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Gold-Catalyzed Cascade Reaction of Skipped Diynes for the Construction of a Cyclohepta[b]pyrrole Scaffold

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(5) Supporting Information

ABSTRACT: A gold-catalyzed cascade reaction of skipped diynes (1,4diynes) and pyrroles has been developed. This reaction proceeds by the consecutive regioselective hydroarylation of two alkynes with a pyrrole, followed by a 7-*endo-dig* cyclization to give 1,6-dihydrocyclohepta[b]pyrroles in good yields. The direct synthesis of cyclohepta[b]indoles using indole nucleophiles has also been reported.



🕻 kipped diynes (1,4-diynes) have been used extensively as Duilding blocks for the synthesis of polyunsaturated fatty acids (PUFAs).^{1,2} Following the pioneering work of Raphael and Sandheimer, PUFAs are generally prepared by the reaction between skipped diynes and metal acetylides used as a carbon chain elongation strategy, followed by a partial reduction with Lindlar's catalyst. Skipped diynes are also recognized as versatile synthons for the construction of various hetero- and carbocyclic systems. For example, activated skipped diynes bearing an 3-oxo/ 3-methylidene group or tetrasubstituted carbon at their 3position have been used to prepare pyrrole,³ pyridine,⁴ furan,⁵ benzene,⁶ pyrone,⁷ and 1,1'-bitriphenylene derivatives.⁸ Furthermore, Czekelius and co-workers9 reported the development of a gold-catalyzed reaction for the synthesis of carbocycles from skipped diynes bearing a nucleophilic moiety at their tetrasubstituted 3-position by the desymmetrization of two alkynes. Despite considerable progress in this area, there have been very few reports pertaining to cyclization reactions of this type involving 3-unsubstituted 1,4-divnes. The lack of progress in this area has been attributed in part to the importance of disubstitution or a conjugated functional group at the 3-position to the stabilization of these systems or the cyclization (i.e., Thorpe-Ingold effect¹⁰) of skipped 1,4-diynes. One important exception to this observation is the Khand reaction reported by Kerr and co-workers, where skipped diynes were stabilized in a conformation that supported their cyclization via the formation of a dicobalt complex.

Homogenous gold catalysis has emerged as a powerful synthetic tool for the activation of alkynes, thereby facilitating nucleophilic addition to the alkyne bond to provide cyclization products with high atom economy.¹² Recent advances in this area, including considerable contributions from Czekelius,⁹ have shown that diynes are useful substrates for gold-catalyzed cascade reactions.^{13,14} We recently reported the development of a gold-catalyzed formal [4 + 2] reaction between 1,3-diynes and pyrroles (Scheme 1A).¹⁵ This reaction proceeded through a double hydroarylation cascade involving the initial intermolecular hydroarylation of a 1,3-diyne at the 2-position of a pyrrole, followed by an intramolecular hydroarylation to give a 4,7-disubstituted indole.

Scheme 1. Sequential Gold(I)-Catalyzed Hydroarylation of a Diyne with a Pyrrole

(A) our recent work: [4 + 2] indole synthesis



Following on from this work, we switched our attention to the reactivity of skipped diynes in the double hydroarylation cascade, especially those not bearing a substituent at their 3-position. We envisaged that the biggest challenge associated with this work would be controlling the regioselectivity of both steps. For example, intermolecular hydroarylation could occur at the 1-position or the 2-position to give the corresponding regioisomeric enyne intermediates **A** and **B** (paths a and b, respectively).

