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Authors: Shifa Zhu, Feng Wu, and Shiwei Lu

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COMMUNICATION

Regioselectivity-Switchable Intramolecular Hydroarylation of Ynone

Feng Wu,^a Shiwei Lu,^a and Shifa Zhu^{*a}

^a Key Lab of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China, E-mail: zhusf@scut.end.cn

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Abstract. The switchable catalytic approach to the regioselective intramolecular hydroarylation of ynone has been developed. When ZnI_2 was used as catalyst, the umpolung α -arylation of ynone was realized *via* an addition-elimination process of iodine ion to generate the *ortho*-phenanthrenequinone methide (*o*-PQM), which could be trapped by styrene to form benzo[*f*,*h*]chromenes through *hetero*-Diels-Alder reaction. While IPrAuCl/AgSbF₆ was applied, however, the β -arylation of ynone took place to afford benzocycloheptene-5-ones in moderate to excellent yields.

Keywords: ynone; catalyst selective synthesis; regioselective hydroarylation; phenanthrenequinone methides; umpolung

Ynones are easily available and highly useful molecules, which have often been applied as diverse building blocks to access to a wide range scaffolds.^[1] One of the most important reaction type of ynones is 1,4-Michael addition to provide the β -addition products (Scheme 1A).^[2] However, direct attack of the ynones at α -position is unfavored due to the inherent electronic characteristics. The classical Morita-Baylis-Hillman (MBH) reaction gives access to umpolung α addition product of enones.^[3] Similar umpolung process was also observed in the phosphine-catalyzed transformation of ynones (Scheme 1B).^[4] Since the pioneering work of Trost group,^[4a] umpolung α addition of ynone facilitated by phosphine with heteronucleophiles, such as O-H (alcohol, phenol),^[4b] N-H (amide, aniline, aromatic nitrogen heterocycle)^[4a,c-d] and S-H (thioalcohol)^[4e] were well established. As for carbon nucleophiles, the use of cyanide^[4f] and enolate^[4g] were also investigated. However, in the case of aromatic carbon nucleophiles without acidic proton, the aromaticity and lower nucleophilicity increase the reaction activation energy barrier. Furthermore, the protonation of the phosphonium zwitterion would be impeded in the absence of an acidic proton. Comparing with nucleophiles mentioned above, the umpolung α hydroarylation of ynone has not yet been reported.



Scheme 1. Background and challenges of this work.

Although some examples using aryl groups as nucleophiles in oxidative α -arylation of ynone *via* gold-catalyzed carbenoid transfer process were reported recently,^[5] the development of efficient regioselective α -hydroarylation of ynone is highly desirable and challenging.

Underpinned by the concept of catalyst selective synthesis,^[6] simple starting materials can rearrange into different scaffolds.^[7] As part of our continuous effects in developing practical transformations of vnones,^[8] we herein describe the successful intramolecular regioselective hydroarylation of 2arylphenyl alkynyl ketone with different aromatic nucleophiles (Scheme 1C). Employing ZnI₂ or cationic gold(I) as catalyst, both the α - and β -arylation product could be achieved selectively. From a synthetic pointof-view, the intramolecular α -hydroarylation of 2arylphenyl alkynyl ketone would afford the orthophenanthrenequinone methides (o-PQM), which is an important intermediate in the construction of benzofused O-heterocycles via hetero-Diels-Alder reaction. Until now, the o-PQM intermediate has very restricted substrate scope and has not been widely utilized since it was firstly reported in 1969^[9] owing to the lack of convenient precursors.[10]

The *o*-thienyl substituted alkynyl ketone **1a** was initially chosen to explore the hydroarylation (Table 1),

Table 1. Optimization of the regioselective cyclization. [a,b]

