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Metal-Free Nitrogenation of 2-Acetylbiphenyls: Expeditious Synthesis of Phenanthridines

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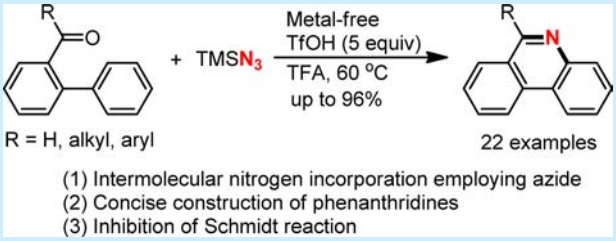
Supporting Information

ABSTRACT: An intermolecular nitrogenation reaction toward the synthesis of phenanthridines has been developed. This metal-free protocol provides a novel nitrogen-incorporation transformation using azides as the nitrogen source. Phenanthridines, which are of great interest in pharmaceutical and medicinal chemistry, are synthesized efficiently in one step. Moreover, the byproducts derived from the Schmidt reaction are inhibited, which further demonstrated the high chemoselectivity of this transformation.



Nitrogen-containing compounds show great importance in chemistry, biology, and material sciences.[1] Many novel and efficient methodologies on C−N bond formation for the synthesis of nitrogen-containing compounds have been developed over the past decades.[2]

Phenanthridines, which are representative core fragments in a large number of natural products and alkaloids, have generated great interest in the fields of medicinal chemistry, biochemistry, and material sciences (Figure 1).[3] Hence,

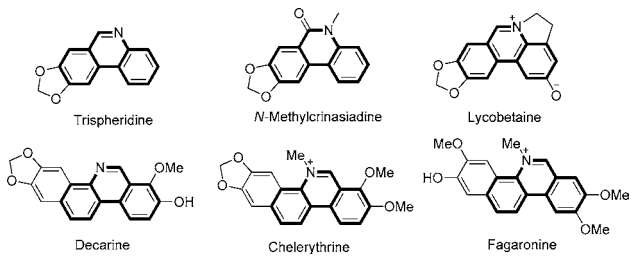


Figure 1. Examples of natural products and alkaloids containing a phenanthridine core.

considerable attention has been paid to the synthesis of substituted phenanthridines for a long time. The Bischler−Napieralski cyclization involving P_4O_{10}, $POCl_3$, or PCl_5 at elevated temperature has been extensively used.[4] To avoid the harsh reaction conditions and limited functional group tolerance, much effort has been focused on mild and efficient synthetic routes to phenanthridines. Recent achievements include palladium catalyzed cascade reactions,[5] annulations employing arynes,[6] aza-Wittig reactions,[7] oxidative cyclization of 2-isocyanobiphenyls,[8] biaryl-2-carbonitriles with organometallic reagents,[9] transition-metal-catalyzed cyclization of imines,[10] anionic ring closure reactions,[11] UV promoted phenanthridine syntheses from iminyl radicals,[12] photochemical processes,[13] and microwave-mediated cyclizations.[14] Albeit great achievements have been reached, further exploration of convenient, efficient, and milder protocols are still significant due to the broad applications of phenanthridine derivatives.

In the past decades, the direct functionalization of simple substrates through C−H bond and/or C−C bond cleavage has been significantly developed.[15] Constructing nitrogen-containing compounds employing azides as a nitrogen source was a classical as well as enduring strategy.[16] The click chemistry has been widely used in organic synthesis and in bioconjugation.[17] Some well-known named reactions also realized nitrogen incorporation using azides, such as the Schmidt reaction,[18] Curtius rearrangement,[19] and Staudinger reaction.[20] Recently, by using azide reagents, the direct functionalization of the C−H bond to construct the C−N bond in the absence of an additional oxidant has attracted considerable attention.[21,22] Through this strategy, some acyclic nitrogen-containing compounds have been easily prepared.

However, by using azides as the nitrogen source, the construction of *N*-heterocyclic compounds through two bond cleavages and two bond formations in one step is still challenging and has been rarely achieved. More recently, Glorius and co-workers reported a Rh-catalyzed 1*H*-indazoles synthesis with sulfonyl azide (Scheme 1, eq 1).[23] The Ellman group realized Rh-catalyzed acridines and phenazines synthesis with aromatic azides (Scheme 1, eq 2).[24] Jiao and co-workers developed a Pd(II)-catalyzed pyrido[1,2-*b*]indazoles preparation with sodium azide (Scheme 1, eq 3).[25] The transition metal catalysts were required in these elegant works.

