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Metal/Benzoyl Peroxide (BPO)-Controlled Chemoselective Cycloisomerization of (*o*-Alkynyl)phenyl Enaminones: Synthesis of *α*-Naphthylamines and Indeno[1,2-*c*]pyrrolones

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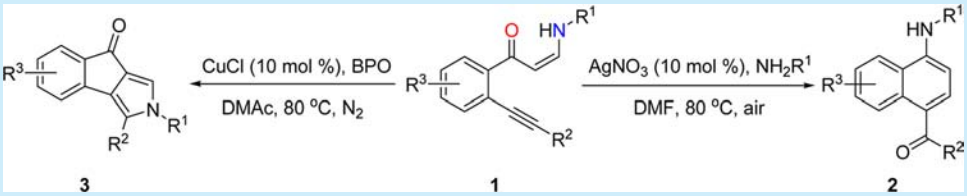
Supporting Information

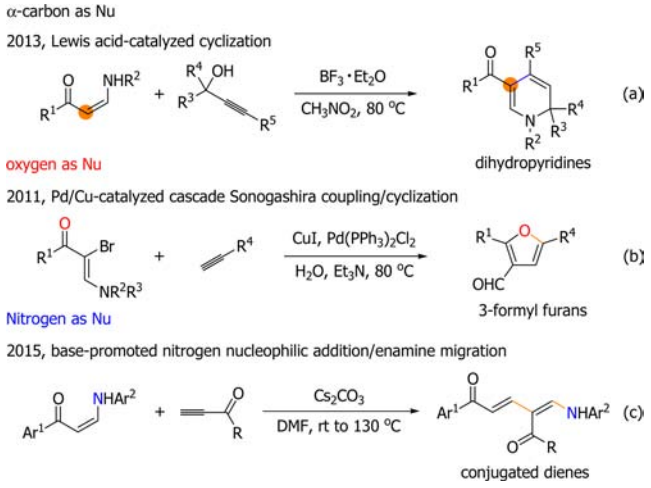


ABSTRACT: Synthetic methods involving chemoselective tandem reactions for the synthesis of *α*-naphthylamines and indeno[1,2-*c*]pyrrolones starting from (*o*-aklynyl)phenyl enaminones are described. When reactions were carried out in *N*,*N*-dimethylformamide (DMF) using a $AgNO_3$ catalyst, *α*-naphthylamines were obtained in up to 89% isolated yields within 2 h. Whereas indeno[1,2-*c*]pyrrolones were produced in high isolated yields in the presence of benzoyl peroxide (BPO) and CuCl catalysis.

Aromatic compounds containing nitrogen are of great importance and abundance in nature.[1] Among them, arylamines are valuable building blocks and play important roles as intermediates in synthesis of pigments, agrochemicals, and pharmaceuticals.[2] Substituted pyrroles as key structural units are present in many bioactive compounds, natural products, and functional materials.[3] The development of convenient and efficient methods for the synthesis of arylamines and pyrrole derivatives has attracted considerable attention. In the preparation of arylamines, the transition-metal-mediated amination of aryl halides with amines and amides via C(aryl)−N bond-forming processes has recently been regarded as a powerful tool.[2c,4] Other strategies for the synthesis of naphthylamines includes the simultaneous construction of aromatic rings. Recently, Wen's group reported Cu-catalyzed aminobenzannulation for the synthesis of *α*-naphthylamines.[5] In 2009, Liang's group developed a one-pot synthesis of *β*-naphthylamines via Pd-catalyzed aminobenzannulation.[6] Lu's group disclosed an intramolecular addition to a cyano group initiated by nucleopalladation of alkynes to construct *β*-naphthylamines.[7] The synthetic methods to pyrrole derivatives mainly include the classical approaches, modern transition-metal-mediated cyclizations, multicomponent reactions, et al.[8]

Chemoselectivity in organic synthesis is of great value, and controlling the selective reaction of one specific functional group among several others is challenging.[9] Enaminones as versatile building blocks have several nucleophilic centers, such as the *α*-carbon, oxygen, and amino group. They are widely employed in synthetic organic chemistry, such as the preparation of heterocycles, including alkaloids, *α*- and *β*-amino acids, peptides, and other synthetically relevant compounds.[10] We have disclosed novel protocols for the selective synthesis of nitrogen- or oxygen-containing cyclic and/or acyclic compounds starting from enaminones by variation of catalysis systems, ensuring an *α*-carbon, oxygen, or amino group as nucleophilic centers (Scheme 1).[11] As part of our continuing efforts to explore enaminone chemistry, we envision that it might be possible to prepare different heterocycles starting from exactly the same substrates by

