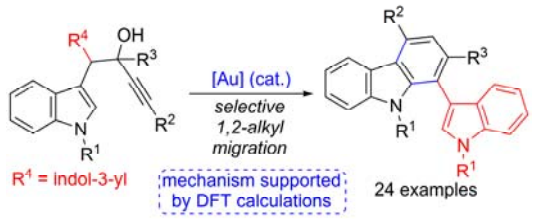
Gold-Catalyzed Synthesis of 1-(Indol-3-yl)carbazoles: Selective 1,2-Alkyl vs. 1,2-Vinyl Migration

Anisley Suárez,[†] Samuel Suárez-Pantiga,[†] Olalla Nieto-Faza,[‡] and Roberto Sanz*,[†]

[†]Departamento de Química, Área de Química Orgánica, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001-Burgos, Spain

[‡]Departamento de Química Orgánica, Facultade de Ciencias, Universidade de Vigo, Campus As Lagoas, 32004-Ourense, Spain

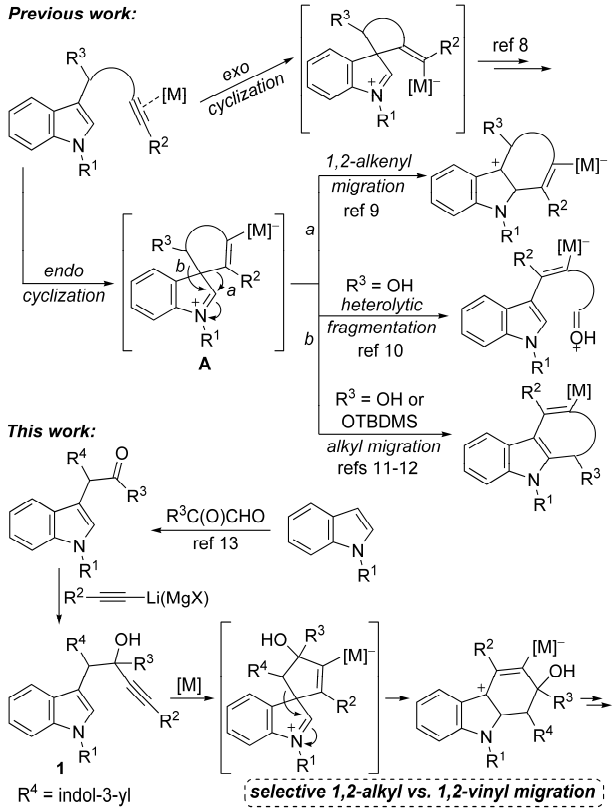
Supporting Information Placeholder



ABSTRACT: Gold(III)-catalyzed cycloisomerization of α-bis(indol-3-yl)methyl alkynols selectively affords 1-(indol-3-yl)carbazoles, in a transformation that takes place through a selective 1,2-alkyl vs. 1,2-vinyl migration step in the vinyl-gold intermediate generated from the initial 5-*endo*-spirocyclization. The reaction proceeds well with either tertiary or secondary starting alkynols as well as with a wide variety of alkyne substituents. The key role of the other indol-3-yl substituent for the unexpected selectivity in the 1,2 rearrangement has also been supported by DFT calculations that reveal a low barrier, two-step mechanism in the alkyl migration path where the second indole significantly stabilizes a carbocationic intermediate.

Carbazoles are relevant compounds mainly due to a wide variety of properties, ranging from biological activity to usefulness as building blocks in material science.[1] Among the methodologies developed for accessing the carbazole core,[2] the benzannulation of C-2 or C-3 functionalized indole derivatives,[3] as well as 2,3-unsubstituted ones,[4] is one of the most powerful. A variety of these approaches is catalyzed by gold complexes.[5] Gold(I)-catalysis is nowadays well established as a powerful tool for the straightforward construction of complex molecules from readily available starting materials.[6] In this field, different authors have studied the behavior of indole derivatives bearing alkynes tethered to the C-3 position.[7] Depending on the relative position of the triple bond and its electronic nature two cyclization modes can take place. *Exo*-cyclizations usually evolve through gold carbenoids that afford different functionalized indoles depending on the subsequent evolution of the intermediate.[8] However, most of the reported *endo*-cyclizations give rise to anellated indoles involving selective 1,2-shifts of vinyl moieties in the initially formed spirocyclic intermediate **A** (Scheme 1, pathway *a*).[9] In some particular cases (when R^3 is an hydroxyl group), the alternative migration of the alkyl group (pathway *b*) has been observed instead of the expected migration of the vinyl substituent. So, Liu and co-workers have reported an heterolytic fragmentation route for intermediate **A** involving a 1,5-indole migration and yielding 3-allenylindoles from 3-alkynyl-bearing indoles with diol groups.[10] In the same way, from 1-(indol-3-yl)-3-alkyn-1-ols,[11] or the related TBDMS ether derivatives,[12] a variety of functionalized carbazoles have been