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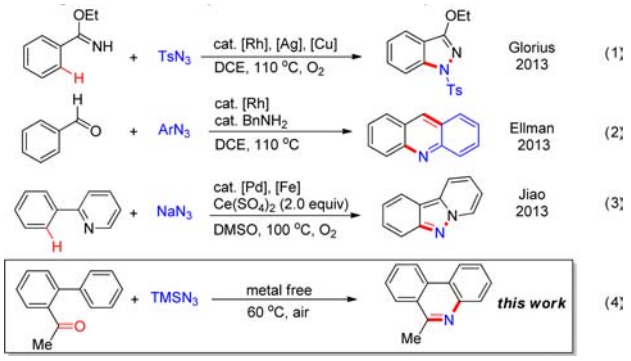
Scheme 1. Intermolecular Nitrogen Incorporation Using Azides to Synthesize Heterocycles

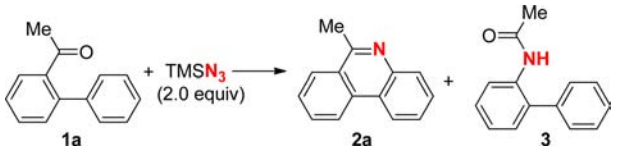


Herein, we would like to report a novel metal-free nitrogenation of 2-acetylbiphenyls for the efficient synthesis of phenanthridine derivatives (Scheme 1, eq 4). To the best of our knowledge, this is the first example of intermolecular phenanthridine synthesis using azides as a N atom donor. Multiple chemical bonds are transformed involving double C−N bond formations. This reaction proceeds under mild conditions with high efficiency and functional group tolerance.

In the beginning of this project, we employed 2-acetylbiphenyl (**1a**) as the model substrate. When the reaction of **1a** and azidotrimethylsilane ($TMSN_3$) was catalyzed by $FeCl_2$ at 60 °C in TFA as the solvent, to our delight, 6-methylphenanthridine (**2a**) was obtained in 43% yield (Table 1, entry 1). It is noteworthy that the Schmidt reaction product *N*-acetyl-2-aminobiphenyl (**3**) was not detected in this case (Table 1, entry 1). The reaction at higher temperature (80 °C) gave a higher yield of **2a**, but with a 32% yield of byproduct **3** (Table 1, entry 2). When the reaction atmosphere was changed from air to dioxygen or argon, only a moderate yield of **2a** was obtained respectively (Table 1, entries 3, 4). It should be noted that when TFA was changed by other acidic solvents, such as MsOH, TCA, or Tf_2NH, this reaction was completely inhibited (Table 1, entries 5−7). Gratifyingly, when triflic acid (TfOH) was added as an additive, **2a** was highly selectively obtained quantitatively (Table 1, entry 8). Decreasing the reaction temperature from 80 to 60 °C gave a slightly lower yield of 94% (Table 1, entry 9), while a reduced amount of the additive TfOH (from 5 equiv to 2.5 equiv) led to a significant loss of **2a** (Table 1, entry 10). To our surprise, the target product **2a** was obtained in 86% yield even in the absence of $FeCl_2$, indicating that the $FeCl_2$ was a promoter rather than a catalyst (Table 1, entry 11). Consequently, we decided to use entry 11 as the optimal conditions to investigate the application of this transformation.

Next, a variety of diaryl-ketones and aryl alkyl ketones were tested as substrates under the standard conditions (Table 2).

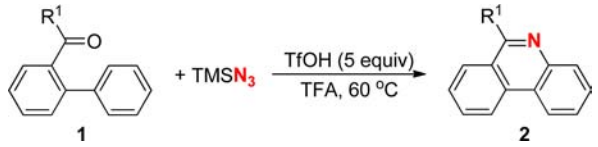
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	additive	solvent	t (°C)	yield (%)[b] 2a	3
1	$FeCl_2$ (10)	–	TFA	60	43	N.D.
2	$FeCl_2$ (10)	–	TFA	80	67	32
3[c]	$FeCl_2$ (10)	–	TFA	80	55	42
4[d]	$FeCl_2$ (10)	–	TFA	80	46	N.D.
5	$FeCl_2$ (10)	–	MsOH	80	0	trace
6	$FeCl_2$ (10)	–	TCA	80	0	0
7	$FeCl_2$ (10)	–	Tf_2NH	80	0	0
8	$FeCl_2$ (10)	TfOH (5 equiv)	TFA	80	99	0
9	$FeCl_2$ (10)	TfOH (5 equiv)	TFA	60	94	0
10	$FeCl_2$ (10)	TfOH (2.5 equiv)	TFA	60	75	0
11	**none**	**TfOH (5 equiv)**	**TFA**	**60**	**86**	**0**
12	none	TfOH (5 equiv)	TFA	80	81	0

