Fig. 1). In spite of recent advances, the synthesis of such natural products is often complicated by the lack of adequate synthetic methods for producing the tricyclic azepino- or azocino-[*c*,*d*]indolone core. Considering the importance of such fused heterocycles, we have recently reported various sequential Ugi–gold-catalyzed intramolecular hydroarylation approaches for the synthesis of indoloazocines,[6] spiroindolines,[7] pyrrolopyridinones and pyrroloazepinones.[8]

Motivated by these findings and as a result of our interest in exploring the combination of transition metal-catalysis[9] and multicomponent reactions,[10] we envisaged that a post-Ugi regioselective intramolecular hydroarylation reaction could provide an expedient access to azepino- and azocino-[*c*,*d*]indolone systems.

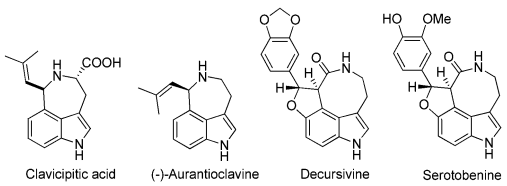

Fig. 1 Selected examples of azepino- and azocino-[*c*,*d*]indolone alkaloids.

As a result of our recent endeavours regarding the chemistry of the indole core,[6,7] the Ugi four-component reaction (4-CR)[11] of indole-4-carboxaldehyde (**1a**) with *p*-methoxybenzyl amine (**2a**), 2-butynoic acid (**3a**) and *tert*-butylisonitrile (**4a**) in methanol at 50 °C gave Ugi-adduct **5a** in 98% yield. This was further used for investigating intramolecular hydroarylation. The application of cationic (Ipr)AuNTf$_2$ (10 mol%) at 80 °C furnished 40% of azocinoindolone **7a**, while heating at 100 °C gave 100% conversion with an isolated yield of 78% (Table 1, entries 1 and 2). However, employing (Ipr)AuSbF$_6$, (Ipr)AuOTf, (Ipr)AuBF$_4$, Au(PPh$_3$)NTf$_2$ or Au(Phos)NTf$_2$ did not improve the yield but led to a mixture of azepinoindolone **6a** and azocinoindolone **7a** (Table 1, entries 3–7). The application of AuCl$_3$, AuCl, (Ipr)AuCl, and AgNTf$_2$ gave almost no conversion (Table 1, entries 8–11). However, these observations encouraged us to further optimize the conditions for the switch of selectivity for the formation of **6a** or **7a** selectively.

Interestingly, experiments with In(OTf)$_3$ (10 mol%) at 80 °C for 24 h gave 85% conversion into azepinoindolone **6a**, while upon heating at 100 °C, 100% conversion was obtained in 3 h with **6a** being the major product in 80% isolated yield (Table 1, entries 12 and 13). No or a very small conversion was observed in the case of Bi(OTf)$_3$, Ln(OTf)$_3$, Eu(OTf)$_3$ and PtCl$_2$ (Table 1, entries 14–17). A change of the solvent, when cationic gold was used, decreased the yield and selectivity (Table 1, entries 18 and 19), while for the indium catalyst decomposition of the product was observed (Table 1, entries 20 and 21). Diminishing the catalyst loading to 5 mol% resulted in a decreased conversion in both cases (Table 1, entries 22 and 23).

A plausible mechanism[1a,2b,3a,b,6–8] is depicted in Scheme 1. Coordination of the metal with the alkyne in **5a** generates intermediate **A**. In the case of indium the nucleophilic attack of the indole C3-positon on the activated alkyne occurs in an *exo*-dig fashion generating intermediate **B**, which upon deprotonation (**C**) and protodemetallation forms azepinoindolone **6a**. When cationic gold is used, the nucleophilic attack of the

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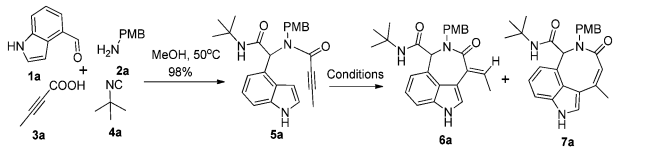
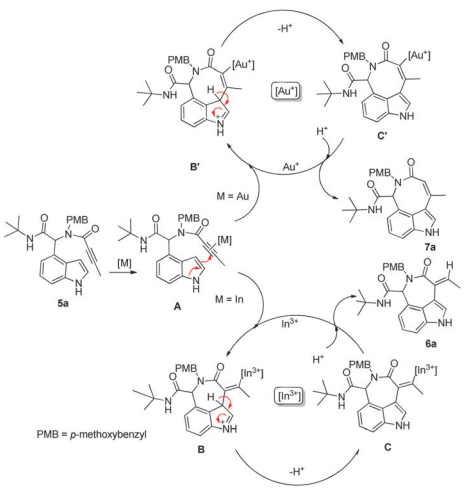
Table 1 Optimization of the intramolecular hydroarylation[a]