Scheme 1. Previous Work



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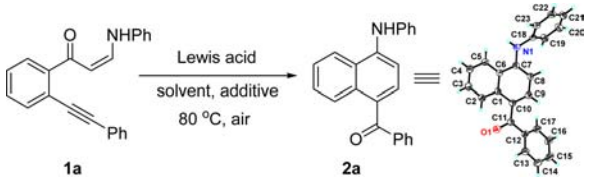
tuning the reaction parameters. It is of great value from the point of view of drug discovery, where rapid access to a broad diversity of skeletal classes is required. Herein we report metal-controlled selective reactions of *o*-alkynylphenyl enaminones for the synthesis of α-naphthylamine and indeno[1,2-*c*]-pyrrolone derivatives by modifying reaction conditions.

We started our study by investigating the reaction of the enaminone **1a** in the presence of different silver salts in dimethylformamide (DMF) at 80 °C under air (Table 1, entries 1−8). The results were not so promising when Ag_2SO_4 (20 mol %, 6 h, 38% yield) and AgOTf (20 mol %, 5 h, 34% yield) were employed in this system (Table 1, entries 1 and 2). When $AgNO_3$ was applied, the yield of **2a** was increased to 69%, and the same yield could be achieved with a reduced amount of $AgNO_3$ (10 mol %) (Table 1, entries 3 and 4). The yield of **2a** was decreased to 52% even after 17 h when the reaction was carried out at room temperature (Table 1, entry 5). Moderated yields were obtained using $AgClO_4$ (58%), $AgSbF_6$ (53%), and $AgPF_6$ (43%) in 3.5 h (Table 1, entries 6−8). In addition, **2a** was obtained as a yellow solid and characterized by X-ray crystallography.

Table 1. Screening of Reaction Conditions[a]



entry	catalyst (mol %)	solvent	additive (equiv)	time (h)	yield (%)[b]
1	Ag_2SO_4 (20)	DMF	–	6	38
2	AgOTf (20)	DMF	–	5	34
3	$AgNO_3$ (20)	DMF	–	6	69
4	$AgNO_3$ (10)	DMF	–	6	68
5	$AgNO_3$ (10)	DMF	–	17	52[c]
6	$AgClO_4$ (10)	DMF	–	3.5	58
7	$AgSbF_6$ (10)	DMF	–	3.5	53
8	$AgPF_6$ (10)	DMF	–	3.5	43
9	$AgNO_3$ (10)	DMAc	–	5	trace
10	$AgNO_3$ (10)	toluene	–	5	trace
11	$AgNO_3$ (10)	dioxane	–	5	trace
12	$AgNO_3$ (10)	DMF	HOAc (2.0)	6	68
13	$AgNO_3$ (10)	DMF	$PhNH_2$ (2.0)	2	86
14	$AgNO_3$ (10)	DMF	$PhNH_2$ (3.0)	2	79
15	$AgNO_3$ (10)	DMF	$PhNH_2$(1.0)	2	80
16	$AgNO_3$ (5)	DMF	$PhNH_2$ (2.0)	2	73
17	$AgNO_3$ (10)	DMF	$PhNH_2$ (2.0)	2	86[d]

[a]Unless otherwise noted, the reactions were carried out at 80 °C under air. [b]Isolated yield. [c]At room temperature. [d]Under N_2.

Next, the solvents and additives were screened with 10 mol % of $AgNO_3$ at 80 °C under air. Solvents, such as DMAc, toluene, and 1,4-dioxane gave only a trace amount of the desired **2a** (Table 1, entries 9−11). HOAc (2.0 equiv) as an additive had no influence on the reaction outcome, whereas $PhNH_2$ (2.0 equiv) shortened the reaction time and increased the yield of **2a** dramatically (Table 1, entries 4 vs 13). Then, when the amount of $PhNH_2$ was examined, it was found that either an increase or a decrease in the amount of $PhNH_2$ resulted in lower yields of **2a** (Table 1, entries 14 and 15). By lowering the amount of $AgNO_3$ to 5 mol %, the yield of the desired naphthylamine was reduced to 73% (Table 1, entries 13 vs 16). When the reaction was performed under N_2, **2a** was obtained in 86% yield (Table 1, entry 17). So, the optimal reaction conditions for the preparation of **2a** included 10 mol % of $AgNO_3$ as the catalyst and 2.0 equiv of the corresponding arylamine as the additive at 80 °C in DMF under air.

