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COMMUNICATION

Gold catalysis on immobilized substrates: a heteroannulation approach to the solid-supported synthesis of indoles†

Agustina La-Venia, Sebastián A. Testero, Mirta P. Mischne* and Ernesto G. Mata*

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A gold-catalyzed cyclization of immobilized 2-alkynylanilines was developed as the key step in the synthetic sequence for the preparation of 2-substituted indoles. These results demonstrate the potential of the unexplored combination of gold catalysis and solid-phase organic synthesis.

Introduction

Over recent years, research in homogeneous gold catalysis has reached a high level of development, showing its potential in a series of metal-catalyzed transformations that lead to new carbon–carbon or carbon–heteroatom bonds.[1] The outstanding feature of gold complexes is their soft carbophilic Lewis acid character, which allows the activation of unsaturated moieties toward the attack by a variety of nucleophilic species.[2]

Application of organometallic chemistry to solid-phase organic synthesis has increased substantially in the last decade.[3] This originated from the emergence of new and more efficient catalysts and the inherent advantages of solid-supported chemistry. Apart from the classical advantage of easy purification, this chemistry has grown in interest due to the spatial separation of substrates achieved by immobilization on a polystyrene resin. Such site–site isolation is particularly useful in cross coupling reactions to avoid undesired homocoupling products.[4,5] Despite the arrival of homogeneous gold catalysis in mainstream chemistry, applications of this metal in solid-supported synthesis have not, to the best of our knowledge, been disclosed.

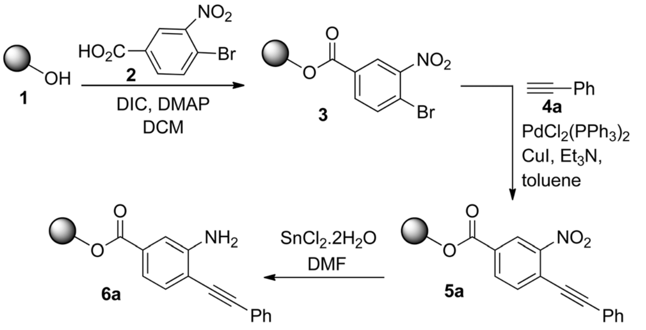
As part of our research program concerning the application of organometallic chemistry to the solid-phase synthesis of biologically relevant compounds,[6] herein we report the first example of gold catalysis in solid-phase organic chemistry in which the substrate is immobilized.[7] This methodology is illustrated by its application to the synthesis of 2-substituted indoles.

Indoles are arguably one of the most important heterocyclic systems. A large number of indole-based natural products and indole-derived synthetic drugs have demonstrated a wide range of biological activities.[8,9] Among the extensive literature on the synthesis of indoles,[10] only a few solution-phase studies involve gold catalysis.[11–13] Even though the annulation of 2-alkynylanilines is a logical approach, intermolecular dimerization may occur under gold catalysis, as depicted by Praveen *et al.*[14] We envisaged that a solid-supported substrate will avoid the homocoupling products.

Results and discussion

The synthetic sequence[15] started with the immobilization of the 4-bromo-3-nitrobenzoic acid (**2**) to Wang resin (**1**) by a standard coupling procedure to obtain the resin-bound ester **3** (Scheme 1). Resin **3** was then subjected to Sonogashira coupling. In initial studies, we utilized phenylacetylene (**4a**) for an exploratory sequence. High-yielding conditions were found when resin **3** was treated with phenylacetylene (**4a**) (5 equiv), $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) for 4 h.[16] Formation of the expected resin-bound 2-alkynylnitrobenzene **5a** was corroborated by FTIR and gel-phase ^{13}C NMR.

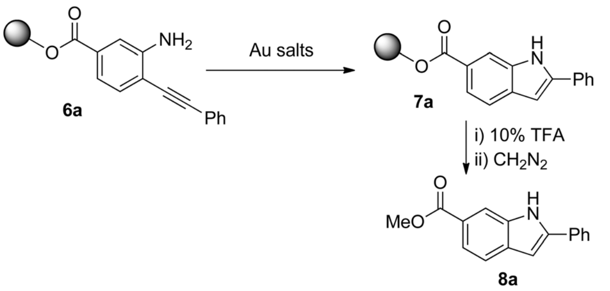
Reduction of the nitro group was then carried out in the presence of tin(II) chloride dihydrate. The best results were obtained by treating resin **5a** with 10 equivalents of $SnCl_2{\cdot}2H_2O$ in DMF[17] to give the desired 2-alkynylaniline derivative tethered to Wang resin (**6a**). After 10 min at 153 °C, formation of **6a** was



Scheme 1 Synthesis of the immobilized 2-alkynylaniline derivative **6a**.

