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Light-enabled, AlCl₃-catalyzed regioselective intramolecular nucleophilic addition of non-nucleophilic alkyl to alkyne

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Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Light-enabled, AlCl₃-catalyzed regioselective intramolecular nucleophilic cyclization of alkyne using non-nucleophilic alkyl as the nucleophile was reported. Upon photoexcitation, *o*-alkylphenyl alkynyl ketones can be transferred into (*E*)-photoenols. Thus, a nucleophilic methylene is formed from the non-nucleophilic alkyl. AlCl₃ catalyst can stabilize (*E*)-photoenol intermediate and facilitate further intramolecular nucleophilic cyclization. DFT calculations indicated that the AlCl₃-catalyzed cyclization is the regioselectivity determining step.

Nucleophilic addition of alkyne is one of the well-studied reactions,¹ as it provides a convenient way to synthesize functionalized alkenes. The general activation mode is summerized in Scheme 1A. The alkyne moiety normally requires the coordination with Lewis acid or $\boldsymbol{\pi}$ acid to increase its electrophicility.² Upon activation, a suitable nucleophile can attack the alkyne, forming an alkene intermediates. This is normally the rate-determining step (RDS) of the whole reaction.³ Finally, quenching by electrophiles gives the corresponding multi-substituted alkene products. Nucleophile plays an essential role in this reaction process. Nucleophiles can be generally divided into three types: (1) σ type, like NaBH₄, lithium reagents, Grignard reagents, etc.; (2) π type, like enol ethers, alkenes, aromatic rings, etc.; (3) lone pair electron type, like ROH, RNH₂, RSH, etc.⁴ Alkyls are not considered as a nucleophile compared with those typical examples due to its lack of any nucleophilic atoms. To the best of our knowledge, alkyls have not been reported as a nucleophile in the addition to alkynes.

Organic photoreactions normally proceed via excited state of reactants,⁵ which shows different reactivity toward thermal reactions at ground state. One example is the photochemistry of *o*-alkylaromatic ketones (Scheme 1B).⁶ At the ground state, the pKa of the benzylic proton of the substrate is about 27 (referenced by phenyl(*o*-tolyl)methanone), indicating the benzylic H is non-acidic.⁷ Thus, the benzyl group can be rationalized to be a rather weak nucleophile. At the (A) Classic Lewis acid-catalyzed nucleophilic addition of alkyne



normal alkyl has NO nucleophilicity

(B) Generation of enol from non-nucleophilic alkyl



(C) This work: AICI₃-catalyzed nucleophilic cyclization of non-nucleophilic alkyl



photoexcited state of o-alkylaromatic ketones, 1,5-H transfer occur via the triplet hyperface. Further rotation and intersystem-crossing (ISC) results in the (E)-photoenols.⁸ Thus, the non-nucleophilic benzylic C(sp³) is transformed into a nucleophilic C(sp²), which has been proved useful in many classic enol type reactions.9 Our previous study also showed that the similar strategy could achieve 6π -photocyclization of non-6π substrates.¹⁰ With continued interest in photo-induced cyclization reactions, we questioned whether this photoenol can be used in more challenging nucleophilic addition to alkynes. Specifically, if o-alkylphenyl alkynyl ketones are employed as potential substrates, the in situ generated photoenols may attack the activated alkyne (Scheme 1C). Herein, we wish to report our recent results in AlCl₃-catalyzed regioand stereoselective intramolecular nucleophilic cyclization of o-alkylaromatic alkynyl ketones.

The initial attempt was carried out using *o*-tolyl 4methoxyphenylacetylenyl ketone (**1a**) as the model substrate. A series of Lewis acids were tested and AlCl₃ gave 12% yield of *5exo-dig* product (**2a**) (Table 1, entries 1-4). Notably, 6-*endo-dig* product (**3a**) was also formed. The regioselectivity of **2a** and **3a** was 12:1 for AlCl₃ (Table 1, entry 4). Considering the high

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Electronic Supplementary Information (ESI) available: Experimental procedures and NMR copies. See DOI: 10.1039/x0xx00000x

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regioselectivity, AlCl₃ was chosen as the optimal catalyst. Solvent screening revealed that 1,4-dioxane gave the highest regioselectivity and a promising yield (Table 1, entries 4-9). To further accelerate the *5-exo-dig* cyclization, higher temperatures were tested (Table 1, entries 10-12). The reaction at 60 °C showed higher yield than that of room temperature (Table 1, entry 10). Further raising the temperature to 80 °C resulted in 88% yield and >20:1 regioselectivity (Table 1, entry 11). At a higher reaction temperature of 100 °C, the yield slightly decreased (Table 1, entry 12). Decreasing the catalyst loading to 5 mol% gave 92% of 2a with excellent regioselectivity (Table 1, entry 13). Notably, only (E)-product was formed in the above reactions, showing the high stereoselectivity of the conversion. Control experiments without AlCl₃ showed that 2a can be formed by simple heating, but with a lower efficiency and poorer regioselectivity (Table 1, entry 14). Further mechanistic studies indicated that AlCl₃ could stabilize the (E)-photoenol intermediate and facilitate the nucleophilic addition to form 2a, and unexpected reaction pathway could be inhibited (vide infra). Light was proved to be essential for the formation of 2a (Table 1, entry 15). Thus, conditions of entry 13 (1 and 5 mol% of AlCl₃ in 1,4-dioxane (0.02 M) irradiated by purple LED under argon atmosphere at 80 °C for 72 h) was chosen as the optimized conditions for further studies.

