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Gold-catalyzed synthesis of tetrahydrocarbazole derivatives through an intermolecular cycloaddition of vinyl indoles and *N*-allenamides†

Cite this: *Chem. Commun.*, 2013, **49**, 3594

Received 27th February 2013,
Accepted 12th March 2013

DOI: 10.1039/c3cc41514g

www.rsc.org/chemcomm

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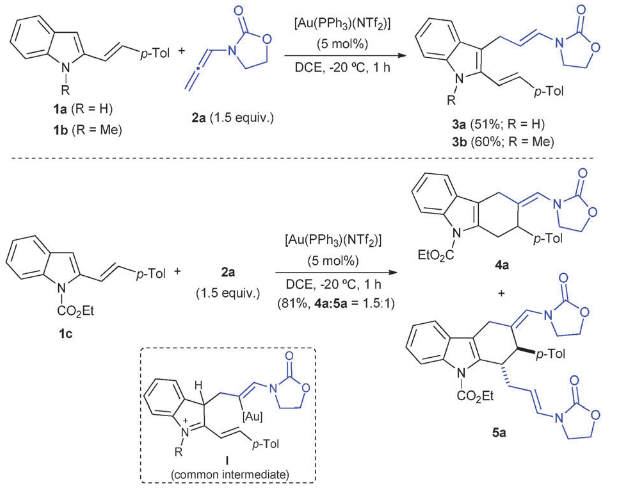
A gold-catalyzed formal [4+2] cycloaddition of vinyl indoles and *N*-allenamides leading to tetrahydrocarbazoles is described. Moreover, new multicomponent reactions of vinyl indoles with two allene molecules are reported.

Recent developments in homogeneous gold catalysis have impacted on organic chemistry, becoming nowadays a common and valuable synthetic tool.[1] *Intramolecular* gold-catalyzed cyclizations have been broadly studied offering a forthright access to a plethora of relevant scaffolds. Among unsaturated substrates involved in these transformations, allenes offered an incomparable versatility since they participate in [2+2], [4+2] or [4+3] cyclizations.[2] In contrast, *intermolecular* gold-catalyzed cycloadditions with allenes have been less studied.[3] In this sense, significant gold-catalyzed intermolecular [2+2][4] and [4+2][5] cycloadditions have been recently reported,[6] including examples of enantioselective versions.[7,8]

Besides, tetrahydrocarbazole derivatives are important structures which are key motifs in natural alkaloids and biologically active compounds.[9] Thus, the development of synthetic approaches to this class of compounds constitutes a relevant field of research. Due to our interest in the preparation of functionalized carbazole derivatives[10] and based on the recent work of Mascareñas *et al.*,[5b] we decided to study the viability of gold-catalyzed *intermolecular* cycloadditions of allenes and vinyl indoles,[11] which might offer a simple and selective access to these relevant structures. Herein, we report our findings on selective formal [4+2]-cycloadditions of vinyl indoles and *N*-allenamides, as well as, gold-catalyzed multicomponent reactions, leading to densely functionalized tetrahydrocarbazoles.

At the outset, we evaluated the reaction of vinyl indoles with representative allenes. Among various allenes probed,[12] we found that the use of vinyl indoles **1a-b** with allenamide **2a** gave rise to hydroarylation products **3a-b** in moderate yields when using the cationic gold catalyst [Au(PPh$_3$)(NTf$_2$)].[13] Assuming that the reaction took place *via* intermediate **I**, enhancement of the electrophilicity of the β-carbon on the vinyl moiety might likely facilitate the ring closure. Indeed, when we employed vinyl indole **1c**, bearing a carbamate at N-1, under the previous reaction conditions, the desired tetrahydrocarbazole **4a** was obtained, along with the unexpected compound **5a** (81% combined yield) (Scheme 1). The formation of **5a** is remarkable since it resulted from a three-component reaction involving two allene molecules. To our knowledge, there are no reports on this transformation in gold catalysis with allenes. Therefore, we searched for selective reaction conditions and evaluated the scope of these transformations.

An extensive screening led us to find reaction conditions which enabled a selective access to the desired products (Scheme 2a).[14]



Scheme 1 Gold-catalyzed reactions of vinyl indoles **1a–1c** with allene **2a**: initial findings (isolated yields with respect to **1**).