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The subsequent 7-endo-dig-type hydroarylation of intermediate $\mathbf{A} \cdot [\mathbf{A}\mathbf{u}^+]$ (path c) would give cyclohepta [b] pyrrole 3, whereas the generally favored 6-*exo-dig* cyclization¹⁶ of $\mathbf{A} \cdot [\mathbf{A}\mathbf{u}^+]$ (path d) or 6-endo-dig cyclization of $\mathbf{B} \cdot [\mathbf{A}\mathbf{u}^+]$ (path e), followed by an aromatization step, would lead to the regioisomeric indoles 4 and 5, respectively. Notably, the use of unsymmetrical skipped divnes could result in up to six isomeric products. The lack of any positive effects associated with the substitution of the 3-position, as described above, would also provide another challenging issue. Herein, we report the regioselective formation of 1,6dihydrocyclohepta[b]pyrrole derivatives 3, which are homologues of 4,7-disubstituted indoles, by the gold-catalyzed [5 + 2]reaction of skipped diynes with pyrroles. We also report consecutive hydroarylation reactions using an indole as a nucleophile for the direct synthesis of cyclohepta [b] indoles, which are important structural motifs found in numerous natural products and pharmaceutical compounds.1'

We initially examined the reaction of 1,5-diphenylpenta-1,4diyne (1a) with pyrrole (2a) (2 equiv) in the presence of various gold catalysts (10 mol %) (Table 1). The use of IPrAuCl/AgSbF₆ allowed for the formation of the [5 + 2] cyclization product 1,6dihydrocyclohepta[b]pyrrole (3a) (14%) along with a small amount of the regioisomeric indoles 4a (1%) and 5a (2%) (entry 1). Although the use of PPh₃, BrettPhos (L1), or JohnPhos (L2) as a phosphine ligand did not lead to an improvement in the





^{*a*}Unless otherwise noted, all of these reactions were carried out using **1a** and 2 equiv of pyrrole **2a** at 50 °C. ^{*b*}Yields were determined by ¹H NMR analysis using dimethyl sulfone as an internal standard. ^{*c*}Reactions were carried out at 80 °C. ^{*d*}Reaction was carried out at 100 °C. ^{*e*}Reaction was conducted using 1.1 equiv of **2a**. ^{*f*}Reaction was conducted using 10 equiv of **2a**. ^{*g*}Not detected.



efficiency of the catalyst (entries 2-4), the commercial gold catalyst JohnPhosAu(MeCN)SbF₆ led to a considerable improvement in the yield of 3a to 69% (entry 5). After a series of different solvents was screened under various reaction temperatures with a 5 mol % loading of the catalyst (entries 6-11), we found that the use of toluene as a solvent at 80 °C led to an increase in the yield of 3a (72%, entry 11). Finally, we examined the stoichiometry of the reaction and found that increasing the amount of pyrrole (10 equiv) had very little impact on the reaction (entry 14). Furthermore, the use of a reduced charge of pyrrole (1.1 equiv) only resulted in a slight reduction in the yield of **3a** (63%, entry 13). It is noteworthy that the second hydroarylation proceeded preferentially via a 7-endo-dig pathway (path c, Scheme 1) rather than a 6-exo-dig pathway (path d). Furthermore, the first hydroarylation occurred regioselectively at the terminal carbon of the skipped divne moiety (path a).

Having established efficient conditions for the selective synthesis of 1,6-dihydrocyclohepta[b]pyrrole 3a, we proceeded to evaluate the substrate scope of this reaction (Table 2). Diaryl

Table 2. Reaction of Symmetrical Skipped Diynes Bearing Various Substituents $\!\!\!\!\!^a$

R + 1a-h		JohnPho N dolu H 2a	asAu(MeCN)SbF ₆ 5 mol %) Jene, 80 °C	R N H B 3a-h
entry	substrate	R	time (h)	yield (%) ^b
1	1a	Ph	3	71
2	1b	$C_6H_4(4-OMe)$	3	80
3	1c	$C_6H_4(4-Br)$	3	64
4	1d	$C_{6}H_{4}(4-CN)$	12	32
5	1e	$C_6H_4(4-Me)$	3	72
6	1f	$C_6H_4(3-Me)$	3	72
7	1g	$C_6H_4(2-Me)$	3	80
8	1h	<i>n</i> -Bu	24	<24 ^c