With optimized conditions in hand, the substrate scope of this reaction was next examined (Scheme 2). The substrate scope on R^1 group was first studied. Aryl groups at R^1 were tried. Strong electron-donating groups (EDGs) substituted aryl, such as methoxy (**2a**) and acetoxy (**2b**), showed good reactivity. Aryl groups with weak EDGs, such as *tert*-butyl (**2c**) and methyl (**2d**), were also tolerated in this reaction. Substrates with 4-F (**2f**), 4-

Table 1 Screening of the conditions ^a					
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Entry	LA (mol%)	Solvent	<i>Т</i> (°С)	2a (%)	2a:3a
1	La(OTf) ₃ (10)	THF	rt	15 (6) ^b	2:1
2	Zn(OTf) ₂ (10)	THF	rt	12 (6) ^b	3:1
3	Sc(OTf) ₃ (10)	THF	rt	6 (16) ^b	6:1
4	AlCl ₃ (10)	THF	rt	12 (31) ^b	12:1
5	AlCl ₃ (10)	EA	rt	23 (26) ^b	3:1
6	AICI ₃ (10)	CH₃CN	rt	24 (43) ^b	5:1
7	AlCl ₃ (10)	DCM	rt	17 (36) ^b	6:1
8	AlCl ₃ (10)	Toluene	rt	47 (6) ^b	9:1
9	AlCl ₃ (10)	1,4-dioxane	rt	45 (40) ^b	>20:1
10	AlCl ₃ (10)	1,4-dioxane	60	64	>20:1
11	AlCl ₃ (10)	1,4-dioxane	80	88	>20:1
12	AlCl ₃ (10)	1,4-dioxane	100	82 (7) ^b	>20:1
13	AlCl ₃ (5)	1,4-dioxane	80	92 (90) ^c	>20:1
14		1,4-dioxane	80	65	5:1
15 ^d	AICl ₃ (5)	1,4-dioxane	80	n.r. (85)	

^{*a*} A solution of **1a** (0.2 mmol) and LA in anhydrous solvent (10 mL) was irradiated by purple LED under argon atmosphere for 72 h. Yield, recovery, regio- and stereoselectivity was determined by ¹H NMR analysis (400 MHz) of the crude reaction mixture, using CH₂Br₂ (0.2 mmol) as the internal standard; ^{*b*} Recovery of **1a**; ^{*c*} Isolated yield of **2a**; ^{*d*} Dark reaction. n.r. = no reaction.

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Cl (2g) and 4-Br (2h) aryl also gave good yields. Strong, electrone withdrawing groups (EWGs), like methological borg (2i), for any (2j) and trifluormethyl (2k), at the aryl group slightly decreased the yields. To further expand the scope at R¹, function groups other than aryl were also tried. TMS-bearing substrate 2l gave a moderate yield, probably due to the reactive nature of TMS under Lewis acidic conditions. Alkyl groups, like *n*-butyl (2m), cyclopropyl (2n) and cyclohexyl (2o), were also tried and gave good yields. Next, modifications at R² were explored. Strong EDG (2l and 2m), weak EDG (2n) and halogen (2o and 2p) at R² did not affect the reaction. Substrates with modifications on both R¹ & R² were also synthesized and tried. Di-EDG (2q),



Scheme 2 Substrate scope.

Conditions: **1** and 5 mol% of AlCl₃ in 1,4-dioxane (0.02 M) irradiated by purple LED under argon atmosphere at 80 °C for 72 h. Isolated yield was reported. The *E:Z* ratio was calculated by isolated yield.