Instituto de Química Rosario (CONICET – UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, 2000 – Rosario, Argentina. E-mail: mischne@iquir-conicet.gov.ar; mata@iquir-conicet.gov.ar; Fax: +54-341-4370477; Tel: +54-341-4370477

† Electronic supplementary information (ESI) available: Detailed experimental procedures, spectroscopic data, ^1H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c2ob06881h



Scheme 2 Synthesis of immobilized indole **7a** by Au-catalyzed cyclization.

evident from the presence of two bands at 3482 cm^{-1} and 3381 cm^{-1} in the FTIR spectrum, corresponding to the N–H unsymmetrical and symmetrical stretching. The yield of the sequence until this step was determined to be 40% by cleaving an aliquot of **6a** with 10% TFA in DCM and subsequent methylation with diazomethane.

With the immobilized precursor **6a** in hand, the catalytic activity of gold salts was evaluated (Scheme 2). We initiated our study by testing gold(I) catalysis, since $AuCl_3$ could be more oxophilic and lead to premature cleavage from the resin.[18]

First we carried out the reaction of resin **6a** with 5 mol% of AuCl in dichloromethane for 4 h at room temperature (entry 1, Table 1). Under these conditions, formation of the desired resin-bound indole **7a** was not spectroscopically detected. After testing different conditions (entries 2–5), only when 10 mol% of AuCl in dichloromethane for 18 h was used, did we detect a peak by gel-phase ^{13}C NMR at 99.9 ppm, corresponding to the C-3 indole atom, corroborating the presence of product **7a**. Final treatment of resin **7a** with 10% TFA in DCM and subsequent methylation with diazomethane afforded the resin-free indole **8a**, albeit in low overall isolated yield (3%, based on the initial loading level of Wang resin) (entry 5). This result represents only 10% yield for the gold-catalyzed step.[19] Although we had proved the feasibility of the gold catalysis on solid-supported substrates, the modest yield obtained prompted us to analyze all the aspects related to the synthetic sequence.

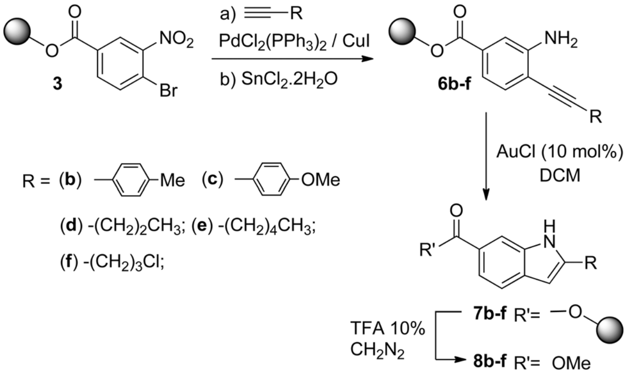
Then, we decided to reconsider the nitro group reduction step. Although $SnCl_2 \cdot 2H_2O$ reduction of nitro groups is one of the most reliable methods in solid-phase chemistry, we were worried about some reports showing that a considerable amount of tin by-products can be retained by the polymer matrix.[20] Since these by-products could interfere with gold(I) catalysis, we thoroughly washed resin **6a** with THF before the cyclization step. To our delight, this simple experimental adjustment led to a significant improvement in the efficiency of the sequence (20% overall isolated yield) (entry 6). The highest yield was obtained when resin **5a** was treated with either 5 mol% or 10 mol% of AuCl in dichoromethane for 4 h (entries 7 and 8). After releasing into solution with 10% TFA–DCM followed by esterification with diazomethane, the crude product was purified by flash chromatography to furnish the indole **8a** in 34–35% overall isolated yield for the five steps (based on the manufacturer's loading of the Wang resin) and 94–95% yield for the gold(I)-catalyzed heteroannulation step.

Interestingly, the use of $AuCl_3$ provided the indole **8a**, although in lower overall yield (20%) (entry 9).[21] Conversely, $AuClPPh_3$ catalysis was unable to promote the cyclization (entry 10).

Table 1 Au-catalyzed heteroannulation of immobilized 2-alkynylaniline **6a**

Entry	Catalyst	Time (h)	Solvent	Yield (%)^{a,b}
1	AuCl (5 mol%)	4	DCM	—
2	AuCl (5 mol%)	20	DCM	—
3	AuCl (5 mol%)	20	THF	—
4	AuCl (10 mol%)	4	DCM	—
5	AuCl (10 mol%)	18	DCM	3 (10)
6	AuCl (5 mol%)	2	DCM	20 (65)^c
7	AuCl (5 mol%)	4	DCM	34 (94)^c
8	AuCl (10 mol%)	4	DCM	35 (95)^c
9	$AuCl_3$ (10 mol%)	4	DCM	20 (65)^c
10	$AuClPPh_3$ (10 mol%)	4	DCM	—^{c}

[a] Overall isolated yield of indole **8a**, after flash column chromatography (based on the initial loading level of Wang resin (**1**), five reaction steps). [b] Data in brackets are yields for the gold-catalyzed cyclization step, calculated from the ratio between the overall yield of indole **8a** and the overall yield of the immobilized 2-alkynylaniline **6a**, after releasing from resin and methylation. [c] Starting resin **6a** was thoroughly washed with THF before the cyclization step.



