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Arylative Cyclization of 2-Isocyanobiphenyls with Anilines: One-Pot Synthesis of 6-Arylphenanthridines via Competitive Reaction Pathways

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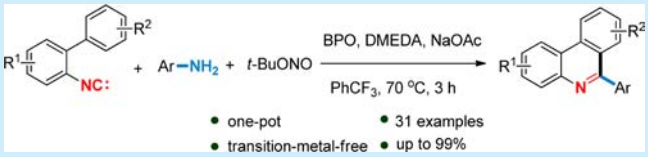
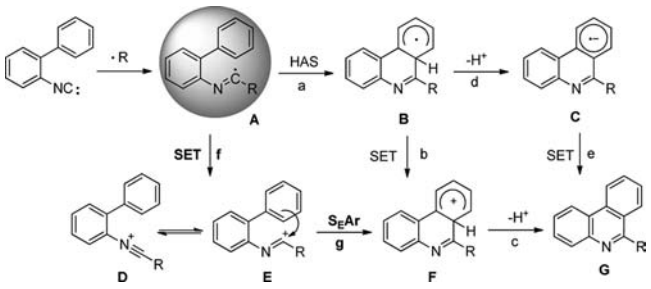
Supporting Information

ABSTRACT: A transition-metal-free method for the synthesis of C6 phenanthridine derivatives by arylative cyclization of 2-isocyanobiphenyls with arylamines in one pot was developed. Mechanistic studies suggest that electrophilic aromatic substitution (S_EAr) of a nitrilium intermediate and homolytic aromatic substitution (HAS) of an imidoyl radical intermediate are two competitive reaction pathways involved in the annulation step.



The synthetic versatility of isocyanide is illustrated by the Ugi, Passerini, and related multicomponent reactions,[1] transition-metal-catalyzed imidoylation,[2] and radical-based transformations as well. Addition of a carbon- or heteroatom-centered radical to the terminal carbon of isocyanide generates a geminal carbon radical intermediate, the imidoyl radical ($R^1N{=}C^{\bullet}R^2$).[3] Subsequently, the resulting imidoyl radical can add to double or triple carbon−carbon bonds, as well as onto intramolecular aromatic rings to construct various nitrogen-containing heterocycles. At least two chemical bonds are formed sequentially in this process. This highly efficient bond-forming strategy has been elegantly applied to the synthesis of camptothecin by Curran.[4] Recently, several groups have successively reported their efforts to synthesize phenanthridine derivatives[5] through key biphenyl imidoyl radical intermediates, formed by addition of various radicals to 2-isocyanobiphenyls (Scheme 1). For example, in 2012, Chatani[6a] reported the first example of using aryl/alkyl boronic acids as radical precursors in the presence of 3 quivalents of $Mn(acac)_3$ to synthesize 6-aryl/alkyl phenanthridines. Later on, Studer and co-workers demonstrated that trifluoromethyl,[6b] aroyl,[6c] and phosphoryl radicals[6d] can react with 2-isocyanobiphenyls, affording corresponding C6 diversified phenanthridines. Independently, groups of Yu[6e] and Zhou[6f] reported their synthesis of C6-alkylated and -trifluoromethylated phenanthridines via the imidoyl radical intermediates under photoredox neutral and metal-free conditions, respectively. Intramolecular homolytic aromatic substitution[7] (HAS, step a, Scheme 1) of the imidoyl radical on the pending phenyl ring, forming the cyclohexadienyl radical intermediate, was proposed as a common step in these reactions. Subsequently, there are two possible pathways directed toward the formation of phenanthridine products. One is single electron transfer (SET, step b) oxidation to afford cyclohexadienyl cation followed by deprotonative aromatization (step c), and the other is deprotonation of the cyclohexadienyl radical first (step d) followed by SET (step e). Our recent study disclosed that SET oxidation of biphenyl imidoyl radical to biphenyl nitrilium (step f) was a competitive pathway to HAS in an arylative cyclization of 2-isocyanobiphenyls using in situ generated diazonium salts as arylation agents.

