Abstract
An Ugi four-component reaction of propargylamine with 3-formylindole and various acids and isonitriles produces adducts which are subjected to a cationic gold-catalyzed diastereoselective domino cyclization to furnish diversely substituted spiroindolines. All the reactions run via an exo-dig attack in the hydroarylation step followed by an intramolecular diastereoselective trapping of the imminium ion. The whole sequence is atom economic and the application of a multicomponent reaction assures diversity.

Introduction
The importance of nitrogen containing heterocyclic molecules in chemical biology is undisputed. The synthesis of such biologically interesting heterocycles is generally target-oriented, inspired by nature or randomly directed. In all these cases the design of a synthetic sequence to produce a library of diversely substituted molecules is the first and most important step. The basic concept of diversity-oriented synthesis (DOS) involves short reaction sequences, a strong focus on bond construction, and functional group compatibility [1-3]. Reactions that involve multiple bond formation, such as multicomponent reactions [4-9] and tandem reactions [10-16], are very useful in this context.

As an efficient activator of alkynes, gold has recently attracted a lot of attention [17-36]. Many tandem approaches have been reported which utilize this coinage metal for the construction of variously substituted complex molecules [37-43]. We have recently reported a post-Ugi gold-catalyzed intramolecular
domino cyclization sequence which produces spiroindolines (Scheme 1) [44]. The first step in this sequence is an Ugi four-component reaction (Ugi-4CR) [4,5] with 2-alkynoic acid as an alkyne source. The second step is a cationic gold-catalyzed intramolecular hydroarylation tandem cyclization to produce spiroindolines with complete diastereoselectivity. This synthetic sequence is atom economic and mild conditions are applied to generate a very complex molecular structure from readily available starting materials. Based on this work and our continuous interest in transition metal catalysis [45-54], multicomponent reactions [55-57] and the chemistry of the indole core [58-60], we herein report a post-Ugi gold-catalyzed intramolecular domino cyclization sequence for the synthesis of spiroindolines with propargylamines as an alkyne source (Scheme 1).

Results and Discussion
The use of benzoic acid as an acid component in the Ugi-4CR did not produce the Ugi-adduct in good yield even after a prolonged reaction time. Therefore, we switched to phenylacetic acid. The Ugi-4CR of indole-3-carboxaldehyde (1a), propargylamine (2a), phenylacetic acid (3a) and tert-butylisonitrile (4a) in methanol at 50 °C gave the Ugi-adduct 5a with an excellent yield of 94%. With compound 5a in hand we were keen to apply the previously developed conditions for intramolecular hydroarylation [44]. Reaction of 5a with 5 mol % of Au(PPh₃)SbF₆ in chloroform at room temperature produced the desired spiroindoline 6a in a moderate yield of 55% along with some unidentified byproducts (Table 1, entry 1). The use of a protic acid with a gold catalyst is known in the literature [61-64]. To our delight, when the above reaction was carried out with 1 equivalent of trifluoroacetic acid (TFA) the yield was improved to 81% (Table 1, entry 2). Apart from being a good proton source TFA might be working as a coligand.

Experiments with PtCl₂ as a catalyst did not show any conversion and the starting material was recovered quantitatively (Table 1, entries 3 and 4). In absence of the gold catalyst no product could be observed (Table 1, entry 5). The application of p-toluenesulfonic acid (PTSA) instead of TFA did not improve the outcome (Table 1, entry 6).

| Entry | Catalyst (mol %) | Acid (1 equiv) | Time h | % Yield |
|-------|-----------------|----------------|--------|---------|
| 1     | Au(PPh₃)SbF₆ (5) | —              | 2      | 55°     |
| 2     | Au(PPh₃)SbF₆ (5) | TFA            | 2      | 81°     |
| 3     | PtCl₂ (5)       | —              | 10     | —d      |
| 4     | PtCl₂ (5)       | TFA            | 10     | —d      |
| 5     | —               | TFA            | 10     | —d      |
| 6     | Au(PPh₃)SbF₆ (5) | PTSA           | 2      | 70°     |

*All the reactions were run on 0.1 mmol scale of 5a with chloroform (2 mL) as a solvent at rt. °Isolated yields. °Unidentified byproducts were formed. °No conversion.

![Scheme 1: Gold-catalyzed approaches towards spiroindolines.](image)
Having the optimized conditions in hand (Table 1, entry 2), various Ugi-adducts 5b–q were synthesized and subjected to this hydroarylation domino cyclization sequence (Table 2). Different substituents are well-tolerated and the spiroindolines were obtained in good to excellent yields. A methyl substituent on the indole nitrogen did not hamper the domino cyclization (Table 2, entries 4, 6, 11, 12, 14, 15). Substituents like tert-butyl, cyclohexyl and n-butyl on the isonitrile are well-tolerated for the domino cyclization on the second position of the indole (Table 2, entries 1–16). Regarding the substituents coming from the acid part, tert-butyl gave a decreased yield probably due to steric hindrance (Table 2, entry 5). It is noteworthy that the gold-catalyzed intramolecular hydroarylation exclusively gives the exo-dig product in all cases and with complete diastereoselectivity.

