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Platinum-Catalysed Bisindolylation of Allenes: A Complementary Alternative to Gold Catalysis

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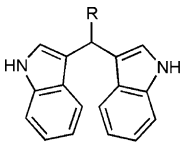
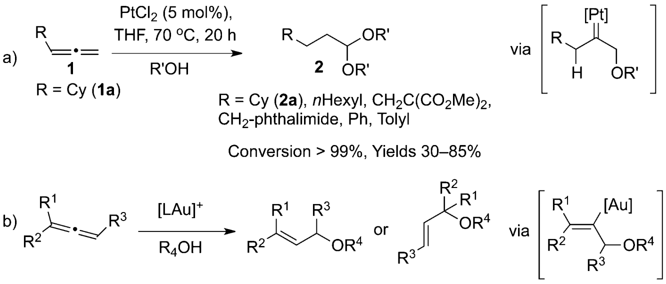
Indoles and bis(indolyl)alkanes[1] are present in a large variety of natural products isolated from terrestrial and marine natural sources and have shown to have very important biological activities,[2] such as antibacterial, antimicrobial, anti-inflammatory, antibiotic, anti-carcinogenic, genotoxicity or DNA-damaging properties (Figure 1).[3] The syntheses of bis(indolyl)alkanes have been classically carried out by condensation of indole derivatives with different aldehydes and ketones in the presence of stoichiometric amounts of Lewis or protic acids.[4]



R = CH_3, Vibrindole
R = H, Bis(3-indoyl)methane
R = CH_2OAc, Streptindole

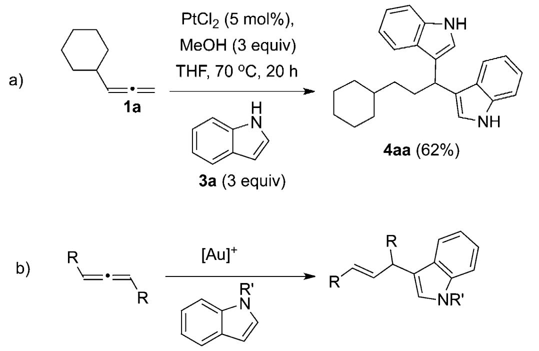
Figure 1. Examples of bis(indolyl)alkanes with biological activity.

Allenes are rather unique structures that contain two π orbitals perpendicular to each other. The synthetic utility of allenes is extensive and new chemo-, regio-, stereo- and positional-selective transformations have been developed over the past 15 years.[5] We have recently reported the platinum-catalysed dihydroalkoxylation of monosubstituted allenes, in which two molecules of an alcohol are added to the terminal carbon of the allene moiety with complete saturation of the second double bond via Pt-zwitterionic carbene intermediates (a, Scheme 1).[6] This reaction differs from the Au-catalysed one (b, Scheme 1) in the outcome and in the mechanism, in which allyl ethers are obtained via a Au-vinyl complex intermediate.[7]



Scheme 1. Pt-catalysed dihydroalkoxylation[6] versus Au-catalysed hydroalkoxylation[7] of allenes.

We found that other nucleophiles were also able to react with this new distinct reactivity pattern in the presence of platinum catalysts, and we described the first intermolecular addition of indole nucleophiles to allenes to give the [2+1] bis(indolyl)-adducts, in which two molecules of indole are bonded through the C3 to the terminal carbon of the allene with complete saturation of the other double bond (a, Scheme 2).[8,9] Preliminary studies[6] indicated that the Pt-catalysed reaction again shows complementarity with the Au^I-catalysed process reported recently by Widenhoefer et al. (b, Scheme 2).[10,11] Closer examination of the reaction reinforced this assumption and optimised conditions led to smooth bisindolylation (see the Supporting Information for details).[12] The two-fold reactivity observed in our reaction has also been reported for the gold(I)-catalysed reaction of



Scheme 2. Pt-catalysed bisindolylation[6] versus Au-catalysed hydroarylation of allenes.[10]

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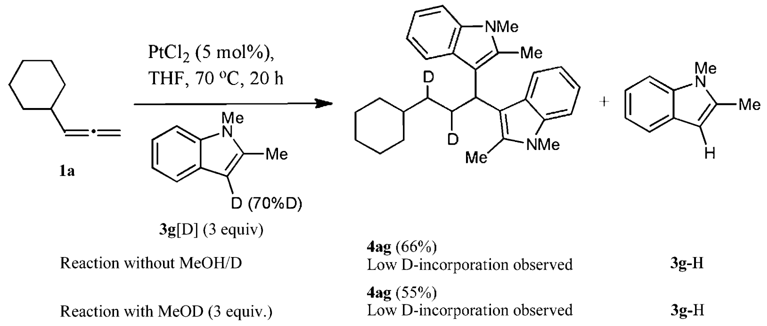
Supporting information (including experimental procedures, characterization of all the products, ^1H and ^{13}C NMR spectra, and additional tables, deuteration experiments and other information) for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103337.