[a]Reaction conditions: **1a** (0.4 mmol), $TMSN_3$ (0.8 mmol, 2.0 equiv), solvent (2.0 mL). [b]Isolated yields. [c]The reaction was carried out under an O_2 atmosphere. [d]The reaction was carried out under an argon atmosphere. TMS = trimethylsilyl, TFA = trifluoroacetic acid, TCA = trichloroacetic acid, MsOH = methanesulfonic acid, TfOH = trifluoromethanesulfonic acid, Tf_2NH = trifluoromethanesulfonimide. N.D. = not detected.

Table 2. Substrate Scope of 6-Substituted Phenanthridines Synthesis[a]



entry	**1**, R^1	**2**, yield[b]
1	**1a**, Me	**2a**, 86%
2	**1b**, 4-Me-C_6H_4	**2b**, 83%
3[c]	**1c**, 2-Me-C_6H_4	**2c**, 56%
4	**1d**, 3,5-dimethyl-C_6H_3	**2d**, 95%
5	**1e**, 4-*t*-Bu-C_6H_4	**2e**, 62%
6	**1f**, 4-F-C_6H_4	**2f**, 95%
7	**1g**, 4-Cl-C_6H_4	**2g**, 89%
8	**1h**, 4-NO_2-C_6H_4	**2h**, 94%
9	**1i**, 4-CF_3-C_6H_4	**2i**, 86%
10	**1j**, 4-*N*,*N*-dimethyl-C_6H_4	**2j**, 83%
11	**1k**, 2-naphthyl	**2k**, 70%
12	**1l**, 3-pyridyl	**2l**, 86%
13	**1m**, CH_2Ph	**2m**, 83%
14	**1n**, *t*-Bu	**2n**, 96%
15	**1o**, *c*-hexyl	**2o**, 81%
16	**1p**, *n*-pentyl	**2p**, 81%

[a]Reaction conditions: **1** (0.2−0.4 mmol), $TMSN_3$ (2.0 equiv), TfOH (5.0 equiv), TFA (1.0−2.0 mL), stirred at 60 °C under air. [b]Isolated yields. [c]Reflux.

For diaryl-ketones, the position of the substituent on R^1 (when R^1 = Ar) affected the reaction efficiency greatly. A methyl group at the *para* position yielded **2b** in 83% yield while the *ortho* position yielded **2c** in only 56% yield (Table 2, entries 2 and 3). Two methyl substituents at the *meta* position showed excellent reactivity with a 95% yield (**2d**) (Table 2, entry 4). A series of *para*-substituted electron-donating and -withdrawing groups were examined for details. All these substrates reacted smoothly to afford the phenanthridines in good to excellent yields (Table 2, entries 5−10). When R^1 was changed from substituted phenyl rings to naphthalene, the corresponding phenanthridine was generated in 70% yield (Table 2, entry 11). Notably, aromatic heterocycles such as pyridine was also tolerated and

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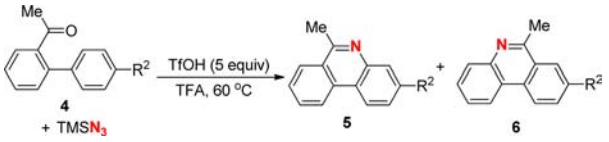
gave an 86% yield (Table 2, entry 12). For aryl alkyl ketones, all of them performed well to give 6-alkyl substituted phenanthridines in 81%−96% yield (Table 2, entries 13−16).