Entry	Catalyst (mol%)	Solvent	Time (h)	Temp (°C)	Conversion (%) (**6a**/**7a**)[b]
1	(Ipr)AuNTf$_2$(10)	DCE	24	80	40 (0/40)
2	**(Ipr)AuNTf$_2$(10)**	**DCE**	**8**	**100**	**100 (0/78)**[c]
3	(Ipr)AuSbF$_6$(10)	DCE	24	100	100 (15/64)[c]
4	(Ipr)AuOTf(10)	DCE	24	100	80 (20/60)
5	(Ipr)AuBF$_4$(10)	DCE	24	100	90 (25/65)
6	Au(PPh$_3$)NTf$_2$(10)	DCE	24	100	50 (20/30)
7	Au(Phos)NTf$_2$(10)	DCE	24	100	80 (50/30)
8	AuCl$_3$(10)	DCE	24	100	0 (0/0)
9	AuCl(10)	DCE	24	100	0 (0/0)
10	(Ipr)AuCl(10)	DCE	24	100	0 (0/0)
11	AgNTF$_2$(10)	DCE	24	100	10 (0/10)
12	In(OTf)$_3$(10)	DCE	24	80	85 (85/0)
13	**In(OTf)$_3$(10)**	**DCE**	**3**	**100**	**100 (80/0)**[c]
14	Bi(OTf)$_3$(10)	DCE	24	100	0 (0/0)
15	Ln(OTf)$_3$(10)	DCE	24	100	0 (0/0)
16	Eu(OTf)$_3$(10)	DCE	24	100	0 (0/0)
17	PtCl$_2$(10)	DCE	24	100	10 (10/0)
18	(Ipr)AuNTf$_2$(10)	Toluene-d$_8$	24	100	60 (10/50)
19	(Ipr)AuNTf$_2$(10)	THF-d$_8$	24	100	85 (20/60)
20	In(OTf)$_3$(10)	Toluene-d$_8$	20	100	100 (58/0)[c,d]
21	In(OTf)$_3$(10)	THF-d$_8$	14	100	100 (60/0)[c,d]
22	(Ipr)AuNTf$_2$(5)	DCE	24	100	50 (0/50)
23	In(OTf)$_3$(5)	DCE	24	100	20 (20/0)

[a] All reactions were run on a 0.1 mmol scale of **5a**. [b] Conversion and ratio based on ^{1}H NMR analysis. [c] Isolated yields. [d] Decomposition of the product takes place. PMB = *p*-methoxybenzyl.

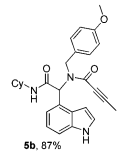
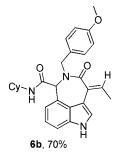
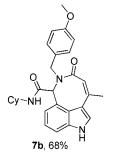
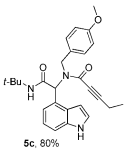
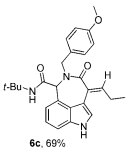
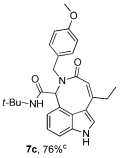
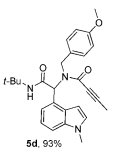
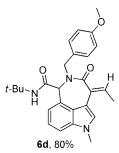
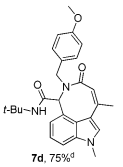
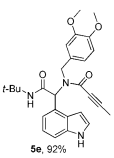
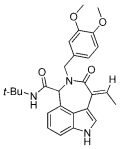
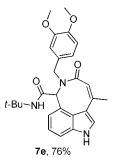
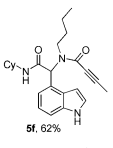
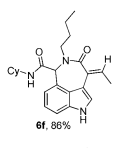
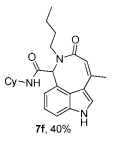
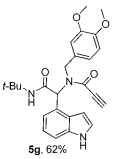
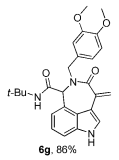
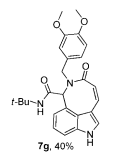
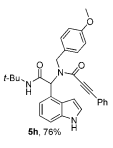
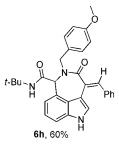
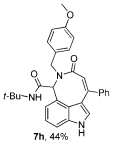
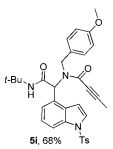
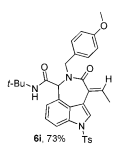
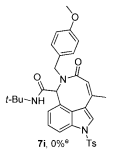
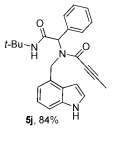
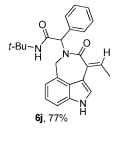
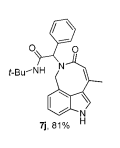


Scheme 1 Plausible mechanism of the regioselective intramolecular hydroarylation reaction.