Scheme 1. Previous Work and Proposed Study

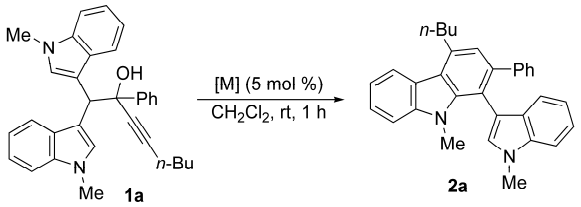


prepared involving a selective 1,2-alkyl migration under gold(I)-catalysis (Scheme 1).

In this context, we envisaged that 3-(2-hydroxybut-3-yn-1-yl)indoles **1**, bearing an activating substituent as the R^4 group such as other indol-3-yl group, could evolve to the corresponding carbazole derivatives through a selective 1,2-rearrangement step involving the migration of the indolylmethyl group instead of the vinyl one (Scheme 1).

To start our investigations, we selected 3,3-bis(indolyl)methane derivative **1a** as model substrate. For its preparation we took advantage of our previously reported efficient synthesis of α,α-bis(indol-3-yl) ketones from commercially available indoles and 2-oxoaldehydes under Brønsted acid catalysis.[13] Their reactions with lithium or magnesium acetylides afford the corresponding alkynols **1** used in this work.[14] We first investigated the reaction of **1a** in the presence of various catalysts and the results are summarized in Table 1. Substrate **1a** was treated under $Ph_3PAuNTf_2$ catalysis in DCM at rt and carbazole derivative **2a** was obtained, albeit in 32% yield (entry 1). Interestingly, the presence of the indol-3-yl substituent at C-1 of the carbazole structure instead of at C-4 shows that the 1,2-migration step has involved the sp^3 carbon instead of the expected sp^2 carbon. Moreover, carbazoles bearing indolyl substituents are highly interesting as some of them have been reported as biologically active compounds,[15] whereas efficient approaches to them have been scarcely reported,[16] and to the best of our knowledge no routes to 1-(indol-3-yl)carbazoles are known. To increase the yield of this process, other catalysts were examined. Whereas Ag(I), Cu(II), Zn(II), and Pt(IV) proved not to be specially useful for the desired transformation (entries 2–5), $PtCl_2$ at refluxed toluene or the cationic Pt complex generated from $Pt(COD)Me_2$ and HBF_4[17] at rt significantly improved the result obtained with Au(I) (entries 6 and 7). Interestingly, focusing on simple Au(III) complexes as catalysts, we found that $NaAuCl_4$ provided carbazole **2a** in very high yield (entries 8–10).[18] Finally, control experiments with Brønsted acids ruled out the possibility that a protic acid, in situ formed from the gold (or platinum) complex, was the real catalyst (entries 11 and 12).