A plausible mechanism [30,44] is shown in Scheme 2 with only the R-isomer of the Ugi-adduct 5a to simplify the discussion. The cationic gold coordinates with the terminal alkyne which becomes activated for a nucleophilic attack. This can occur from both sides of the indole core. When the attack occurs from the back side of the indole core, spiro intermediate **B**

**Table 2: Scope and limitations of intramolecular domino cyclization.**

| Entry | Ugi adduct 5 | Spiroindolines 6 (+/−) | Entry | Ugi adduct 5 | Spiroindolines 6 (+/−) |
|-------|-------------|------------------------|-------|-------------|------------------------|
| 1     | ![5b](image) 87% | ![6b](image) 70% | 9     | ![5j](image) 89% | ![6j](image) 75% |
| 2     | ![5c](image) 86% | ![6c](image) 60% | 10    | ![5k](image) 63% | ![6k](image) 80% |
| 3     | ![5d](image) 69% | ![6d](image) 76% | 11    | ![5l](image) 77% | ![6l](image) 74% |
| 4     | ![5e](image) 72% | ![6e](image) 66% | 12    | ![5m](image) 74% | ![6m](image) 68% |
| 5     | ![5f](image) 68% | ![6f](image) 40% | 13    | ![5n](image) 65% | ![6n](image) 72% |
Table 2: Scope and limitations of intramolecular domino cyclization.\(^a\) (continued)

|   | Structure | Yield | Structure | Yield | Structure | Yield |
|---|-----------|-------|-----------|-------|-----------|-------|
| 6 | ![Structure 6](image) | 77%   | ![Structure 14](image) | 68%   | ![Structure 6](image) | 60%   |
| 7 | ![Structure 5h](image) | 79%   | ![Structure 6h](image) | 83%   | ![Structure 5p](image) | 58%   |
| 8 | ![Structure 5l](image) | 67%   | ![Structure 6l](image) | 69%   | ![Structure 5q](image) | 59%   |

\(^a\)All the reaction were run on a 0.2 mmol scale of 5 in a screw capped vial employing the optimal conditions of Table 1. Cy = cyclohexyl, Bn = benzyl, PMB = p-methoxybenzyl, Bu = n-butyl.

Scheme 2: Plausible mechanism for the domino sequence.

will be formed. However, in this spiro intermediate the intramolecular trapping of the imminium ion by the amidic NH is sterically impossible and thus the intermediate reopens to intermediate A. If the attack takes place from the front side of the indole core, intermediate C is formed and trapping is possible. After deprotonation and protodeauration the desired spiro-
indoline 6a is formed with the stereochemistry of two new stereocenters S.

Conclusion

In conclusion we have developed a diversity-oriented post-Ugi gold-catalyzed intramolecular hydroarylation domino cyclization sequence for the diastereoselective synthesis of spiroindolines. The mild reaction conditions and short synthetic sequence are the merits of this method. The flexibility given by the multi-component reaction assures the generation of diversity.

Experimental

General procedure for the synthesis of spiroindolines 6a–q

To a screw capped vial Au(PPh₃)Cl (5 mol %) and AgSbF₆ (5 mol %) were loaded along with chloroform (2 mL). Ugi product 5 (0.2 mmol) was added followed by TFA (1 equiv), 32 N K₂CO₃ solution (2 × 50 mL). The reaction mixture was stirred at rt. After completion, the reaction mixture was partitioned between EtOAc (100 mL) and 2 N K₂CO₃ solution (2 × 50 mL). The organic layer was washed with brine (50 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (10% diethyl ether in dichloromethane) to afford compound 6a–q.

Supporting Information

Supporting Information File 1
Experimental section.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-246-S1.pdf]

Acknowledgements

The authors wish to thank the F.W.O [Fund for Scientific Research – Flanders (Belgium)] and the Research Fund of the University of Leuven (KU Leuven) for financial support. A.K. is thankful to EMA2experts (Erasmus Mundus Action 2, Lot 11 Asia: Experts) for providing a doctoral exchange scholarship, and D.D.V. is thankful to EMECW, lot 13 (Erasmus Mundus External Cooperation Window, Lot 13) for providing a doctoral scholarship. The authors thank Ir. B. Demarsin for HRMS measurements.