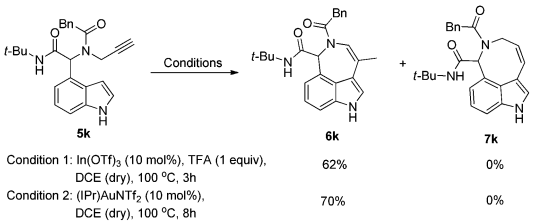
indole C3-position on the activated alkyne occurs in an *endo*-dig fashion generating intermediate **B′**, which upon deprotonation (**C′**) and protodeauration forms azocinoindolone **7a**.

Having established the optimized conditions for this regioselective intramolecular hydroarylation, diversely substituted Ugi-adducts **5b–j** were synthesized and the substrate scope of the reaction was investigated (Table 2). Mostly the *exo*-dig cyclization proceeded smoothly when indium was used, giving azepinoindolones **6b–j** in good yields. Various substituents on the starting isonitrile, amine, alkyne and indole are well tolerated (Table 2). A bulky alkyne substituent like phenyl is also well tolerated, delivering **6h**. Surprisingly the application

Table 2 Substrate scope for regioselective hydroarylation

Entry	Ugi adduct **5**	Azepinoindolone[a] **6**	Azocinoindolone[b] **7**
1	 **5b**, 87%	 **6b**, 70%	 **7b**, 68%
2	 **5c**, 80%	 **6c**, 69%	 **7c**, 76%[c]
3	 **5d**, 93%	 **6d**, 80%	 **7d**, 75%[d]
4	 **5e**, 92%	 **6e**, 89%	 **7e**, 76%
5	 **5f**, 62%	 **6f**, 86%	 **7f**, 40%
6	 **5g**, 62%	 **6g**, 86%	 **7g**, 40%
7	 **5h**, 76%	 **6h**, 60%	 **7h**, 44%
8	 **5i**, 68%	 **6i**, 73%	 **7i**, 0%[e]
9	 **5j**, 84%	 **6j**, 77%	 **7j**, 81%

[a] Conditions **A:** reactions were run on a 0.25 mmol scale of **5** with In(OTf)$_3$ (10 mol%) in DCE (2 mL) in a screw capped vial at 100 °C for 3 h. [b] Conditions **B:** reactions were run on a 0.25 mmol scale of **5** with (Ipr)AuCl (10 mol%), AgNTf$_2$ (10 mol%) in DCE (2 mL) in a screw capped vial at 100 °C for 8 h. [c] 15% of **6c** was formed. [d] 8% of **6d** was formed. [e] No product was formed even after 48 h; only starting **5i** was recovered.



Scheme 2 Amine as an alkyne source.

of a tosyl protected indole did not affect the nucleophilicity of the ring and **6i** was obtained in 73% yield.

The same Ugi-adducts **5b–j** were subjected to *endo*-dig cyclization by reaction with cationic gold. Pleasingly, most of the reactions proceeded well and the corresponding azocinoindolones **7** were isolated in good yields (Table 2). Upon using an aliphatic amine or a phenyl substituted alkyne only 40% and 44%, respectively, of the *endo*-dig cyclized product was observed (Table 2, **7f** and **7h**). Also with terminal acetylene only a moderate yield of 40% was obtained (Table 2, **7g**). Surprisingly, in contrast to the *exo*-dig cyclization (**6i**), a tosyl protected indole did not undergo *endo*-dig cyclization.

To further demonstrate the synthetic utility of the developed methodology, propargyl amine was used as the alkyne source for the synthesis of Ugi-adduct **5k**. When it was subjected to intramolecular hydroarylation employing $In(OTf)_3$ in the presence of TFA as a co-catalyst and $Ipr(Au)NTf_2$, exclusive formation of the *exo*-dig cycloisomerized product **6k** was observed in 62% and 70% yield respectively (Scheme 2).

In conclusion we have developed an efficient post-Ugi regioselective intramolecular hydroarylation approach for the synthesis of azepinoindolones and azocinoindolones. Employing indium(III)- or gold(I)-catalysis, the ring closure can be directed towards an *exo*-dig or *endo*-dig cyclization, respectively, resulting in the formation of a 7- and 8-membered ring in compounds **6** and **7**. A wide range of functional groups, introduced during the Ugi reaction, is tolerated.

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