Scheme 3. Deuteration experiments.

indoles and furans with alkynes.[13] In the case of the gold-catalysed reaction with alkynes and heteroarenes, the Markovnikov product is observed,[13b] whereas in the case of acceptor-substituted allenes a two-fold hydroarylation with Markovnikov regioselectivity is observed and in this case the first addition is faster than the second.[13c] However, to the best of our knowledge, this is the first example of platinum-catalysed bisindolylation of allenes.

It was found that methanol is a key additive in this process (an increased of yield from 23 to 62 % was found in the reaction of **1a** with indole **3a** when three equivalents of MeOH were added).[6] At first sight, a straightforward explanation for this observation would be a stepwise process in which a previously reported Pt-catalysed dihydroalkoxylation reaction occurs,[6] followed by indolylation through known simple pathways. However, it is important to note that the reaction works without the addition of methanol, albeit in lower yields; most likely methanol stabilises the zwitterionic intermediates involved in the course of the reaction or it could also take the role of a proton shuttle, as reported for small water and water–alcohol clusters.[14] However, this possibility was excluded because of the results obtained in the deuterium labelling experiments carried out and detailed in the paragraph below. Besides, we have observed that reaction of isolated dimethyl acetal **2a** in the presence of three equivalents of indole **3a** under our Pt-catalysed conditions, gives bis(indolyl) **4aa** in 58 % yield. The reaction also works without a Pt catalyst, in THF at 70 °C, but only 77 % conversion was achieved after three days. However, we have never observed the formation of acetal **2a** during the Pt-catalysed reaction of **1a** and **3a** in the presence of MeOH, even at short reaction times (45 min, 2 or 4 h), which rules out the hypothesis of this being the main reaction pathway under our reaction conditions.

The reaction using indole **3a** and MeOD gave the corresponding bisindole **4a** with no deuterium incorporation in any position. Moreover, deuteration studies were also performed with C3-[D]indoles with and without MeOH/D. Although the same deuteration pattern was observed in the formation of products **4**[D_2] as for the Pt-catalysed dihydroalkoxylation of allenes (one deuterium added to the internal (more substituted) carbon from the 3 position of the indole transferred in the first step to the internal carbon to form the platinum-carbene intermediate key in the reaction, and one deuterium incorporated in the central carbon of the allene from the last step of protonolysis of the platinum complex (see later, Scheme 7),[6] deuterium incorporation was low in all the conditions tested and the excess of indole **3**[D] left over in the reaction was recovered with partial or total loss of deuterium in all the cases, even when MeOD was used as an additive (Scheme 3). The deuteration in the platinum-catalysed dihydroalkoxylation of allenes was shown to be greater than 98 %. If acetals are intermediates in the formation of the bisindoles, the deuterium from the first dihydroalkoxylation should be retained because these positions are not involved in the reaction to form the bisindoles, so the fact that the deuterium incorporation is low in the final products rules out the hypothesis of acetals being intermediates of the bisindolylation reaction.

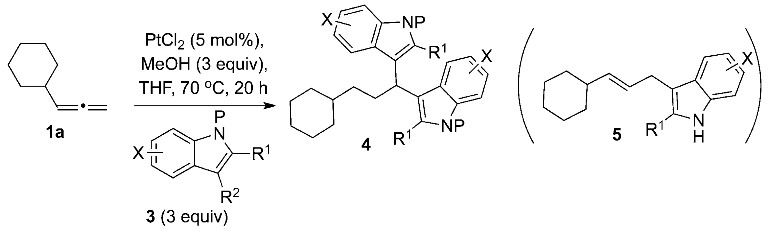
The substitution on the indole and the allene were studied by using the optimum conditions obtained under platinum catalysis. Table 1 shows the bisindolylation process is general under these conditions and it works well for unsubstituted indoles, as well as *N*-alkyl and differently substituted indole derivatives (see entries 1–6 and 8–10, Table 1).[15] The 2-methyl-substituted indole **3f** gave the 3-allyl-indole **5af** in 51 % yield, as well as the expected bis(indolyl) derivative **4af** (entry 5, Table 1). This derivative was also observed in the reaction with 5-OH indole derivative **3i** (entry 8, Table 1), indicating a pronounced influence of the substituent on the reactivity. When the C3 position of the indole was blocked, the bis(indolyl) product from attack at C2 position was obtained (**4ah**, entry 7, Table 1). Pyrrole **3l** also gave the [2+1] adduct **4al** under these platinum-catalysed conditions, although in a lower yield (entry 11, Table 1).[16]