References

1. Rajter, E.; Soheflaor, R.; Orru, R. V. A. Angew. Chem., Int. Ed. 2011, 50, 6234–6246. doi:10.1002/anie.201006615
2. Ganem, B. Acc. Chem. Res. 2009, 42, 463–472. doi:10.1021/ar900214s
3. El Kaïm, L.; Grimaud, L. Mol. Diversity 2010, 14, 855–867. doi:10.1007/s11030-009-9175-3
4. Dömling, A.; Ugi, I. Angew. Chem., Int. Ed. 2000, 39, 3168–3210. doi:10.1002/1521-3773(2000915)39:18<3168::AID-ANIE3168>3.0.CO ;2-U
5. Dömling, A. Chem. Rev. 2006, 106, 17–89. doi:10.1021/cr0505728
6. Ramón, D. J.; Yus, M. Angew. Chem., Int. Ed. 2005, 44, 1602–1634. doi:10.1002/anie.200460548
7. Dömling, A.; Wang, W.; Wang, K. Chem. Rev. 2012, 112, 3083–3135. doi:10.1021/cr200233r
8. Shriki, M. Chem. Rev. 2012, 112, 3508–3549. doi:10.1021/cr2003954
9. Chen, Z.; Zheng, D.; Wu, J. Org. Lett. 2011, 13, 848–851. doi:10.1021/ol20775s
10. Tietze, L. F.; Rackelmann, N. Pure Appl. Chem. 2004, 76, 1967–1983. doi:10.1351/pac200476111967
11. Yang, J.; Xie, X.; Wang, Z.; Mei, R.; Zheng, H.; Wang, X.; Zhang, L.; Qi, J.; She, X. J. Org. Chem. 2013, 78, 1230–1235. doi:10.1021/jo302404v
12. Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. Angew. Chem., Int. Ed. 2013, 52, 3250–3254. doi:10.1002/anie.201209998
13. El Kaïm, L.; Grimaud, L.; Le Goff, X.-F.; Menes-Arzate, M.; Miranda, L. D. Chem. Commun. 2011, 47, 8145–8147. doi:10.1039/c1cc12236c
14. Bai, B.; Li, D.-S.; Huang, S.-Z.; Ren, J.; Zhu, H.-J. Nat. Prod. Bioprospect. 2012, 2, 53–58. doi:10.1007/s13659-012-0003-6
15. Lajiness, J. P.; Jiang, W.; Boger, D. L. Org. Lett. 2012, 14, 2078–2081. doi:10.1021/ol300599p
16. Fan, F.; Xie, W.; Ma, D. Org. Lett. 2012, 14, 1405–1407. doi:10.1021/ol300349e
17. Fürstner, A. Chem. Soc. Rev. 2009, 38, 3208–3221. doi:10.1039/b816696j
18. Dyker, G. Angew. Chem., Int. Ed. 2000, 39, 4237–4239. doi:10.1002/1521-3773(20001201)39:23<4237::AID-ANIE4237>3.0.CO ;2-A
19. Hashmi, A. S. K.; Hutchings, G. Angew. Chem., Int. Ed. 2006, 45, 7896–7936. doi:10.1002/anie.200602454
20. Fürstner, A.; Davies, P. W. Angew. Chem., Int. Ed. 2007, 46, 3410–3449. doi:10.1002/anie.200604335
21. Gorin, D. J.; Sherry, B. D.; Toste, F. D. Chem. Rev. 2008, 108, 3351–3378. doi:10.1021/cr078430g
22. Jiménez-Núñez, E.; Echavarren, A. M. Chem. Rev. 2008, 108, 3326–3350. doi:10.1021/cr0784319
23. Li, Z. G.; Brouwer, C.; He, C. Chem. Rev. 2008, 108, 3239–3265. doi:10.1021/cr078434l
24. Arcadi, A. Chem. Rev. 2008, 108, 3266–3325. doi:10.1021/cr078435d
25. Hashmi, A. S. K.; Rudolph, M. Chem. Soc. Rev. 2008, 37, 1766–1775. doi:10.1039/b715629k
26. Rudolph, M.; Hashmi, A. S. K. Chem. Soc. Rev. 2012, 41, 2448–2462. doi:10.1039/c1cs15279c
27. Echavarren, A. M. Nat. Chem. 2009, 1, 431–433. doi:10.1038/nchem.344
28. Jiménez-Núñez, E.; Echavarren, A. M. Chem. Commun. 2007, 333–346. doi:10.1039/b612008c
29. Rudolph, M.; Hashmi, A. S. K. Chem. Commun. 2011, 47, 6536–6544. doi:10.1039/c1cc10780a
30. Hashmi, A. S. K. Angew. Chem., Int. Ed. 2010, 49, 5232–5241. doi:10.1002/anie.200907076
31. Ferrer, C.; Echavarren, A. M. Angew. Chem., Int. Ed. 2006, 45, 1105–1109. doi:10.1002/anie.200503484