With the optimized reaction conditions in hand, the scope of this reaction was investigated on a series of enaminones with different substituents of electronic properties (Figure 1). First,

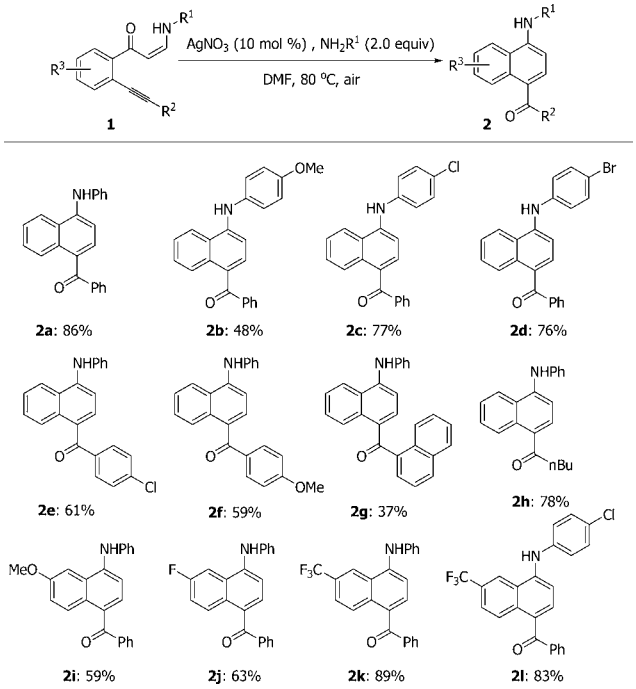


Figure 1. Synthesis of α-naphthylamines. Unless otherwise noted, the reactions were carried out in DMF with 2.0 equiv of corresponding NH_2R^1 using 10 mol % of $AgNO_3$ at 80 °C under air. Isolated yield.

enaminones (**1b−d**) with different substituents on nitrogen were examined and good to high yields of the corresponding products were obtained, in which enaminone (**1b**) with a *p*-methoxyphenyl group on nitrogen gave a lower yield than that with electron-withdrawing groups (**2b**: 48% vs **2c**: 77%, **2d**: 76%). Second, the effects of substituents on the triple bond terminus were investigated. Enaminones (**1e−h**) both with aryl or alkyl groups were compatible in the reaction and produced the desired naphthylamines in moderate to good yields, respectively (Figure 1, **2e−2h**). It is noteworthy that *n*-butyl offered a good result (**2h**, 78% yield). A bulky group such as 1-naphthyl resulted in a lower yield of the desired product (**2g**, 37% yield). Lastly, the electronic effect of R^3 was examined (**2i−2l**). An electron-donating group (−OMe) gave a good yield of desired **2i**. Enaminones with a highly electron-withdrawing group ($-CF_3$) provided much better yields of the corresponding α-naphthylamine (**2k**, 89%; **2l**, 83%).

In order to clarify the reaction mechanism, several controlled reactions were performed. First, the reaction of **1a** was carried out with 10 equiv of $H_2{}^{18}O$ under optimized conditions to check the oxygen source of α-naphthylamine **2a** (Scheme 2a). None of the product containing ^{18}O was detected, indicating that the carbonyl oxygen of the final product did not come from H_2O. The cross-reaction with different arylamines was also investigated (Scheme 2b). When the reaction of **1a** was