C	$\beta = \frac{4 - \text{Me-styrene}}{2a}$ $\beta = \frac{2a}{\text{Catalyst}}$ Sol., Temp. 12 h 1a		Ph 4-Tol Baa	+	S- 	Ph
Entry	Catalyst ([%])	Sol.	Temp. (°C)	3aa [%]	4a [%]	1a [%]
1	PtCl ₂ (5)	DCE	100	-	-	nr
2	$PdCl_{2}(10)$	DCE	100	-	-	nr
3	IPrAuBF ₄ (5)	DCE	25	-	70	0
4	In(OTf) ₃ (10)	DCE	80	-	-	nr
5	Zn(OTf)2 (20)	DCE	100	-	-	nr
6	Cu(OTf) ₂ (10)	DCE	80	-	-	0
7	ZnCl ₂ (20)	DCE	80	10	-	65
8	ZnBr ₂ (20)	DCE	80	32	-	-
9	ZnI ₂ (20)	DCE	80	41	-	-
10	ZnI ₂ (20)	PhMe	80	17	-	69
11	ZnI ₂ (50)	PhMe	100	37	-	42
12	ZnI ₂ (50)	PhH	100	52	-	0
13	ZnI ₂ (50)	PhCl	100	62	-	0
14	ZnI ₂ (50)	PhF	100	88	-	0
15	ZnI ₂ (30)	PhF	100	74	-	0
16 ^[c]	PPh ₃ AuBF ₄ (5)	DCE	80	-	-	nr
17 ^[c]	^t BuPhosAuNTf ₂ (5)	DCE	25	-	78	0
18 ^[c]	IPrAuSbF ₆ (5)	DCE	25	-	95	0

^{a)} The reaction was performed under N₂ for 12 h; **1a** (0.1 mmol) in 1 mL solvent, **2a**:**1a**=2:1(mol ratio). ^{b)} The yield and *dr* value were determined by ¹H NMR spectroscopy with dimethyl terephthalate as internal standard; the *dr* value of **3aa** was >95:5. ^{c)} Without **2a**.

given that S-containing fused heteroarenes with rigid planar backbones and extended π -conjugation have received tremendous attention due to their electronic and optical characteristics.^[11] The 4-Me-styrene 2a was applied as the 2π component to trap the unstable α -arylation product, o-PQM intermediate. Typical transition metal catalysts, which were reported efficiently for the hydroarylation of electron-neutral alkyne were tested first. PtCl₂ and PdCl₂ were ineffective in this reaction (entries 1 and 2). While the cationic gold(I) salt only afforded the β -arylation product 4a (entry 3). Other Lewis acid catalysts, such as $In(OTf)_3$, $Cu(OTf)_2$ and $Zn(OTf)_2$, were also tested, but only resulted in no reaction or complex mixtures (entries 4-6). To our delight, the desired product 3aa was obtained in 10% NMR yield when ZnCl₂ was used as catalyst (entry 7). During the evaluation of zinc halides, a significant improvement in the yield of 3aa was observed with ZnI₂ (entry 9). A higher yield based on recovered starting material (17%, brsm: 55%) was obtained when using PhCH₃ as solvent (entry 10). The efficiency of the reaction can be promoted by increasing the reaction temperature (100 °C) and the catalyst loading (entry 11). Solvent effects were further revealed using aromatic solvents with different electronic effects (entries 11-14). The highest yield (88%) was achieved in PhF solvent. Attempts to

Table 2. Substrate scope of the α -arylation/[4+2] reaction.



x = 5, 3na, 46% (60.40) x = 5, 3pa, 97% (91.9) $R^1 = Me$, $R^2 = MeO$, 3sa, 85% (92.8) x = 0, 3aa, 74% (87.13) x = 0, 3qa, 82% (89.11) $R^1 = H$, $R^2 = H$, 3ta (n.r.) Reaction condition: **1** (0.2 mmol), **2** (0.4 mmol), 50 mmol% ZnI_2 in 2 mL PhF were stirred at 100 °C. Isolated yield. The dr value were determined by ¹H NMR of crude products. Unless otherwise noted, the dr value was >95:5.

decrease the loading of ZnI_2 indicated that 50 mol% of catalyst was necessary to achieve superior performance (entries 14-15). Furthermore, the optimal condition of the β -arylation was also identified (see Supplementary information).