Table 1. Effect of the Catalyst on the Cyclization of 1a

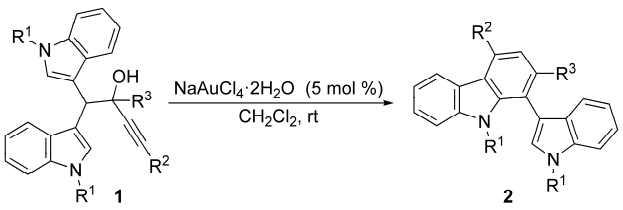


entry	[M]	yield[a] (%)	entry	[M]	yield[a] (%)
1	$Ph_3PAuNTf_2$	32	7	$Pt(COD)Me_2$ / 2 HBF_4	75
2	AgOTf	15	8	$AuCl_3$	71
3	$PtCl_4$	24	9	$HAuCl_4{\cdot}3H_2O$	81
4	$Cu(OTf)_2$	–[b]	10	$NaAuCl_4{\cdot}2H_2O$	93
5	$Zn(OTf)_2$	19	11[d]	PTSA	–[b]
6	$PtCl_2$	60[c]	12[d]	TfOH	–[b]

[a]Yield determined by ^1H NMR using CH_2Br_2 as internal standard. [b]**2a** was not observed. >80% starting material was recovered. [c]Carried out in toluene at reflux. In CH_2Cl_2 at rt no reaction took place. [d]Similar results were obtained with longer reaction times (20 h).

To examine the scope of this gold-catalyzed transformation, we applied the developed procedure to a variety of 3,3-bis(indolyl)methanes **1** possessing different substituents at the propargylic and terminal position of the alkyne moiety as well as the nitrogen atoms. Their reactions under $NaAuCl_4$–catalysis gave rise efficiently to the corresponding 1-(indol-3-yl)carbazoles **2** (Table 2). *N*-Substituted (**1a-h**, entries 1–8) or *N*-H indoles (**1i-r**, entries 9–18) behave in a similar way. Regarding the terminal position of the alkyne, (cylo)alkyl (entries 1–3, 9, and 13), aryl (entries 4, 5, 10, 14–16, and 18), heteroaryl (entry 6), alkenyl (entries 7 and 11), and even hydrogen (entries 8, 12, and 17) groups proved to be compatible with the process. Both aromatic (including functionalized phenyl rings) (entries 1–15) and alkyl groups (entries 16–18) could be present at the hydroxyl α-position without affecting the reaction outcome. So, a wide variety of new 1-(indolyl)carbazoles **2** with alkyl or aryl groups at C-2 and a wide variety of substituents at C-4 have been synthesized with this strategy.

Table 2. Synthesis of 1-(Indol-3-yl)carbazoles 2a-r[a]