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EDG/EWG (**2r**-**t**), EWG/EDG (**2u**) and tri-substituted (**2v**) reactants worked well. Notably, neither (*Z*)- nor *6-endo-dig* products were detected for the substrates tested above, which highlighted the high regio- and stereoselectivity when $R^3 = H^{.11}$ Finally, the scope of R^3 was studied. Ethyl (**2aa** & **2ad**), isopropyl (**2ab** & **2ae**) and benzyl (**2ac**) were installed at *ortho* position forming the corresponding products in excellent yields. However, with the increasing of the steric hindrance, the *E:Z* ratio decreased to ca. 1:1.¹²

After the substrate scope investigation, mechanistic studies were next carried out. UV-Vis spectrum indicated that AlCl₃ could enhance the absorption of **1a**, but led to no appreciable wavelength change (for the spectrum, see Figure S1). Thus, upon the light irradiation, AlCl₃-1a complex is more likely to absorb light to be excited than the un-coordinated 1a. Next, DFT calculations of the intermediates and transition states energies were computed, and the results were shown in Scheme 3. First, the AlCl₃-coordinated (E)-photoenol (5) showed lower energy (-2.6 kcal/mol) than the uncoordinated (E)-photoenol. This result indicated that the AlCl₃ not only serves as a Lewis acid to activate the alkyne, but also stabilizes the (E)-photoenol intermediate. This calculated energetic result also met the experimental observation without AlCl₃ catalyst (Table 1, entry 14). As the unstabilized (E)-photoenol might undergo unexpected decomposition leading to lower yield, AlCl₃ could prevent (E)-photoenol from decomposition and facilitate the following cyclization to give higher yield. Next, the transition state energy surfaces were calculated to explain the regioselectivity between 5-exo-dig product and 6-endo-dig product. Compared with 6-endo-dig pathway, 5-exo-dig pathway has a much lower activation energy ($\Delta\Delta G = -7.7$ kcal/mol). The conformation of AlCl₃-coordinated (E)-photoenol (5) is also more similar with 5-exo-dig transition state (TS-5)

than *6-endo-dig* transition state (**TS-6**). Both energy barrier and the conformation indicated **TS-5** is the favored transition state than **TS-6**. Thus the regioselectivity originates from this cyclization process, leading to the *5-exo-dig* product **2** as the predominant product.

Deuterium labeling and KIE experiments were also carried out to understand the H atom transfer process in this reaction. $1a-d_3$ was synthesized and subjected to the standard conditions. 62% of 2a-d was formed with 26% of $1a-d_3$ recovered. ¹H NMR analysis indicated that the deuterium in 2ad located at both benzylic position and alkenyl position (Scheme 4). The D at alkene strongly suggested that an intramolecular protolysis occurred in the reaction process. The deuterium content difference between benzylic position and alkenyl position might be due to the intermolecular protolysis process, which could bring H to the alkene position. 26% of $1a-d_3$ was recovered with 82% deuterated incorporation. The deuterium content loss (both in recovered $1a-d_3$ and benzylic position of 2a-d) could be reasoned in H-D exchange in 1,4-biradical intermediate and (Z)-photoenol (vide infra) with solvent or moisture in the solvent. (for detailed discussion, see Figure S3 in ESI)^{8b, 13} This could also be an evidence for occurrence of Norrish Type II process of 1a.10 Kinetic isotopic experiment showed k_H/k_D = 1.3, indicating that H abstraction process is not the rate-determining step.

With the information above and literature precedent, a possible reaction pathway was proposed in Scheme 5. Coordination of AlCl₃ to the alkyne moiety of **1** gives complex **3**.^{2a, b} Then, the photoexcitation and ISC of **3** results in **3*** (T₁). 1,5-Hydrogen transfer affords 1,4-biradical **4** as the key intermediate. **4** undergoes rotation and ISC affording AlCl₃-coordianted (*E*)-photoenol **5**.^{8b} With the activation of AlCl₃,



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Scheme 3 DFT calculations of the energy surface.



Scheme 4 Deuterium labelling and KIE experiments



intramolecular nucleophilic addition of **5** yields *5-exo-dig* intermediate **6** with high regioselectivity. Subsequent inter- or intramolecular protolysis of **6** finally yields **2**. On the other hand, the direct ISC of 1,4-biradical **4** forms (*Z*)-photoenol. The (*Z*)-photoenol is conformationally-favored for another 1,5-H shift to return to the starting complex **3**.^{8b} The H-D exchange of the hydroxyl in 1,4-biradical **4** and (*Z*)-photoenol accounts for the deuterium loss in deuterium labelling experiments.

In conclusion, we successfully achieved a regioselective intramolecular nucleophilic addition of a non-nucleophilic carbon to alkyne. With the irradiation of purple LED, the non-nucleophilic methyl in *o*-alkylphenyl alkynyl ketones were transferred into a nucleophilic (*E*)-photoenol. Under the catalysis of AlCl₃, intramolecular nucleophilic cyclization occurred with high regioselectivity. Mechanistic studies indicated that AlCl₃ showed triple functions: enhancing absorption, stabilizing (*Z*)-photoenol and increasing selectivity. Further photophysics studies and application of the strategy are ongoing in our group.

We greatly acknowledge the financial support from Shanghai Science and Technology Committee (18DZ1201605).

Conflicts of interest

There are no conflicts to declare.

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View Article Online DOI: 10.1039/D0CC04636A

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