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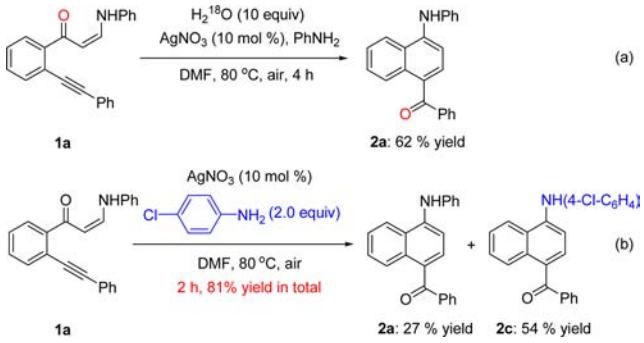
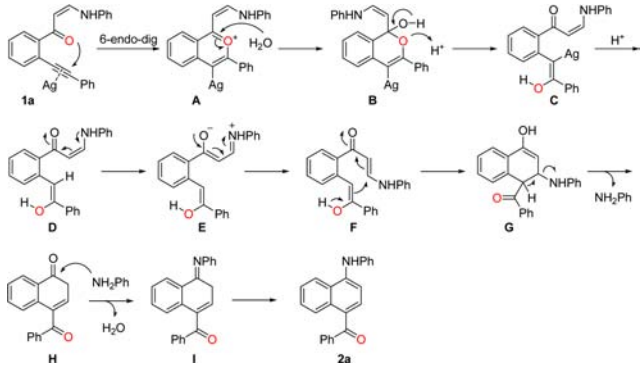
Scheme 2. Reaction Mechanism Investigation



carried out under the standard reactions with 4-chloroaniline (2 equiv) as the additive, a mixture of two products with different substituted amino groups (**2a**, 27%; **2c**, 54%) was obtained. The ratio of **2a**:**2c** was 1:2 which was the same as the ratio of free arylamines in the system. It indicated that the amino group of α-naphthylamine came from the free arylamine in this reaction system, and the amino moiety of enaminone was transformed to free amines during the reaction process.

Based on our results and reported work,[12] a mechanistic proposal is outlined in Scheme 3. The alkynyl moiety of **1a** first

Scheme 3. Plausible Mechanisms



is activated by silver and attacked by the oxygen of the carbonyl group yielding an oxonium ion as intermediate **A**. Nucleophilic attack of H_2O to the carbonyl group followed by ring opening via protonation gives intermediate **C**. Protonolysis of **C** provides **D**. *Z*/*E* isomerization gives **F**. Intramolecular annulation of intermediate **F** forms six-membered ring **G**. Free aniline relieved from intermediate **G** attacks the newly formed carbonyl group to give imine **I**, followed by aromatization to give desired product **2a**.

Considering the interesting structure of substrate **1a**, we envisioned that different modes of reactivity may be accessed by modification of reaction conditions, such as the addition of oxidants. Thus, $K_2S_2O_8$ (1.5 equiv) was added to the reaction system under the aforementioned optimal reaction conditions. Unfortunately, a complex reaction mixture was detected. Interestingly, when CuCl was used instead of $AgNO_3$, a new product of indeno[1,2-*c*]pyrrolone **3a** was generated selectively over **2a**. To improve the yield of **3a**, different reaction parameters, such as temperature, solvents, and oxidants, were screened (see Supporting Information, Table S1). It was found that the best result for the synthesis of **3a** was to use 10 mol % CuCl in combination with 1.2 equiv of benzoyl peroxide (BPO) as the oxidants and DMAc as the solvent. Structural identification of **3a** was carried out by X-ray crystallography.

Thus, the scope of the reaction was explored using various (*o*-alkynyl)phenyl enaminones with different electronic properties (Figure 2). This method is so efficient that reactions could