"Reactions were conducted using a mixture of 1, pyrrole 2a (2 equiv), and catalyst (5 mol %) in toluene (0.1 M) at 80 °C. ^bIsolated yields. ^cContained inseparable impurities.

substituted skipped divne 1b bearing an electron-donating methoxy group at the 4-position of its phenyl rings reacted smoothly to afford the corresponding [5 + 2] product **3b** in 80% yield within 3 h (entry 2). The 4-brominated derivative 1c also reacted efficiently to produce 3c in 64% yield (entry 3), whereas 1d bearing cyano-substituted phenyl groups gave a much lower yield (32% yield after 12 h, entry 4). The influence of the position of the substituent on the phenyl ring was evaluated using tolyl derivatives 1e-g. Interestingly, the reaction of the o-tolylsubstituted skipped diyne 1g proceeded most efficiently to give 3g in 80% yield, whereas the *p*- and *m*-tolyl derivatives (1e and 1f, respectively) gave slightly lower yields of the desired products (72%). It is noteworthy that the aliphatic skipped diyne 1h showed low reactivity toward the desired cyclization (entry 8). These observations implied that electron-rich aryl groups facilitated the formation of alkyne-gold complexes by stabilizing the developing cationic charge to promote the desired cyclization. In contrast, aliphatic and electron-deficient aryl substituents failed to afford similar benefits (entries 4 and 8).

We then switched our focus to the reaction of unsymmetrical skipped diynes (Table 3). In this case, we envisaged that the regioselectivity of the first hydroarylation would determine the Table 3. Reaction of Unsymmetrical Skipped Diynes Bearing Various Substituents^a



"Reactions were conducted using a mixture of 1', pyrrole 2a (2 equiv), and the catalyst (5 mol %) in toluene (0.1 M) at 80 °C. ^bDetermined by ¹H NMR analysis based on the combined isolated yields.

distribution of the two possible products (i.e., 3' vs 3''). Given that the reactivity of the unsymmetrical skipped diynes could vary depending on the electronic properties of their substituents, we tested substrates 1'a-c bearing substituents with different electronic properties. The reaction of unsymmetrical diaryl diyne 1'a ($R^1 = Ph$, $R^2 = 4$ -anisyl) gave cyclohepta[b]pyrrole 3'a (52%), along with the corresponding regioisomeric product 3''a(27%).¹⁸ Skipped diyne **1**'b, which was substituted with electronrich and -deficient aryl groups, led to an increase in the regioselectivity of the reaction (79:21) in favor of **3'b** (47%) over 3''**b** (13%). The major isomers 3'**a**,**b** were most likely formed as a consequence of the first intermolecular hydroarylation occurring at the more electron-rich triple bond of the divne (i.e., the one directly attached to the anisyl group). In contrast, the reaction of diyne 1'c bearing phenyl and ethyl groups was less efficient, leading to lower yields of 3'c (22%) and 3"c (17%), with very little regioselectivity.

Next, we investigated the effect of having a substituent on the pyrrole ring using methylated pyrroles 2b-d (Table 4).

Ph	Ph 1a	+ R // N H/R 2a–d	JohnPhosAu((5 mo toluene,	MeCN)SbF ₆ I %) 80 °C	Ph R // H/R Ph 3a, 6b-d
entry	pyrrole	R	time (h)	product	yield (%) ^b
1	2a	Н	3	3a	71
2	2b	1-Me	9	6b	25
3	2c	2-Me	22	6c	57
4	2d	3-Me	24	6d	19

Table 4. Reaction with Substituted Pyrroles^a

^{*a*}Reactions were conducted using a mixture of 1a, pyrrole (2 equiv), and the catalyst (5 mol %) in toluene (0.1 M) at 80 $^{\circ}$ C. ^{*b*}Isolated yields.