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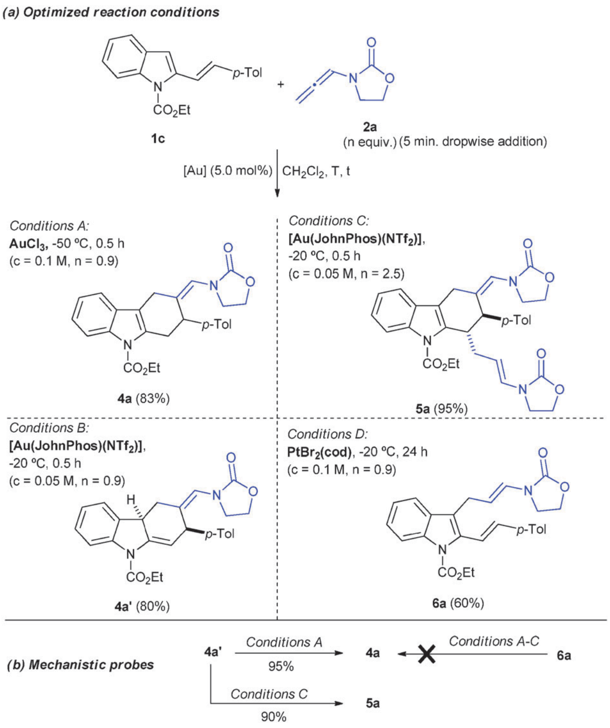
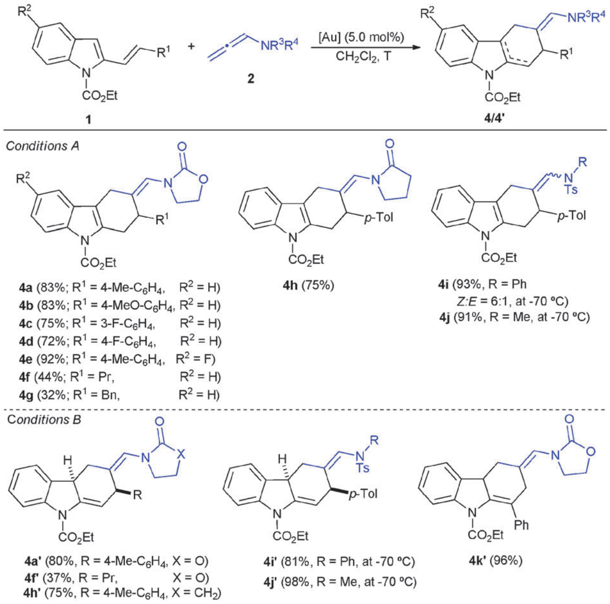
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and NMR spectra of new compounds. CCDC 923923 (**4a**), 923924 (**4a′**) and 924119 (**5a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc41514g



Scheme 2 Gold-catalyzed selective cycloadditions of **1c** with **2a**: (a) optimized reaction conditions; (b) mechanistic probes.

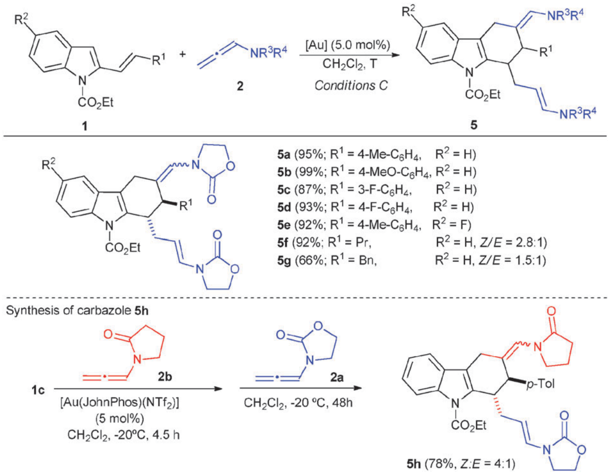
Thus, tetrahydrocarbazole **4a** was obtained in 83% yield as the only reaction product using $AuCl_3$ at −50 °C in CH_2Cl_2 (0.1 M) with a dropwise addition of a solution of the allene (0.9 equiv., *conditions A*). Interestingly, a change of the catalyst to [Au(JohnPhos)(NTf_2)], under similar reaction conditions, gave rise solely to isomeric tetrahydrocarbazole **4a′** in 80% yield as a single diastereoisomer (*conditions B*). As expected, the formation of multicomponent cycloadduct **5a** was favoured using an excess of the allene (2.5 equiv.). For this transformation, [Au(JohnPhos)(NTf_2)] provided **5a** with complete selectivity in almost quantitative yield (95%, *conditions C*). It should be noted that $PtCl_2$ did not promote any reaction, while $PtBr_2$(cod) afforded the hydroarylation product **6a** (*conditions D*). The structure of compounds **4–5a** was established using NMR studies and confirmed using X-Ray analysis.† Moreover, various experiments showed that both **4a** and **5a** arise from compound **4a′** (Scheme 2b). Thus, treatment of **4a′** with $AuCl_3$ or [Au(PPh_3)(NTf_2)] led to the aromatized product **4a** (>95%). In contrast, the use of [Au(JohnPhos)(NTf_2)] as catalyst in the presence of **2a** (1.5 equiv.) gave rise to **5a** (90%) likely through a hydroarylation process.[15,16] Interestingly, compound **6a** could not be converted into **4–5a** under optimized reaction conditions, pointing out that the cyclization occurred through the proposed intermediate **I**.[16]