Scheme 1. Reaction Pathways of Biphenyl Imidoyl Radical



Diazonium salts,[8] presynthesized or generated in situ from anilines, are widely used as precursors of aryl radicals, as exemplified in the well-known Sandmeyer reactions[9] and Meerwein arylation.[10] Recently, Grimaud[11a] and our group[11b] successively described a novel preparation of arylcarboxyamides from diazonium salts and isocyanides under transition-metal-free conditions. It was believed that the reaction was sequenced by aryl radical generation, radical addition to isocyanide, SET oxidation of the resulting imidoyl radical, nucleophilic addition to the nitrilium intermediate, and tautomerization in the case of water as a nucleophile. This process suggests that when an intra- or intermolecular radical acceptor is absent, oxidation of imidoyl radical to nitrilium takes place. As these imidoyl radicals ($R^1N{=}C^{\bullet}R^2$) are rather electron rich,[3] they have great potential to be oxidized to the nitrilium ions ($R^1N^+ \equiv CR^2$) by SET process.[11] It is anticipated that in a reaction of diazonium

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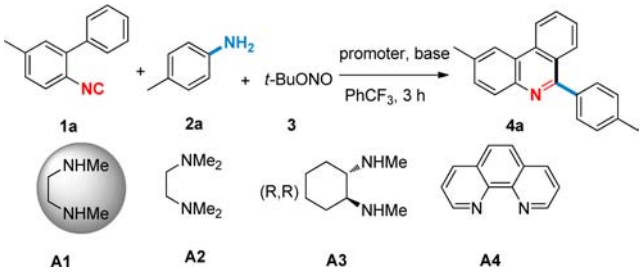
salts with 2-isocyanobiphenyls where an intramolecular radical trap is present, the intramolecular HAS will compete with intermolecular SET followed by electrophilic aromatic substitution (S_EAr, Scheme 1). Our study demonstrates that in situ formed aryl diazonium salts can react smoothly with 2-isocyanobiaryls to afford 6-aryl phenanthridines in the absence of transition metals. In addition, mechanistic studies suggest that intermolecular SET followed by intramolecular S_EAr via the nitrilium intermediate is a competitive pathway to HAS.

Initially, 2-isocyano-5-methyl-1,1′-biphenyl **1a** was chosen to react with *p*-tolyldiazonium salt, generated in situ from *p*-toluidine **2a** and *t*-BuONO **3** in $PhCF_3$ at 80 °C in argon (entry 1, Table 1). To our delight, the desired C6 tolyl phenanthridine

Table 1. Optimization of the Reaction Conditions[a]



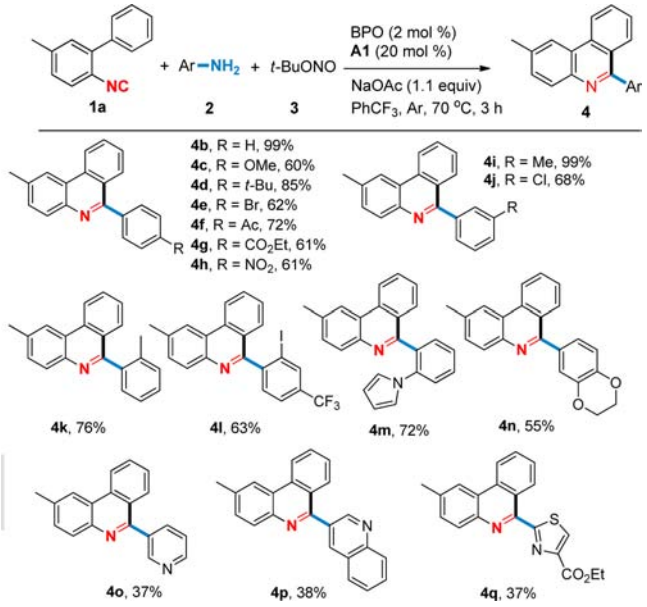
entry	promoter (mol %)	base (1.1 equiv)	ratio of **1a**:**2a**:**3**	temp (°C)	yield[b] (%)
1	none		1:1.2:1.5	80	11
2	BPO (20)		1:1.2:1.5	80	22
3	BPO (2)		1:1.2:1.5	110	41
4	BPO (2)		1:3:3.5	70	64
5	none	NaOAc	1:3:3.5	70	62
6	none		1:3:3.5	70	55
7	BPO (2) + **A1** (10)	NaOAc	1:3:3.5	70	81
8	BPO (2) + **A2** (10)	NaOAc	1:3:3.5	70	76
9	BPO (2) + **A3** (10)	NaOAc	1:3:3.5	70	81
10	BPO (2) + **A4** (10	NaOAc	1:3:3.5	70	71
11	BPO (2) + **A1** (20)	NaOAc	1:3:3.5	70	89

[a]Reaction conditions: All reactions were performed with **1a** (0.2 mmol), and the ratio of **1a**:**2a**:**3** is indicated, in 1.0 mL of $PhCF_3$ at 70−110 °C as indicated, in Ar, for 3 h. [b]Isolated yields of **4a**.