Although 2-methylpyrrole (2c) gave the corresponding cyclohepta[b]pyrrole 6c in acceptable yield (57%, entry 3), the *N*-methylpyrrole (2b) and 3-methylpyrrole (2d) gave much lower yields of the desired products (19–25%, entries 2, 4). These poor results were attributed to steric hindrance from the 1- or 3-methyl group during the first or second hydroarylation, as well as the unproductive nature of the first hydroarylation step at the 2-position of 2d.

A plausible mechanism for the reaction is shown in Scheme 2. As reported in our previous work,¹⁵ the cationic gold catalyst would activate one of the triple bonds of skipped diyne 1 to facilitate the first hydroarylation at the 2-position of pyrrole^{14f,15}

Scheme 2. Plausible Mechanism



to form intermediate **A**. The subsequent 7-*endo-dig* hydroarylation of **A** would proceed via intermediate **C** to give 1,6dihydrocyclohepta[b]pyrrole **3**. The remarkable high 7-*endo-dig* selectivity in the second hydroarylation can be attributed in part to the stabilization of the cation by the aryl group in positively charged complex $\mathbf{A} \cdot [\mathbf{A} \mathbf{u}^+]$,¹⁹ as well as the five-membered ring fusion in the transition states.²⁰ However, further studies are required to elucidate the observed regioselectivity.

Finally, we extended this cyclization to the synthesis of various cyclohepta[b]indoles (Table 5). Cyclohepta[b]indole derivatives have been reported to display a broad range of biological activities,¹⁷ prompting considerable interest in the development

Table 5. Reaction with Indoles^a

Ph	Ph 1a	R ¹ , , , , , , , , , , , , , , , , , , ,	PPh ₃ / (5 m toluene	$\begin{array}{c} \text{AuNTf}_2 \\ \text{ol } \%) \\ \hline \phi, 80 \ ^\circ \text{C} \end{array} \xrightarrow{\text{R}^1} \end{array}$	Ph N R ² Ph 8a-e
entry	indole	\mathbb{R}^1	\mathbb{R}^2	time (h)	yield (%) ^b
1	7a	Н	Н	15	74
2	7 b	OMe	Н	6	88
3	7 c	Br	Н	15	70
4	7d	CO ₂ Me	Н	24	56
5	7e	Н	Me	20	75

^{*a*}Reaction conducted using a mixture of **1a**, indole (2 equiv), and catalyst (5 mol %) in toluene (0.1 M) at 80 °C. ^{*b*}Isolated yields.

of efficient strategies for the synthesis of these compounds. We thus investigated the reaction of skipped diyne 1a with unsubstituted indole 7a in the presence of PPh₃AuNTf₂. Pleasingly, this reaction afforded the desired cyclohepta[*b*]indole derivative 8a in 74% yield (entry 1). Several other indoles 7b-e, including 5-methoxy, 5-bromo, 5-methoxycarbonyl, and *N*-methyl-indole also reacted smoothly to give the corresponding cyclohepta[*b*]indoles (entries 2-5). Among the indoles tested (7a-e), 5-methoxyindole (7b) was discovered to be the most reactive, affording the corresponding cyclohepta[*b*]indole 8b in 88% yield.

In summary, we developed a gold-catalyzed cascade reaction for the construction of the cyclohepta[b]pyrroles from skipped diynes and pyrroles. Remarkably, the second hydroarylation proceeded selectively in a 7-*endo-dig* manner. The use of an indole as a nucleophile in this reaction allowed for the direct synthesis of cyclohepta[b]indoles. Further studies toward the [5 + 2] cyclization of skipped diynes and pyrroles, including elucidating the regioselectivity of this reaction, are currently underway in our laboratory.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01759.

Experimental procedures, characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(18) The structures of the major isomers 3' were confirmed by the NOE between the pyrrole 3-H and the proton of R^1 group. For more details, see the Supporting Information.

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(20) In our related study,^{14b} a five-membered fusion favored 7-*endo-dig* cyclization, whereas a six-membered ring fusion favored 6-*exo-dig* cyclization.