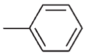
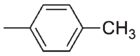
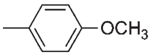
Scheme 3 Sequence for a gold(I)-catalyzed generation of 2-substituted indoles.

With the optimal conditions in hand, we further explored the potential of the gold(I)-catalyzed heteroannulation by testing different immobilized 2-alkynylanilines. With this purpose in mind, a series of alkynes were coupled to the resin-bound *o*-bromonitrobenzene derivative **3** (Scheme 3).

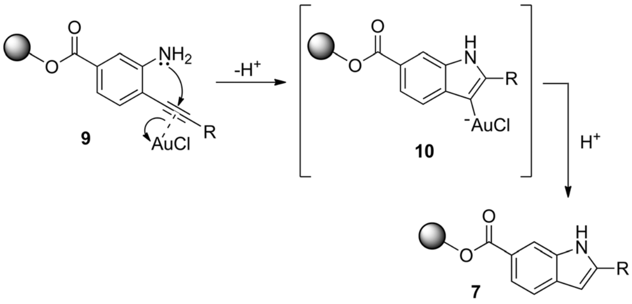
After Sonogashira coupling and reduction, the corresponding resin-bound 2-alkynylanilines (**6b–f**) were obtained in yields ranged from 14 to 60%, for the overall synthetic sequence.[22] As before, the reduction was the less efficient step. Gold-catalyzed cyclization was then performed under the optimized conditions (5 mol% AuCl in DCM, 4 h). The results are summarized in Table 2.‡ Examination of the scope of the alkyne substituents revealed that aromatic moieties give excellent yields for the Au-catalyzed heteroannulation step (entries 1–3, data in brackets). In the case of supported 2-alkynylanilines bearing non-aromatic alkyne substituents (entries 4–6, data in brackets), gold catalysis was less efficient.

Being a classical gold-catalyzed activation of an alkyne, the reaction mechanism[23] can be rationalized by the nucleophilic

Table 2 Solid-phase synthesis of 2-substituted indoles based on gold(I) catalysis[a]

Entry	Product	R	Yield (%)[b,c]
1	**8a**		34 (94)
2	**8b**		14 (93)
3	**8c**		13 (93)
4	**8d**	$-(CH_2)_2CH_3$	5 (14)
5	**8e**	$-(CH_2)_4CH_3$	22 (45)
6	**8f**	$-(CH_2)_3Cl$	15 (25)

[a] Conditions: 5 mol% of AuCl in dichoromethane for 4 h, at room temperature. [b] Overall isolated yield of indole **8**, after flash column chromatography (based on the initial loading level of Wang resin (**1**), five reaction steps). [c] Data in brackets are yields for the gold-catalyzed cyclization step, calculated from the ratio between the overall yield of indole **8** and the overall yield of the immobilized 2-alkynylaniline **6**, after releasing from resin and methylation.



Scheme 4 Proposed reaction mechanism

attack of the amino group to the π-coordinated alkyne in a 5-*endo-dig* manner, to lead to the vinyl–Au intermediate (**10**) (Scheme 4).[24] Finally, this intermediate undergoes a proto-demetallation to afford the indole **7**.

Conclusion

In summary, we report the first solid-phase example of a gold-catalyzed reaction in which the substrate is supported. The reaction conditions developed above were found to be applicable to the preparation of a small library of 2-substituted indoles. In our hands, AuCl was more efficient than its Au(III) counterpart for the heteroannulation step. Under the optimized conditions, AuCl catalyzed the formation of the indoles in high yield, particularly for aromatically substituted alkynes. The present work provides a proof of concept of the combination of gold catalysis and solid-supported chemistry, expanding the use of this kind of catalyst. Further studies are in progress to extend our knowledge of this combination and the results will be detailed in due course.

Acknowledgements

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Notes and references

‡ Representative procedure for the Au-catalyzed hetero-annulation of immobilized 2-alkynylanilines: Support-bound 2-alkynylaniline (**6a**) (210 mg, 0.95 mmol g^{-1}, 0.20 mmol) in a 20 mL polypropylene filtration tube with polyethylene frit was suspended in anhydrous dichloromethane (3 mL), AuCl (2.5 mg, 0.01 mmol, *ca.* 5 mol%) was added under a nitrogen atmosphere, and the mixture was shaken at room temperature for 4 h. After that, the resin was filtered, washed with THF (3 × 3 mL), MeOH (3 × 3 mL), CH_2Cl_2 (4 × 3 mL), and dried under high vacuum. For releasing the product from the solid phase, the resin was treated with 5 mL of 10% TFA in CH_2Cl_2 for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure. This crude material was dissolved in CH_2Cl_2 (3 mL) and treated with diazomethane at 0 °C until yellowish coloration was achieved. After 30 min, diazomethane was quenched by AcOH, solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to afford the indole **8a** (17.5 mg, 35% overall yield from Wang resin).

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