With optimized reaction conditions in hand, we next evaluated the scope of these cycloadditions. First, we focused on isomeric tetrahydrocarbazoles **4/4′** (Scheme 3). Under reaction *conditions A* using allenamide **2a**, we tested various vinyl indoles bearing arenes with different electronic properties at the β-position. In this manner, compounds **4a–4e** were obtained in good yields as single *Z*-stereoisomers. Similarly, β-alkyl substituted vinyl indoles (R^1 = Pr, Bn) were also converted into the desired tetrahydrocarbazoles **4f-g**, albeit with lower yields. Modifications of the allenamide were probed as well using allenes derived from 2-pyrrolidone (**2b**) and tosylamides (**2c-d**). In this manner, the corresponding derivatives **4h–4j** were selectively obtained in good yields. Besides, using reaction *conditions B*, representative examples of isomeric tetrahydrocarbazoles **4′** were prepared, generally in good yields and with complete selectivity (Scheme 3). Other substitution patterns of the vinyl moiety noticeably affected the reaction outcome. Thus, the use of an α-phenyl substituted 2-vinyl indole gave rise to **4k** sluggishly under *conditions A*, however, under *conditions B*, compound **4k′** was obtained almost quantitatively. Moreover, the use of a β,β-disubstituted 2-vinyl indole afforded the hydroarylation product (see ESI† for details).

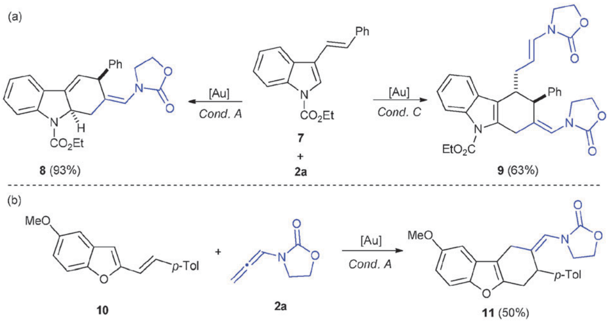


Scheme 3 Gold-catalyzed selective [4+2]-cycloadditions leading to tetrahydrocarbazoles **4/4′** (isolated yields in parentheses).

Next, we focused our studies on the preparation of the multicomponent-derived tetrahydrocarbazoles **5** (Scheme 4). As before, various vinyl indoles were evaluated using allenamide **2a**. Under the optimized *conditions C*, highly substituted tetrahydrocarbazole



Scheme 4 Gold-catalyzed multicomponent synthesis of tetrahydrocarbazoles **5** (isolated yields in parentheses).



Scheme 5 Gold-catalyzed intermolecular cycloadditions: with (a) 3-vinyl indole **7**; (b) and benzofuran **10** (isolated yields in parentheses).

derivatives **5a–5e** bearing aryl substituents (R^1) were obtained in good yields. Similarly, vinyl indoles with alkyl groups gave rise to compounds **5f-g** efficiently. Further modifications of the allene proved difficult, since complex mixtures of isomers arising from the multicomponent process were detected.[17] However, in a preliminary experiment accomplished by means of a sequential addition of the allenes (**2b** and **2a**), tetrahydrocarbazole **5h** was prepared in good yield.

Finally, we extended our study to related substrates (Scheme 5). Thus, the reaction of 3-vinyl indole **7** with allenamide **2a** using the optimized reaction conditions led to tetrahydrocarbazole derivatives **8** and **9**. Importantly, compounds **8** and **9** display a complementary substitution pattern to those obtained previously, which could be relevant for a rational synthetic design for these relevant scaffolds. Moreover, we applied this methodology to the corresponding vinyl benzofuran **10**, which could be converted into the tricycle **11** in moderate yield.

In summary, we have reported a modular approach to synthesis of a relevant class of compounds like tetrahydrocarbazoles through a gold-catalyzed *intermolecular* [4+2]-cycloaddition of readily available 2-vinyl indoles and *N*-allenamides. An appropriate selection of the substituent at N-1 on the indole and the reaction conditions enabled the selective preparation of isomeric tetrahydrocarbazoles **4** and **4′**. Interestingly, we also found conditions which led to carbazole derivatives **5** arising from unusual gold-catalyzed multicomponent cycloaddition cascade sequences with participation of two allene molecules.[18] An extension of this methodology to 3-vinyl indoles enables the preparation of complementarily substituted carbazoles **8** and **9**. Further studies concerning the asymmetric version of these reactions and the scope extension for multicomponent gold-catalyzed reactions are currently ongoing in our laboratories.

We thank the *MINECO*-Spain (Grant CTQ2012-20517-C02-01 and *Ramón y Cajal* fellowship to R.V.) and *MIUR*-Italy (PhD fellowship to V. P.) for financial support. Dr J. Borge and A. L. Suárez-Sobrino are acknowledged for the X-ray analysis. We thank Prof. Dr J. M. González for helpful discussions.

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14 See ESI† for a detailed screening.

15 See ref. 4*c* for gold-catalyzed [2+2]-cycloadditions with enamides.

16 For a mechanistic proposal on these transformations, see ESI†.

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