Next, a set of substrates bearing R^2 substituents were tested under the optimal conditions to figure out the regioselectivity of this nitrogenation reaction (Table 3). In these cases, Me, OMe, ^{t}Bu, Cl substituents all showed good compatibility to obtain products **5** and **6** (Table 3, entries 1−4). Interestingly, the hydroxyl substituted substrate **4e** highly regioselectively delivered a single product (Table 3, entry 5), although the reason is still unclear. The structure of **6e** was determined by an NOESY spectrum (see the Supporting Information).

Table 3. Substrate Scope of Disubstituted Phenanthridines Synthesis[a]

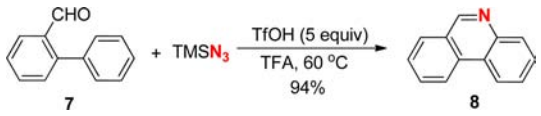


entry	R^2	yield[b,c] (5/6)
1	Me (**4a**)	74% (**5a**/**6a** = 1:1)
2	OMe (**4b**)	71% (**5b**/**6b** = 1:2.6)
3	*t*-Bu (**4c**)	81% (**5c**/**6c** = 1:1.4)
4[d]	Cl (**4d**)	47% (**5d**/**6d** = 1:3.3)
5	OH (**4e**)	59% (**6e**)

[a]Reaction conditions: **4** (0.4 mmol), $TMSN_3$ (0.8 mmol, 2.0 equiv), TfOH (2.0 mmol, 5.0 equiv), TFA (2 mL), stirred at 60 °C under air. [b]Isolated yields. [c]The product ratio was determined by ^{1}H NMR. [d]10 mol % $FeCl_2$ was added.

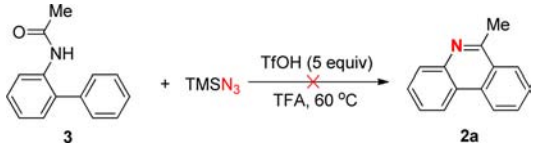
To our delight, 2-biphenylcarboxaldehyde (**7**) was transferred into unsubstituted phenanthridine (**8**) successfully in 94% yield (Scheme 2). It is well-known that aldehyde usually underwent a Schmidt reaction[18] under acidic conditions to give nitriles, while the Schmidt reaction was completely inhibited in the present system.

Scheme 2. Nitrogenation of [1,1′-Biphenyl]-2-carbaldehyde with $TMSN_3$



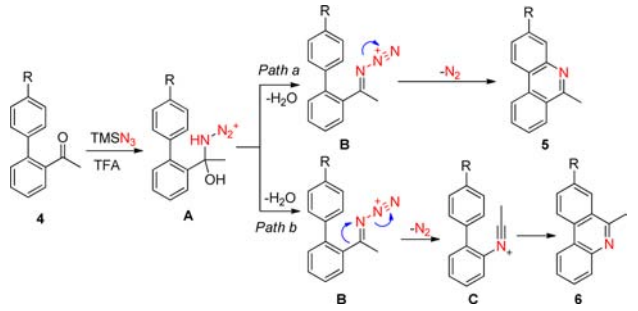
In order to clarify the detailed mechanism of this reaction, *N*-acetyl-2-aminobiphenyl (**3**) was allowed to react under the standard conditions, while **2a** was not observed, which ruled out the possibility of the relay of the Schmidt reaction with the formation of **3** and then cyclization processes in this nitrogenation reaction (Scheme 3).

Scheme 3. Exclusion of the Reaction Intermediate



On the basis of the above-mentioned results, a proposed reaction mechanism is represented in Scheme 4. Hydrazoic acid is easily generated from $TMSN_3$ in the strong acidic media, which attacks the substrate **4** to afford intermediate **A**. Then intermediate **A** undergoes a dehydration process to afford intermediate **B**, which executes a Friedel−Crafts reaction[26] accompanied by loss of N_2 to afford product **5** (Scheme 4, path a). Alternatively, the aryl group migration of intermediate **B** occurs to afford intermediate **C**. Product **6** is finally produced through the electrophilic cyclization of intermediate **C** (Scheme 4, path b).

Scheme 4. Proposed Reaction Mechanism



In summary, a metal-free intermolecular nitrogen incorporation approach to nitrogen-containing heterocycles has been developed. Biologically important phenanthridine derivatives are constructed concisely and efficiently with high chemoselectivity from simple 2-acetylbiphenyls and azides. Further studies on the applications of this protocol are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of products, and copies of 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.

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