4a was formed in 11% yield. A higher yield of 22% was obtained when benzoyl peroxide[12] (BPO, 20 mol %) was present (entry 2). It was observed that the reaction proceeded more efficiently in inert atmosphere than in air or oxygen (for more details, see the Supporting Information).[13] Increasing the amount of diazonium salt relative to isocyanide **1a** led to the formation of **4a** in much higher yield (64%) in the presence of only 2 mol % of BPO at 70 °C (entry 4). Screening of bases revealed that the combination of *N*,*N*′-dimethylethylenediamine (DMEDA, **A1**; 10 mol %), and NaOAc (1.1 equiv) improved the reaction dramatically,[14] affording **4a** in 81% yield (entry 7). Other structurally related diamines **A2**−**A4** cannot improve the yield of **4a** further (entries 8−10). Finally, a best yield of 89% was achieved by increasing the amount of DMEDA to 20 mol % (entry 11, for more details, see the Supporting Information).

Next, the scope of anilines as well as heteroaromatic amines was studied in reactions with 2-isocyano-5-methyl-1,1′-biphenyl **1a** under the optimal reaction conditions as described in entry 11, Table 1. 2-Methyl-6-phenylphenanthridine **4b** was obtained in almost quantitative yield using unsubstituted aniline as an arylation agent (Scheme 2). Anilines bearing electron-donating

Scheme 2. Scope of Arylamines[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (3 equiv) and **3** (3.5 equiv) in 1.0 mL of $PhCF_3$ at 70 °C, in Ar, for 3 h.

OCH_3 (**4c**) and *tert*-butyl (**4d**) as well as electron-withdrawing Br (**4e**), $COCH_3$ (**4f**), CO_2Et (**4g**), and NO_2 (**4h**) groups on the *para* position reacted smoothly with **1a**, delivering corresponding arylated phenanthridines in good to excellent yields. A substituent on the *ortho* position of aniline had a negative effect on this one-pot arylative cyclization reaction (**4k** vs **4a** and **4i**). It was notable that iodide also survived the reaction (**4l**), making further diversification possible. The synthesis of these iodine-containing phenanthridines is a challenging task by using transition-metal-based methods. Heterocycle fused anilines were also compatible with the reaction conditions (**4m**−**n**). In addition, aromatic heterocycles, such as pyridine, quinolone, and thiazole, can be incorporated into the phenanthridine scaffold by using corresponding heteroaromatic amines, albeit in lower yields (**4o**−**q**).

Substitution effect on both aromatic rings of biphenyl isocyanide **1** was then investigated in reactions with aniline **2b** (Scheme 3). 2-Isocyanobiphenyls containing substituents, such as Cl, F, OMe, and Ph, on the *para* position of the nonisocyanide phenyl ring reacted efficiently, affording corresponding 6-phenyl phenanthridine derivatives in yields ranging from 61 to 84% (**4r**−**v**). An electron-deficient pyridine moiety in place of phenyl ring also cyclized to construct a benzo[*c*][2,7]naphthyridine scaffold in low yield (26%, **4w**). Good yields were reported in Studer and Yu's studies using similar pyridine-containing substrates.[6b,e] The low-yielding formation of **4w** indicated that a different mechanism might be involved in our case.[15] When *meta*-methyl-substituted 2-isocyanobiphenyl was subjected to the reaction, a 2.4:1 mixture