Having optimized reaction conditions in hand, we then explored the reaction scope of the α -arylation (Table 2). Styrene derivatives with different electrondonating and -withdrawing groups could be used as effective 2π components to react with the proposed *o*-PQM intermediate to afford the fused O-heterocycles 3aa-af in 62-85% yields. A wide range of benzo[*h*]thieno[3,2-*f*]chromenes possessing both electron-donating as well as -withdrawing groups could be conveniently assembled in 65-95% yields (**3ba-ea**). It's remarkable that the electron donating 4-MeO-C₆H₄ at the alkyne terminal provided the corresponding products in a reduced yield and relatively poor dr value (3da). Similarly, the negative effects of the electron-rich 3-thienyl and 2-naphthyl were also observed in products **3fa** (52%, dr = 85:15) and **3ga** (46%, dr = 92.8). Substrates bearing electrondonating groups on the nucleophilic thiophene rings (Ar^2) underwent effectively to corresponding products

(3ia and 3ja), while the substrate with an electrondeficient thiophene resulted in no conversion (3ka). Thienylene-fused (Ar¹) ynone was compatible with this reaction as well, which provided the product 3la, albeit with diminished yield (28%). The generality of this novel method to the α -arylation was also demonstrated by the displacement of the 2-thienyl to other O- or S- containing heteroarenes (**3ma-ga**). The hydroarylation of the 3-thienylphenyl alkynyl ketone took place regiospecifically at the 2-position of the thienyl group to afford the benzo[h]thieno[2,3f]chromene (**3ma**). Both benzothiophene and benzofuran substituted (Ar²) ynones exhibited high reactivity, and the corresponding products 3na-qa were obtained in 46-97% yields. The relatively poor drvalue were obtained in the case of 2-substituted benzothiophene and benzofuran (3na and 3oa). Finally, vnones with substituted phenyl rings (Ar^2) were also investigated and the α -arylation happened at the lesshindered ortho position of the 1,1'-biphenyl bonds to afford 3ra and 3sa in yields of 54% and 85%. The electron-donating MeO- in Ar² was proven necessary, given that only the starting materials were recovered in the attempt for the synthesis of **3ta**.

With the advent of the successful regioselective α arylation/[4+2] cascades, we next focused on the β arylation of ynones (Table 3). It is relatively easier for β -arylation than α -arylation, presumably due to the inherent electronic characteristics. The reaction could be easily extended to different substrates and provided an array of cyclohepten-5-ones in 50-96% yields (**4a**-**s**). It seems the electronic properties of Ar¹ and R in the substrates have little effect on the reaction results, giving the desired products in 71-93% yields (**4a**-**g**). It is notable that the alkyl-substituted ynone could be

Table 3. Substrate scope of the β -arylation reaction.



Reaction condition: **1a** (0.2 mmol), IPrAuCl/AgSbF₆ (2% mmol) in 2 mL DCE were stirred at 25 $^{\circ}$ C; Isolated yield.

served as an effective substrate, leading to the product **4h** in 60% yield. For the nucleophilic Ar^2 group, substituted-thioenyl, benzothioenyl, benzofuran, and electron-rich phenyl group were all well applicable for this protocol to provide the corresponding products in 50-96% yields (**4i-s**). However, substrate with electron-neutral Ar^2 (**4t**) turned out to be inactive as it performed in the α -arylation process.



Scheme 2. Derivatization reactions of product 4a. Reaction conditions: (a) 2-bromo-1,1'-biphenyl, *n*-BuLi, THF, -78 °C-rt; (b) AcOH, 100 °C.

To highlight the synthetic utility of β -arylation products, several derivatizations of **4a** were performed (Scheme 2). The reduction of the carbonyl group generated cycloheptatriene **5a** (94%). Bromination of product **4a** with NBS afforded the double bromination product **5b** (63%). The ring expansion with TMS-CHN₂ provided practical access to cyclooctrienone **5c** (64%). Finally, the *spiro*-cyclooctriene/fluorene system **5d**, which was largely applied in OLED materials,^[10] was assembled in a two-step transformation (72%).

