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Selectivity Control in Gold-Catalyzed Hydroarylation of Alkynes with Indoles: Application to Unsymmetrical Bis(indolyl)methanes

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ABSTRACT: Gold-catalyzed hydroarylation of unactivated alkynes with indoles have previously been reported to proceed with double indole addition to produce symmetrical bis(indolyl)methanes (BIMs). We demonstrate for the first time that the selectivity of the gold-catalyzed reaction can be fully switched to allow for isolation of the vinyl indole products instead. Furthermore, this selective reaction can be utilized to synthesize the more difficult to access unsymmetrical BIMs from readily available starting materials.

Since the turn of the century, homogenous gold-catalysis has become increasingly popular for facilitating chemoselective nucleophilic additions to unsaturated carbon-carbon bonds. For example, the hydroarylation of alkynes with indoles has been studied extensively using gold catalysis due to the products’ relevance in medicinal and natural products. The intermolecular version of this reaction with unactivated alkynes has previously been reported to occur via double addition of the indole to form symmetrical 3,3′-bis(indolyl)methanes (BIMs) 3 (Scheme 1A). It is usually not possible to isolate the single addition vinyl indole intermediates 4, as 4 reacts further under these conditions to form BIMs 3. The BIM motif appears in many natural and pharmaceutically active compounds, such as echininosulfonic acids A-D and mucronatins A and B (Figure 1), and synthetic methods towards these motifs have therefore been widely investigated. Nevertheless, the majority of synthetic methods available are for accessing symmetrical BIMs (where both indoles are equivalent). Methods for accessing the unsymmetrical BIMs are more challenging. In particular, methods for accessing 3,3′-BIMs with quaternary carbon centers (5) are rare. One of the more general methods involves acid-catalyzed addition of indoles to vinyl indoles such as 4. Nevertheless, since these vinyl indoles are not commercially available and some have limited bench stability, it would be a significant advancement to the field to be able to access 5 directly from commercially available starting materials in a facile manner.

Encouraged by our previous success in switching the selectivity of several gold-catalyzed reactions, we aimed to develop the first gold-catalyzed reactions that could be controlled to stop at and be completely selective for the single addition product 4 (Scheme 1B). Such control should then allow for the rapid synthesis of the more difficult to access unsymmetrical BIMs 5, from commercially available starting materials (Scheme 1C).

Scheme 1. Gold-Catalyzed Hydroarylation of Unactivated Alkynes with Indoles

A) Previously: Double addition to symmetrical BIMs 3

B) This Work: Controlled single addition to vinyl indole 4

C) Application: Unsymmetrical BIMs 5 via 4?
We initiated our studies using model substrates phenylacetylene 2a and 2-methylindole 1a (Table 1), as this combination provided the most promising 1:2.2 ratio of 4a:3a in previously reported kinetic studies by Hashmi.\textsuperscript{4e} After initial experiments had identified acetonitrile as the optimum solvent (see Sup. Info. for full optimization studies), we initially employed PPh$_3$AuNTf$_2$ and IPrAuNTf$_2$ as catalysts at 0 °C, with the rationale that the lower temperature might prevent double addition to 3a. To our delight, a switch in product selectivity to favor the desired vinylindole 4a was observed (entries 1-2). PPh$_3$AuNTf$_2$ was chosen as the optimum catalyst as it was more selective for desired 4a (4.6:1 4a:3a) when compared with IPrAuNTf$_2$ (1.7:1 4a:3a). Increasing the equivalents of indole 1a unsurprisingly increases the amount of undesired 3a (entry 3). Reversing the stoichiometry of reagents successfully eliminates any formation of 3a, although the yield of desired 4a is still modest even after 48 h (entries 4-5). Much to our surprise, increasing the temperature to 30 °C allows for quantitative formation of 4a with no evidence of undesired 3a (entry 6). Although a 1:1 ratio of substrates produces a very good 90% yield of 4a (entry 7), purification from co-eluting unreacted 1a proved problematic, so the conditions in entry 6 were adopted as optimal. It thus appears that it is the combination of conditions that contributed to the successful switching of selectivity from 3a to 4a, rather than any one particular factor.

Table 1. Selected Optimization Studies

<table>
<thead>
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<th>entry</th>
<th>temp (°C)</th>
<th>1a equiv</th>
<th>2a equiv</th>
<th>t (h)</th>
<th>1a\textsuperscript{a} (%)</th>
<th>3a\textsuperscript{a} (%)</th>
<th>4a\textsuperscript{a} (%)</th>
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<tr>
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<td>1</td>
<td>1</td>
<td>24</td>
<td>10</td>
<td>0</td>
<td>90</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Determined by $^1$H NMR analysis with 2,6-dimethoxy-1,4-benzoquinone as internal standard. \textsuperscript{b}Using IPrAuNTf$_2$ as the catalyst; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. n/a = not applicable as 1a in excess.