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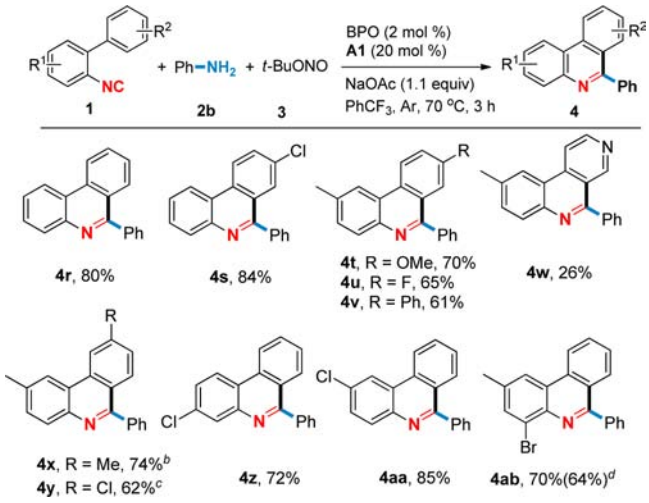
Scheme 3. Scope of Biphenyl Isocyanides[a]



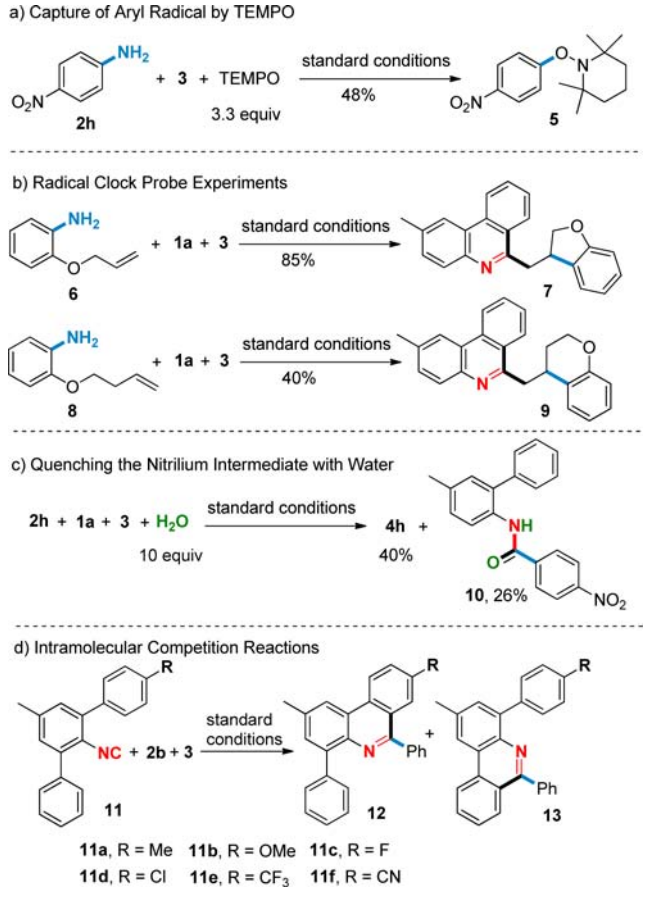
[a]Reaction conditions: **1** (0.2 mmol), **2b** (3 equiv) ,and **3** (3.5 equiv) in 1.0 mL of $PhCF_3$ at 70 °C, in Ar, for 3 h. [b]The ratio of the regioisomers was 2.4:1 as determined by ^1H NMR. [c]The ratio was 2.8:1. [d]Yield in 4.7 mmol scale of **1**, and the reaction time was 4 h.

of two regioisomers was obtained in favor of the less steric demanding C9 substituted isomer (**4x**). A similar ratio of 2.8:1 was determined in the case of chloro-substituted analogue (**4y**). Biphenyl isocyanides containing a chloro group *para* or *meta* to the isocyano moiety were also tolerated (**4z** and **4aa**). A gram scale reaction of 3-bromo-2-isocyano-5-methyl-1,1′-biphenyl with aniline gave the desired product **4ab** (1.05 g, 64%) in a comparable yield with that of a small-scale experiment.

To confirm that aryl radical formation was the initial step of this sequential arylative cyclization reaction, 4-nitrobenzenamine **2h** reacted with *t*-BuONO **3** and 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO), a radical scavenger, in the absence of 2-isocyanobiphenyl **1a** (Scheme 4a). 4-Nitrophenyl radical was trapped by forming an adduct **5** in 48% yield under otherwise identical conditions. Anilines **6** and **8** containing *ortho* ether linked terminal alkenes were examined in reactions with **1a** under the standard conditions (Scheme 4b).[16] Phenanthridine derivatives **7** and **9**, attached by tetrahydrobenzofuran and tetrahydrobenzopyran with a methylene linkage, were obtained as a result of aryl radical addition to the intramolecular C−C double bond before reacting with isocyanide **1a**. It is noteworthy that three C−C bonds are formed sequentially in the above one-pot process, providing a highly efficient approach for the synthesis of multi heterocyclic systems containing a phenanthridine moiety. These experiments undoubtedly indicate that aryl radicals are generated in situ from anilines and biphenyl imidoyl radical intermediates are formed by addition of aryl radicals to 2-isocyanobiphenyls.