Lastly, we turned our attention to investigate the mechanism of the umpolung α -arylation. The *hetero*-Diels-Alder dimerization of o-PQM gave convincing evidence of the formation of corresponding intermediates.^[9] Indeed, the dimerization product **6a** was obtained when ynone 1a was treated with ZnI_2 in the absence of styrene (Scheme 3A). It was noticed that 50 mol% ZnI₂ was necessary to efficiently promote this α -hydroarylation, which indicates that the iodine ion might participate in the reaction. This proposition is pursued with ynones during the development of halo aldol reactions^[13], which were typically mediated by Lewis acids. Toward this, substrate **1a** was subjected using $Zn(OTf)_2$ as catalyst and NaI (1.0 equiv) as iodine source (Scheme 3B). The desiring α hydroarylation/[4+2] product was obtained in 79% yield, while the absence of either Zn(OTf)₂ or NaI only led to recovery of 1a. These results indicated the combination of Zn(II) and iodine ion was crucial for the α -hydroarylation. Inspired by the halo aldol reaction,^[13] we proposed the iodine ion might act as an umpolung nucleophile to form an allenoate intermediate^[5a]. Given the HOAc/NaOAc buffer was employed to facilitate the protonation in Trost's original report,^[4a] we envisioned that the proposed allenoate could also be protonated by HOAc (Scheme



Scheme 3. Mechanistic studies.

3C). The treatment of **1a** under ZnI_2 and HOAc resulted in complex mixture of products, only trace amount of dimer **6a** was identified. In order to rule out the interference of the nucleophilic moiety, simple ynone **1a'** was adopted and the desired β -iodine vinyl ketone **7a'** was achieved in 29% yield, which supports the formation of the allenoate **1a-I** during the reaction.^[14]

Based on the above experimental evidence, a plausible mechanism is proposed in Figure 1A. Initial Lewis acid catalyzed iodo-Michael addition at the β position gives the allenoate intermediate 3-I. Then the 6π cyclization^[15] undergoes followed by isomerization to form intermediate 3-III. Finally, the elimination of iodine from 3-III affords the formal α -arylation product, o-PQM intermediates, and regenerates iodine ion. The cis diastereoselective outcome could be attributed to the secondary orbital overlap between the aryl group of styrene and the π -system of *o*-PQM intermediates.^[16] The relatively poor *dr* value found in substrates the case 2-substitued of with benzothiophene and -furan (3na and 3oa) was due to the deflective distribution to Z isomer owing to the steric interaction between the R group and the nucleophilic Ar (Figure 1B). Base on the same steric



Figure 1. Proposed mechanism.

interaction, the regioselectivity at less hindered positions when using phenyl nucleophiles (**3ra** and **3sa**) is also explained (Figure 1C).

In summary, we have established a divergent catalytic approach for the regioselective hydroarylation of ynones. For the umpolung α -arylation process, ZnI₂ was served as both Lewis acid and iodine source to facilitate the formation of *o*-PQM intermediates *via* an addition/elimination process of iodine ion; the resulted *o*-PQM intermediate were then trapped by styrene to yield [4+2] products **3**. While the cationic gold(I) salt was used as catalyst, the 7-endodig cyclization^[17] was achieved to afford cyclohepten-5-ones **4** in good to excellent yields.

Experimental Section

General Experimental Procedure for the α -arylation/[4+2] reaction (3aa-3sa):

In a Schlenk tube with a magnetic bar was added ZnI_2 (50 mol%), PhF (2mL), substrates (0.2mmol) and styrene (0.4 mmol) respectively. The mixture was stirred at 100 °C until the starting materials was completely consumed monitored by TLC. After that, the solvent was evaporated, and the residue was purified by flash column chromatography to afford the pure products.

General Experimental Procedure for the β -arylation reaction (4a-4s):

In a Schlenk tube with a magnetic bar was added 2 mol% IPrAuCl/AgSbF₆ and 2 mL DCE. After the mixture was stirred for 5 min, substrates (0.2mmol) was added. The mixture was stirred at 25 °C until the starting materials was completely consumed monitored by TLC. After that, the solvent was evaporated, and the residue was purified by flash column chromatography to afford the pure product.

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Feng Wu, Shiwei Lyu and Shifa Zhu*