With optimized conditions in hand, a screen of indoles 1 was carried out (Scheme 2). To our delight, N-alkylation of the indole has no negative impact on the yield (91% 4b vs. 84% 4a). N-Protection of the indole with an electron-withdrawing Boc group, however, results in no reaction (<5% 4c), presuma-
bly as the indole is now not sufficiently nucleophilic. Both electron-withdrawing and electron-donating groups are tolerated at the 5-position, yielding products 4d and 4e in excellent 90% and good 77% yields respectively. Next, the substituent at the 2-position of the indole was varied (4f-4i). Pleasingly, the reaction is not sensitive to sterics at this position, with bulky Ph and \textsuperscript{1}Bu substituents tolerated well to provide excellent yields of 4f (96%) and 4g (quant.) respectively. An electron-withdrawing ester substituent directly attached at the 2-position causes the indole to react sluggishly (21% 4h), although the successful reaction to produce 4i (89%) indicates that the sluggishness of the former is once again due to reduced nucleophilicity rather than the ester moiety, which is well tolerated in 4i. A substituent at the 4-position is tolerated well (4j 80%), as is one at the 3-position, the latter results in nucleophilic attack via the 2-position (4k 75%). Furthermore, the reaction works just as well on 1 mmol scale (quant. 4l).

To our surprise, even under our optimized conditions, unsubstituted indole reacts via double addition to form symmetrical bis(indolyl)methane 3b in 80% yield, with no vinylindole 4 observed (Scheme 3A). In order to test whether the over-reaction of this indole is due to steric or electronic factors, the less nucleophilic nitro-substituted indole was investigated next. Although 1c reacts much more sluggishly than 1b as expected, once again, no vinyl indole 4 was observed, with only 3c formed in 20% yield along with recovered starting material. These observations indicate that the selectivity for vinylindole in 20% yield along with recovered starting material. These observations indicate that the selectivity for vinylindole in 20% yield along with recovered starting material.

Scheme 3. Indoles with No Substituents at Positions 2, 3 or 4 React Differently

A: Problem

\[
\begin{align*}
1b, X=\text{H} & & 2a, X=\text{H} \quad \text{PPh}_2\text{AuNTf}_2 \\
1c, X=\text{NO}_2 & & 3b, X=\text{H}, 80\% \quad \text{No vinylindole 4 observed}
\end{align*}
\]

B: Solution

\[
\begin{align*}
1d-e, \text{Bpin} & & 2a, X=\text{H} \quad \text{PPh}_2\text{AuNTf}_2 \\
& & \text{MeCN, 50 °C, 24 h} \quad \text{R=H, 4o, 58%}\% \quad \text{R=Me, 4p, 64%}\% \quad \text{over 2 steps}
\end{align*}
\]

*Only partially stable to column chromatography*

In order to overcome this limitation, 2-substituted TMS and Bpin indoles were investigated as nucleophiles, (Scheme 2) with the intention that these substituents will provide the steric bulk required to selectively produce 4, while simultaneously being sufficiently labile to be removed in one-pot to form 4o. Unfortunately, TMS is partially labile under the gold-catalyzed conditions (35% 4l), with a range of desilylated by-products observed. Pleasingly, the Bpin-substituted indole fared much better (85% 4m and 84% 4n), and crucially, allows for facile one-pot deprotection to form 4o and 4p successfully upon stirring with silica (Scheme 3B).

Scheme 4. Alkyne Scope

\[
\begin{align*}
\text{Scheme 4. Alkyne Scope} & \\
\text{R}^1 & & \text{R}^2 & & \text{R}^3 & & \text{PPh}_2\text{AuNTf}_2 \\
\text{MeCN} & & (2 \text{ mol\%}) & & \text{MeCN} & & (2 \text{ mol\%}) \\
\text{30 °C, 24 h} & & \text{30 °C, 24 h} & & \text{30 °C, 24 h} & & \text{30 °C, 24 h}
\end{align*}
\]