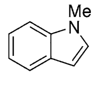
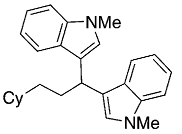
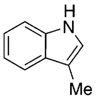
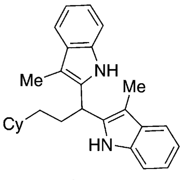
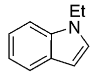
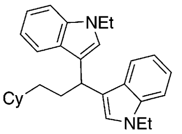
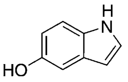
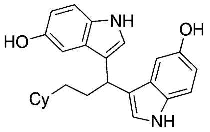
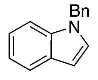
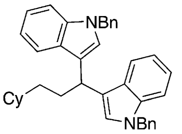
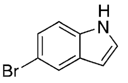
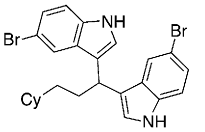
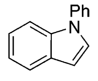
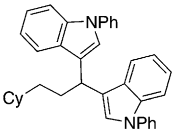
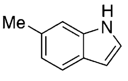
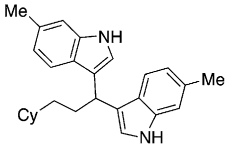
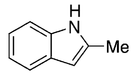
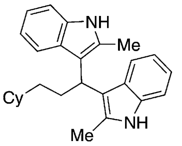
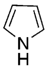
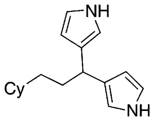
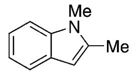
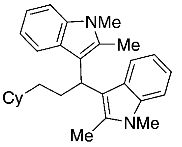
The reaction also works with allenes with different functionalities (entries 1–5, Table 2).[17] In contrast to the dihydroalkoxylation of allenes described previously,[6] the bisindolylation reaction of 1,3- and 1,1-disubstituted allenes also worked under the platinum-catalysed reaction conditions to give the bis(indolyl) products **4**, albeit in lower yields (entries 6 and 7, Table 2).

Moreover, the products from the platinum-catalysed bisindolylation of allenes are not limited to the addition of the same indoles and cross-products could be obtained by reaction of the allenes with different indoles, which increases the utility of this reaction and gives the possibility of new bis(heteroarene) compounds. One example is shown in Scheme 4.

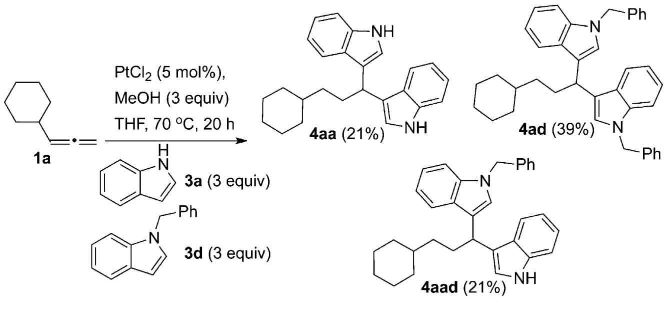
The reaction of *N*-(2,3-butadienyl)indole derivatives **6** (Scheme 5) was also studied in the presence of platinum catalysis and again, we found a divergent reactivity compared with the reactivity found with gold.[18] The platinum-catalysed reaction of **6a** and the 3-methyl derivative **6b** gave the

Table 1. Pt-Catalysed bisindolylation of cyclohexylallene **1a**.

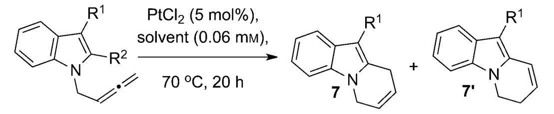


Entry	Indole 3[b]		Products		Yield [%][a]	Entry	Indole 3[b]		Products		Yield [%][a]
1		**3b**		**4ab**	90	7		**3h**		**4ah**	10[e]
2		**3c**		**4ac**	75	8		**3i**		**4ai**	33[f]
3		**3d**		**4ad**	60	9		**3j**		**4aj**	62[g]
4		**3e**		**4ae**[c]	50	10		**3k**		**4ak**	46
5		**3f**		**4af**	44[d]	11		**3l**		**4al**	12
6		**3g**		**4ag**	67						

[a] Conversion >98% unless otherwise stated; isolated product yield. [b] X=H, unless otherwise stated. [c] 12% of dimethyl acetal (**2a**) obtained. [d] 51% of **5af** obtained. [e] Conversion <98%. [f] 15% of **5ai** obtained. [g] Traces of **5aj** observed by ^{1}H NMR spectroscopy.