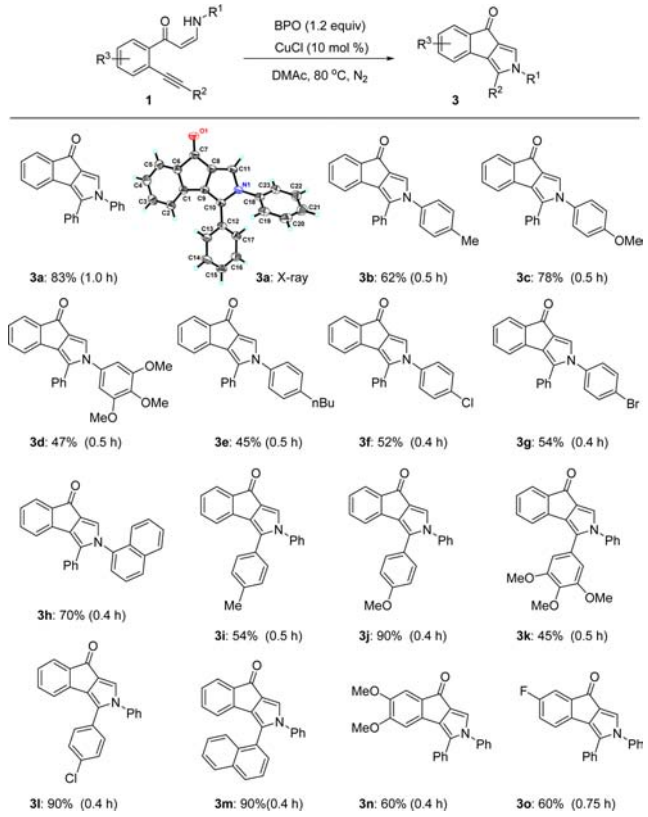


Figure 2. Synthesis of indeno[1,2-*c*]pyrrolones. Unless otherwise noted, the reactions were carried out using 1.2 equiv of BPO with 10 mol % of CuCl in predried DMAc at 80 °C under N_2. Isolated yield.

complete in 1 h with all of the substrates screened. For the substituents R^1 on the nitrogen, substrates with both electron-withdrawing and -donating groups on the aryl ring were suitable for the reaction, offering the desired products (**3a**−**3h**) in yields of 45−83%. Among which electron-rich aryl groups gave slightly higher yields (**3b**, 62% yield; **3c**, 78% yield) than those with electron-poor aryl groups (**3f**, 52% yield; **3g**, 54% yield). The bulky groups resulted in relatively lower yields (**3d**, 47% yield; **3e**, 45% yield; **3h**, 70% yield). For the substituents on the triple bond, excellent yields were obtained with either electron-rich or -poor aryl groups (**3j**, 90%; **3l**, 90%; **3m**, 90% yield) with the exception of a bulky substituent (**3k**, 45% yield), while the *p*-tolyl group afforded **3i** in 54% yield. Substrates bearing different R^3 groups were also compatible in the reaction to give the corresponding products **3n** and **3o** in good yields, respectively.

To understand the reaction mechanism, several controlled experiments were carried out with **1a** (Scheme 4). When the reaction was performed in the absence of BPO, **2a** was obtained in 46% yield with no detection of **3a**. On the other hand, reaction of **1a** in the absence of CuCl resulted in a complex mixture. These results indicate that both CuCl and BPO are essential for the formation of **3a**. When the reaction was performed in the presence of TEMPO (1.0 equiv), **1a** was

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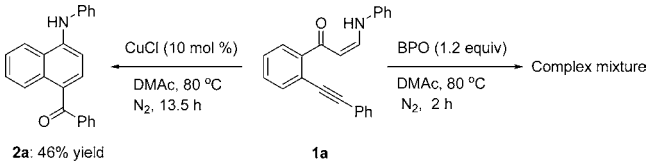
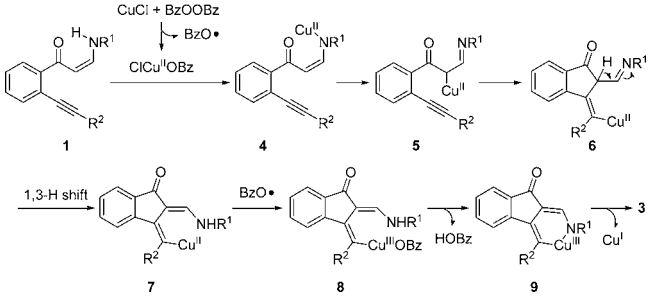
Scheme 4. Control Experiments



consumed within 0.5 h. However, neither **2a** nor **3a** could be detected.

Based on our results and the reported work,[13] we propose the following reaction mechanism for the formation of **3** (Scheme 5). An amido copper(II) intermediate **4** might be

Scheme 5. Possible Reaction Pathway



formed in the presence of CuCl and BPO. Isomerization of **4** gives **5**, which undergoes intramolecular carbocupration to form **6**. A 1,3-H shift of **6** affords **7**, which reacts with the BzO radical to produce **8**. Ligand exchange of **8** gave **9** followed by reductive elimination to make the final product **3** and regenerate the Cu(I) species.

In conclusion, enchanting reactivities of (*o*-alkynyl)phenyl enaminones have been exploited for the synthesis of *α*-naphthylamines and indeno[1,2-*c*]pyrrolone derivatives. Modification of reaction parameters allowed for the completely chemoselective outcome of the products. Further investigation of the detailed mechanisms and synthetic application of these processes are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02615.

X-ray crystallographic data for **2a** (CIF)
X-ray crystallographic data for **3a** (CIF)
Experimental details and spectroscopic characterization of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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