Next, the alkyne scope was investigated (Scheme 4). Arylalkynes proved to be ideal substrates for the reaction (e.g. 96% 4f), with both strongly electron-donating (94%, 4q) and withdrawing (71%, 4r) substituents tolerated. The use of para-, meta- and ortho-Cl-substituents on the aryl shows that increasing steric bulk does not negatively impact the yield (quant. 4s, quant. 4t, 96% 4u). It is worth noting though that the more sterically bulky ortho-substituted chloroarylalkyne reacted more sluggishly and needed a slightly higher temperature of 50 °C and catalyst loading of 5 mol% to proceed to completion, albeit with still excellent yield (96%). To our delight, internal alkynes also react well, and with excellent regio- and stereoselectivity (94% 4v, 96% 4w). Alkyl-substituted alkynes were more temperamental as substrates. While 4x was formed in excellent
yield (90%) and good regioselectivity, 4y was surprisingly poor yielding and with diminished selectivity (30%, 1:1 regioselectivity). The bulky \( \text{B}^\text{Bu} \text{g} \) group also causes sluggish reactivity, presumably due to steric (18% 4z). Heteroaryl alkenes can also react very well (quant. 4aa), although a pyridine moiety is not tolerated (<5% 4ab), presumably due to deactivation of the gold catalyst by the Lewis basic N.

Following successful control of the hydroarylation reaction to form vinyl indoles 4 selectively, we proceeded to investigate its potential application to facile synthesis of unsymmetrical BIMs 5. Thus, we explored the one-pot addition of a second, different indole in the presence of an acid catalyst, following the gold-catalyzed formation of vinyl indole 4 (Scheme 5A).

We discovered that steric bulk on the first indole introduced (1c) into the vinyl indole (4f) results in the unwanted formation of the less sterically bulky symmetrical BIM 3b, indicating that the transformation of 4 to 3 or 5 is reversible (Scheme 5A, see Supporting Information for further studies). Indeed, previous reports on the acid-catalyzed formation of unsymmetrical BIMs 5 from vinylnidole 4 do not mention the use of any bulky vinylnidole substrates such as 4f.12a

**Scheme 5. Application: Formation of BIMs**

**A)** Initial studies: steric bulk in 4 causes scrambling of indoles

**B)** Successful formation of unsymmetrical BIMs 5

We therefore decided to re-investigate the sequence using non-bulky vinylnidoles 4o and 4p instead (Scheme 5B). To our delight, this approach now allows for the desired unsymmetrical BIMs 5 to be successfully formed in a facile manner from commercially available starting materials in reasonably good yields (5a-e, 50-68% over 3 steps, Scheme 5B). Thus, it appears that the very factor that favors successful formation of vinylnidole from 1 → 2 during the first step of the sequence, \( i.e \) steric bulk on the first indole 1, also disfavors the second step, \( i.e \) formation of unsymmetrical BIM 5. Nevertheless, judicious use of Bpin as a labile bulky group successfully overcomes this conundrum (Scheme 5B).

In conclusion, we have developed the first controlled gold-catalyzed hydroarylation of alkenes with indoles to successfully and selectively yield single addition product vinylindole 4, instead of the previously observed double addition product, symmetrical BIM 3. Substituents on the 2-, 3-, or 4-position on the indole were found to be crucial for achieving good selectivity for 4. Therefore, use of labile Bpin at the 2-position of the indole also allows for the formation of less sterically bulky vinylindoles 4. Furthermore, the reaction has been exploited to develop a facile synthesis of unsymmetrical BIMs 5 from commercially available starting materials.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Optimization studies, all experimental details, characterization, copies of NMR data,15 (PDF)

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For examples of related gold-catalyzed reactions of indoles with activated alkynes such as: ynamides, see (b) Barluenga, J.; Fernández, A.; Rodríguez, F.; Fañanás, F. J.; Fan, Y.-S.; Gao, Y.; Liu, S.; Zhang, S.

in much lower conversions with this bulky vinylindole product was when

example In(III) at 110 °C, see: (a) Bhaskar, G.; Saikumar, C.; Perumal, P. T. Tetrahedron Lett. 2010, 51, 57; (b) Shiri, M.; Shiri, S.; Rezaei-Khah, S.

These reactions are not as mild and tend to require elevated temperatures, for example InIII at 110 °C, see: (a) Bhaskar, G.; Saikumar, C.; Perumal, P. T. Tetrahedron Lett. 2010, 51, 57; (b) Shiri, M.; Shiri, S.; Rezaei-Khah, S.


The use of acid 6 under conditions shown in Scheme 5B results in much lower conversions with this bulky vinylindole 4g: only 7% 3b and 93% starting material, albeit still with no desired 5 observed.

The research data underpinning this research can be found at DOI: 10.17861/73291063-2c36-4a54-950e-489dc3a707e.