Scheme 4. Platinum-catalysed cross reaction of allene **1a** with two different indoles.



6a, R^1 = R^2 = H: solvent = THF, **7a/7a'**, 1.4:1 (30%); solvent = MeOH, **7a** (9%); solvent = THF (0.2 mM) + MeOH (3 equiv), **7a/7a'**, 1:1.6 (31%)

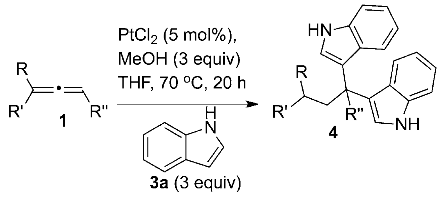
6b, R^1 = Me, R^2 = H: solvent = THF, **7b/7b'**, 1.2:1 (65%); solvent = MeOH, **7b/7b'**, 2.6:1 (83%)

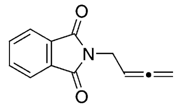
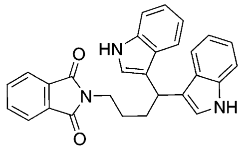
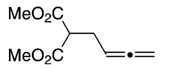
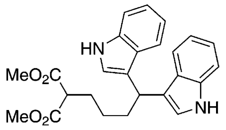
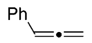
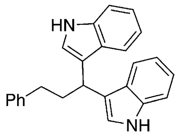
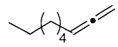
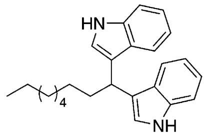
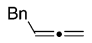
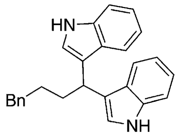
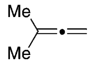
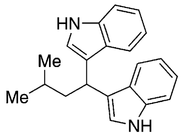
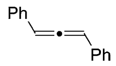
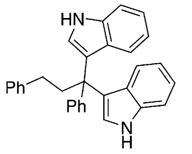
6c, R^1 = H, R^2 = Me: solvent = THF, No reaction; solvent = MeOH, No reaction

Scheme 5. Platinum-catalysed reaction of allene-indole derivatives **6**.

6-*endo* cyclisation products but, in contrast to the clean gold-catalysed reaction in which only derivative **7** is formed, we obtained a mixture of two isomers differing in the position of the double bond in different ratios, depending on the

Table 2. Pt-Catalysed bisindolylation of allenes **1**.



Entry	Allene **1**		Product **4**		Yield [%][a]
1		**1b**		**4ba**	95
2		**1c**		**4ca**	74
3		**1d**		**4da**	42
4		**1e**		**4ea**	32
5		**1f**		**4fa**	17[b]
6		**1g**		**4ga**	13[c]
7		**1h**		**4ha**	7

[a] Conversion >98% unless otherwise stated; isolated product yield. [b] Conversion <100%. [c] Low yield possible due to the volatility of **1g**.

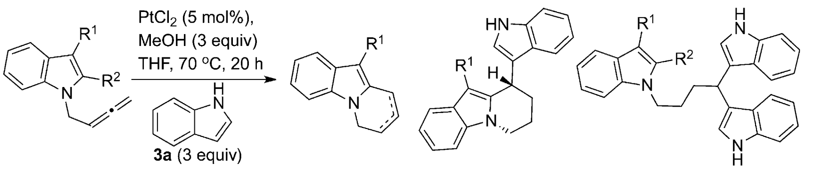
solvent used (**7** and **7′** Scheme 5. See the Supporting Information for details). The unreacted 2-methyl derivative **6c** was recovered in all the conditions tested (**6c** in the presence of Au^{I} gives trimeric-macrocyclic structures).[18]

Given the different reactivity observed under platinum catalysis, the possibility of an intra-intermolecular[19] bisindolylation reaction was then studied using the *N*-(2,3-butadienyl)indole derivatives **6** in the presence of an external indole (Scheme 6). When the reaction of **6a** was carried out in the presence of free indole under the conditions described above, instead of the expected intra-intermolecular reaction, again a mixture of the allylic 6-*endo* cyclic product **7a** (from the attack at the less activated C2 position of the indole) and an inseparable regioisomer **7a′** (with the conjugated double bond), was obtained in 17% yield (Scheme 6).