Interestingly, when 10 equiv of H_2O was added to the reaction between **2h** and **1a** under the standard conditions, the normal cyclization product **4h** was obtained in a reduced 40% yield, together with 26% of amidated product **10**. Although both intramolecular HAS and S_EAr can account for the formation of phenanthridine product **4h**, nucleophilic addition of water to a corresponding nitrilium intermediate was the reasonable explanation for amide formation (Scheme 4c).[11] To gain more insight into the reaction, a series of 2,6-diaryl *p*-tolylisocyanides **11** in which one of the aryl rings were electron biased were designed for intramolecular competition reaction

Scheme 4. Mechanistic Studies



(Scheme 4d).[17] The preference of the aryl ring to be cyclized will hint at the nature of the cyclization precursor. The ratio of cyclization products **12** to **13** was determined by ^1H NMR of the crude reaction mixture after routine workup. The Hammett plot of log **12**/**13** versus Hammett parameter σ_{meta} was a curve with negative ρ value rather than a straight line (see the Supporting Information). Such Hammett curve suggests that a positive transition-state intermediate is involved in the annulation step but cannot be explained by a single reaction mechanism.[18] In other words, both HAS and S_EAr are highly likely involved in cyclization.

Based on mechanistic studies and previous work on aryldiazonium salts[8] and isocyanides,[1,3] two competing reaction pathways involved in the annulation step were proposed (step a and step f in Scheme 1, also see the Supporting Information). Initially, aryldiazonium ion was formed in situ from anilines and *t*-BuONO. Then, the aryl radical was generated by decomposition of aryldiazonium ion with concurrent releasing of N_2 and *t*-butoxyl radical (*t*-BuO$^\bullet$). Many factors might promote this process,[8] such as BPO,[12] NaOAc, and heat. Subsequently, the resulting aryl radical added to the terminal divalent carbon of 2-isocyanobiphenyl **1**, giving the *N*-biphenyl-2-yl imidoyl radical **A**.[3] Next, two competitive reaction pathways were involved in the transformation of intermediate **A**. One was the intramolecular HAS, as proposed by other authors in the synthesis of phenanthridine derivatives.[6] The cyclohexadienyl radical intermediate **B** could undergo SET oxidation first followed by deprotonation (steps b and c) or deprotonation first followed by SET (steps d and e). Both pathways are possible in this process. The other route is SET oxidation to

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nitrilium ion **D**[11] by excess of nitrite. The nitrilium ion **D** could distort to structure **E**, then followed by intramolecular S_EAr on the pending aryl group.[19] Deprotonative aromatization of the resulting cyclohexadienyl cation **F** delivered the final phenanthridine product **G** (steps f, g, and c).

In summary, we have developed a transition-metal-free synthesis of C6 phenanthridine derivatives by arylative cyclization of 2-isocyanobiphenyls using readily available and inexpensive anilines as arylating agents in one pot. A range of anilines as well as heteroaromatic amines react with 2-isocyanobiphenyls bearing various functional groups to afford diversified C6-aryl phenanthridines in good to excellent yields. This reaction proceeds through key biphenyl imidoyl radical intermediates formed by addition of aryl radicals to 2-isocyanobiphenyls. Mechanistic studies reveal that a new reaction pathway which involves SET of biphenyl imidoyl radical to the corresponding nitrilium intermediate followed by S_EAr is taking place as a competitive pathway to previously reported HAS. This method provides a rapid approach to phenanthridine derivatives under mild conditions and evidence of a new mode of action of imidoyl radicals as well.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(15) The low-yielding formation of **4w** is consistent with the formation of nitrilium ion **D** rather than only imidoyl radical **A** in the annulation step (see Scheme 1), since imidoyl radical **A** is rather electron rich, whereas nitrilium ion **D** is the opposite.

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