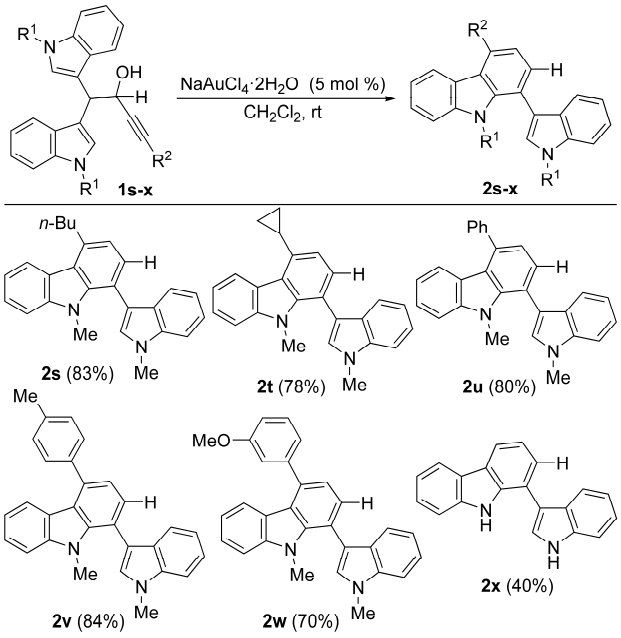


entry	**1**	R^1	R^2	R^3	**2**	yield[b] (%)
1	**1a**	Me	*n*-Bu	Ph	**2a**	86
2	**1b**	Me	*c*-C_3H_5	Ph	**2b**	83
3	**1c**	Me	$(CH_2)_2Ph$	Ph	**2c**	92
4	**1d**	Me	Ph	Ph	**2d**	73
5	**1e**	Me	4-$MeOC_6H_4$	Ph	**2e**	66
6	**1f**	Me	3-Thienyl	Ph	**2f**	90
7	**1g**	Me	*c*-C_6H_9	Ph	**2g**	85
8	**1h**	Me	H	Ph	**2h**	60
9	**1i**	H	*n*-Bu	Ph	**2i**	91
10	**1j**	H	Ph	Ph	**2j**	96
11	**1k**	H	*c*-C_6H_9	Ph	**2k**	75
12	**1l**	H	H	Ph	**2l**	83
13	**1m**	H	*n*-Bu	4-$MeOC_6H_4$	**2m**	81
14	**1n**	H	Ph	4-$MeOC_6H_4$	**2n**	77
15	**1o**	H	Ph	2-$CF_3C_6H_4$	**2o**	80
16	**1p**	H	Ph	Me	**2p**	90
17	**1q**	H	H	Me	**2q**	70
18	**1r**	H	Ph	*t*-Bu	**2r**	61

[a]Reaction conditions: **1** (0.5 mmol), $NaAuCl_4 \cdot 2H_2O$ (5 mol%), CH_2Cl_2 (1 mL), rt, 2–3 h. [b]Yield of isolated product referred to starting product **1**. *c*-C_6H_9 = cyclohexen-1-yl.

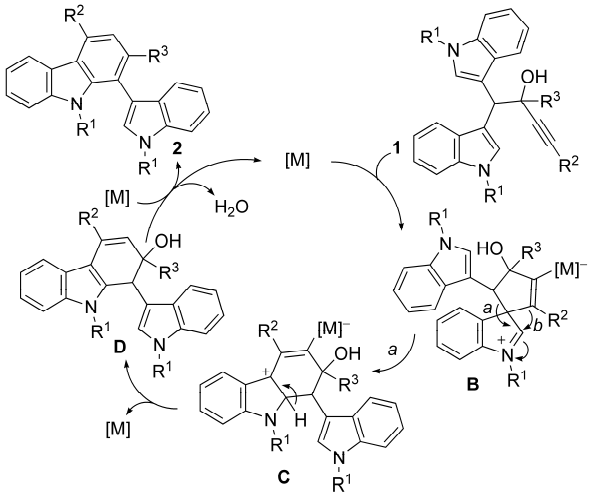
All the prepared 1-(indol-3-yl)carbazoles **2a-r** possess a substituent at C-2 position derived from R^3 in the starting alkynol. At this point we considered that the synthesis of these compounds without any group at C-2 could extend the scope of this methodology. To this end, the required alkynols precursors **1s-x** were obtained through acetylide addition to 3,3-bis(indolyl)methanes prepared from commercially available indoles and aqueous glyoxal or its dimethyl acetal.[14] The carbazole formation from secondary alkynols **1s-x** took place efficiently under the same gold(III)-catalyzed conditions, delivering 1-(indol-3-yl)carbazoles **2s-x**, without substituents at C-2, and with different groups at C-4 including (cyclo)alkyl (**2s,t**) and (functionalized)aryl (**2u-w**). All of them were obtained in high yields except **2x** with *N*-H groups, which could be only isolated in moderate yield (Scheme 2).

Scheme 2. Synthesis of 2-Unsubstituted-1-(indol-3-yl)carbazoles 2s-x from Secondary Alkynols 1s-x



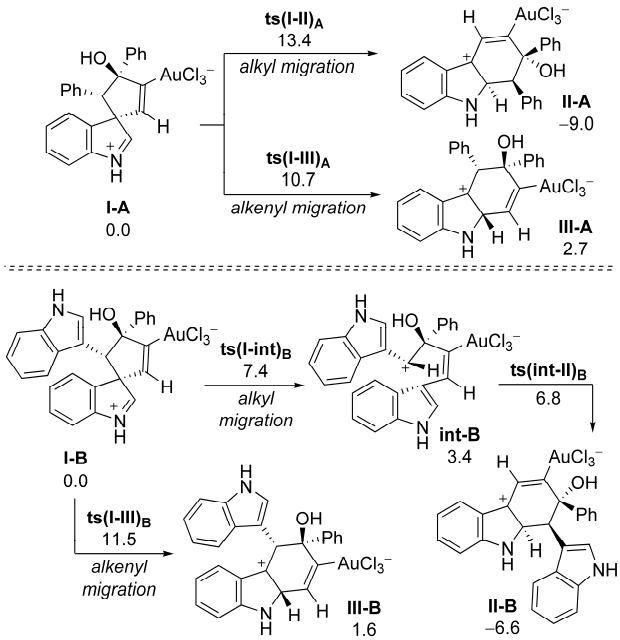
A likely mechanistic proposal for this transformation is outlined in Scheme 3. After the initial activation of the alkyne **1** through π-coordination, the spirocyclic cationic intermediate **B** is generated by attack of one of the two identical indolic fragments. Now, the shift of the indol-3-ylmethyl group (path *a*) takes place instead of the expected migration of the alkenyl substituent (path *b*), giving rise to intermediate **C**. Elimination of a proton and subsequent protodeauration release the catalyst and afford dihydrocarbazole derivative **D**, which by means of water elimination delivers carbazole **2**. The loss of water can also be probably favoured by the presence of the oxophilic gold(III) catalyst,[19] thus showing the remarkable dual role of these gold species as a σ- and π-acid that has been previously highlighted by other authors.[18b]