A mixture of two inseparable isomers **7b** and **7b′**, from the 6-*endo* cyclisation, was also obtained with the 3-methyl indole derivative **6b** under the standard conditions in a higher yield. However, in this case, along with the mixture of **7b** and **7b′**, the expected intra/intermolecular product **8** was obtained as a sole bisindole isomer, as well as traces of the tris(indolyl) derivative **9ba** (Scheme 6). The analogue tris(indolyl) derivative **9ca** was the only product of the reaction of 2-methyl-substituted derivative **6c**, in which the C2 carbon on the indole was blocked for the 6-*endo* cyclisation (Scheme 6).

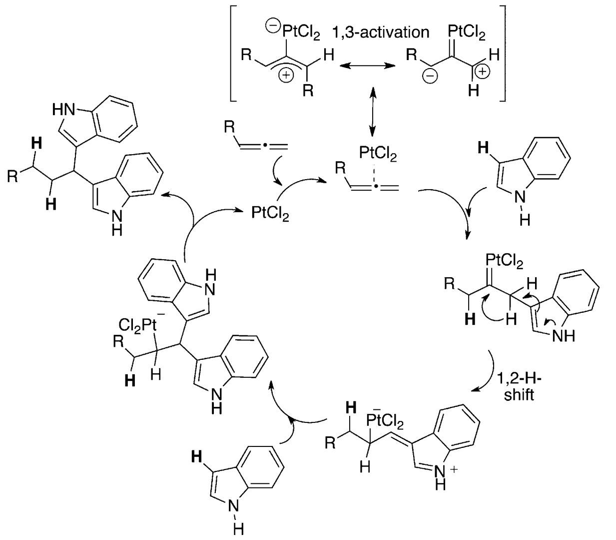
In summary, we have described the first platinum-catalysed intermolecular reaction of indoles with allenes to give bis(indolyl)alkanes. This reaction differs both in outcome and mechanism from the gold-catalysed version in which allyl-indoles are obtained. The preliminary studies suggest that the reaction does not proceed through a stepwise process with formation of the acetal as the first step when carried out in the presence of methanol. Besides the mechanism involving zwitterionic intermediates stabilised by a polar environment, as proposed for the dihydroalkoxylation of allenes (Scheme 7),[6] insertion of platinum into the C3-H of the indole,[8] a reversible reaction involving vinyl indole intermediates,[20] or a gold-type-catalysed reaction[10] (Figure 2) could be taking place during the process as competing pathways to the formation of the bis(indolyl) derivatives, which would explain the low deuterium incorporation observed, the loss of deuterium in the starting deuterated indole and the formation of allyl indoles **5**.

Therefore, further studies on the mechanism of the bisindolylation reaction and the analogous dihydroalkoxylation of allenes, are needed to fully understand this new mode of reactivity, as well as the differences with the gold(I)-catalysed version. Studies to understand these processes could open the possibility of new divergent reactions in organic chemistry, the extension of the methodologies to other



6a, R^1 = R^2 = H	**7a/7a′**, 1:1.6 (17%)	----	----
6b, R^1 = Me, R^2 = H	**7b/7b′**, 2.3:1 (73%)	**8** (21%)	**9ba** (2%)
6c, R^1 = H, R^2 = Me	----	----	**9ca** (42%)

Scheme 6. Platinum-catalysed intra-intermolecular reaction of allene-indole derivatives **6** in the presence of an external indole **3**.



Scheme 7. Preliminary mechanistic hypothesis for the platinum-catalysed bis(indolylation) of allenes.

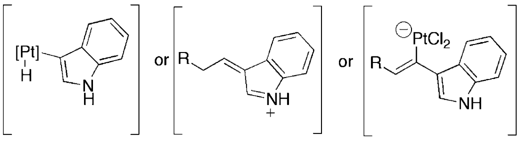


Figure 2. Other possible intermediates in the platinum-catalysed bisindolylation of allenes.

carbon-based nucleophiles and the synthesis of novel and more complex structures not obtained so far containing important motifs found in natural products with potential biological activity.

Experimental Section

General procedure for the bisindolylation of allenes: A solution of the corresponding allene (1 equiv) in dry THF (0.2 mM) and MeOH (3 equiv) was added to $PtCl_2$ (5 mol %) and the corresponding indole (3 equiv) under Ar. The reaction mixture was heated at 70 °C for 20 h. The reaction was then cooled to room temperature, filtered through Celite and washed with Et_2O and CH_2Cl_2. The solvent was evaporated and the crude purified by flash column chromatography on silica gel using hexane/Et_2O as eluent.

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Keywords: allenes • bisindolylation • catalysis • gold • indoles • platinum

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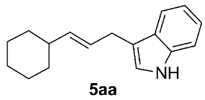

5aa

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