Scheme 3. Mechanistic Proposal



To shed light on the mechanism underlying the complete selectivity of the 1,2-migration step we decided to use DFT calculations.[20] For this, we chose the simplest substrate providing a yield over 80% as a model (**1l** in Table 2). We also used an alternative system where one of the geminal indoles on **1l** had been replaced by a phenyl group, in order to better determine the role of this second indole in selectivity (structure **I-A** in Scheme 4). Starting from spirane intermediate **I-A** we found that the alkenyl migration is slightly preferred (by 2.7 kcal/mol) to the alkyl migration, as would be expected from the general migratory aptitude of these groups. In both cases, the migration proceeds through a concerted transition state, although $\mathbf{ts(I\text{-}II)_A}$ is quite synchronous and loose (C–C distances of 2.37–2.50Å), whereas $\mathbf{ts(I\text{-}III)_A}$ is significantly tighter and asynchronous (it is a late TS, with C–C distances of 1.83 and 1.67 Å). When the second indole is introduced in **I-B**, the migration of the alkenyl moiety proceeds through a very similar concerted TS (C–C distances of 1.84 and 1.60 Å, and an activation energy just 0.8 kcal/mol higher than its **A** counterpart). The effect of the indole, however, is dramatic in the alkyl migration path: there we found a stepwise process initiated by the breaking of the bond between the spiranic carbon and the alkyl fragment (2.15 Å) through a low barrier (7.4 kcal/mol) to yield intermediate **int-B**, where the resultant carbocation is stabilized by conjugation with the vicinal indole.[21] Subsequent nucleophilic attack of this carbocation by the primary indole leads to product **III-B** through an even lower barrier (3.4 kcal/mol), making this path the preferred one.[22]

Scheme 4. Mechanism Based on our Computational Studies[a]



In summary, simple gold(III) complexes have been demonstrated as useful catalysts for accessing elusive 1-(indol-3-yl)carbazoles with further substitution at C-2 and C-4 positions from readily accessible bis(indolyl)methyl alkynols. The key step consists of a selective 1,2-rearrangement involving migration of an indolylmethyl group over an alkenyl group after the initial spirocyclization reaction promoted by attack of the indole to the activated alkyne. DFT calculations reveal that the presence of the bisindolyl functionality is crucial in the observed selectivity, as the second indole significantly stabilizes a carbocationic intermediate in the alkyl migration path.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and copies of NMR spectra. Cartesian coordinates, computational methods and a table of thermodynamic data for the structures in Scheme 4. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: rsd@ubu.es

Notes

The authors declare no competing interest.

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(19) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500–10501. An alternative, although less probable, mechanism would involve a prior loss of water to generate an enyne that further could evolve to the final product.

(20) Calculations were performed at the M06/def2-tzvpp (PCM,CH_2Cl_2)//B3LYP/6-31G*, LANL2DZ (PCM,CH_2Cl_2) level. See Supporting Information for further details

(21) An alternative evolution of cationic intermediate **int-B** through a semi-pinacol rearrangement to generate a carbonyl derivative showed a higher barrier (8.4 vs 3.4 kcal/mol).

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