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$Co(OAc)_2$-Catalyzed Trifluoromethylation and C(3)-Selective Arylation of 2-(Propargylamino)pyridines via a 6-*Endo-Dig* Cyclization

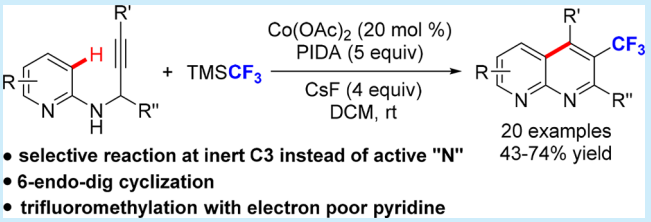
Jianjun Li,[†] Yifan Lei,[†] Yang Yu,[†] Cong Qin,[†] Yiwei Fu,[†] Hao Li,*[,†] and Wei Wang*[,†,‡]

[†]State Key Laboratory of Bioengineering Reactor, Shanghai Key Laboratory of New Drug Design, and School of Pharmacy, East China University of Science and Technology, 130 Mei-long Road, Shanghai 200237, China

[‡]Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001, United States

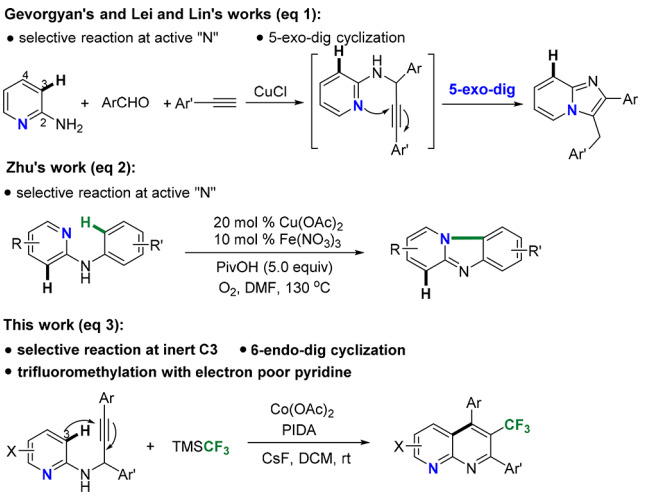
Supporting Information

ABSTRACT: A $Co(OAc)_2$-catalyzed trifluoromethylation and subsequent C(3)-selective arylation of 2-(propargylamino)-pyridines has been developed. A new 6-*endo-dig* cyclization involving an unprecedented C(3) selective arylation of the pyridines instead of a commonly observed 5-*exo-dig* cyclization with "N" is realized. Moreover, the study presents the first case of the installation of a trifluoromethyl group into electron-deficient azaarenes. The process delivers an efficient cascade approach to new trifluoromethylated 1,8-naphthyridine structures with a broad substrate scope.



Pyridines are "privileged" structures that are widely featured in many pharmaceuticals, natural products, and catalyst ligands.[1] Therefore, the functionalization of pyridines has been of long-standing interest in organic and medicinal chemistry. Intensive attention has been paid to developing methods capable of diversifying the structure.[2] Among them, 2-aminopyridines serve as a versatile handle for the synthesis of new pyridine-derived structures.[3] For instance, Lewis acid catalyzed cyclization of 2-(propargylamino)pyridines delivers medicinally useful imidazo[1,2-*a*]pyridine frameworks.[4] The Gevorgyan, Lin, Lei, and Zeng groups, respectively, reported efficient π-philic metal-catalyzed cyclization processes (Scheme 1, eq 1).[5] It is noted that these reactions proceed in a 5-*exo-dig* closure fashion. Moreover, the more nucleophilic nitrogen in the electron-deficient heteroaromatic dictates the cyclization. A similar observation was also seen in C−H amination with pyridine by Zhu and Liang (Scheme 1, eq 2).[6] Although C(3)-selective functionalization could provide valuable methods for the construction of new pyridine structures, the electron-poor C(3) site in pyridine renders this difficult. As far as we are aware, such a process has not been reported.

Scheme 1. Arylation of Pyridines with Alkynes



Herein, we disclose an unprecedented $Co(OAc)_2$-promoted C(3)-selective arylation of pyridines[7] with alkynes in an unusual 6-*endo-dig* fashion. The process creates a distinct C−C bond connection. 6-Membered 1,8-naphthyridine molecular architectures are an important class of heteroaromatics widely used as ligands in catalysis and as quinoline bioisosteres in drug discovery; they can now be synthesized according to eq 3.[8] A new reactivity, harnessed by $Co(OAc)_2$-promoted selective activation of C(3) in pyridine, has been implemented for reaction with electrophilic $CF_3^{\bullet}$ radical, which is produced from $TMSCF_3$ in the presence of phenyliodonium diacetate (PIDA) as oxidant. The study offers the first example of installation of a trifluoromethyl group, a preeminent moiety prevalent in pharmaceuticals, agrochemicals, and materials,[9] into electron-deficient azaarenes in an efficient, regio- and chemoselective cascade manner. It is noteworthy that carbotrifluoromethylation of C=C[10,11] and C≡C[12] bonds and subsequent arylation has been elegantly realized. Nonetheless, electron-rich aromatic systems are essentially used in these reactions.

Our investigation began with a reaction of *N*-(1,3-diphenylprop-2-ynyl)pyridin-2-amine (**1a**) in the presence of

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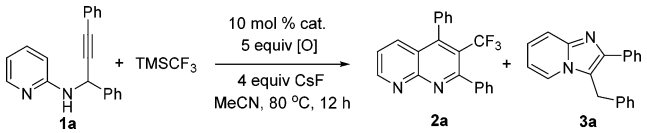
10 mol % of $Cu(OAc)_2$, CsF (4 equiv), and $TMSCF_3$ (4 equiv) in toluene (1.5 mL) at 80 °C for 12 h (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



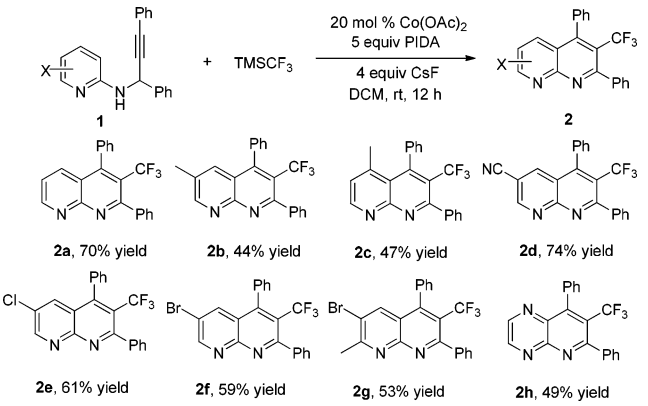
entry	cat.	[O]	2a, yield[b] (%)	3a, yield[b] (%)
1[c]	$Cu(OAc)_2$			50
2[c]	$Cu(OAc)_2$	PIDA	trace	trace
3	$Cu(OAc)_2$	PIDA	41	
4		PIDA	18	
5	$Pd(OAc)_2$	PIDA	30	
6	$Fe(OAc)_2$	PIDA	<10	
7	$Ni(OAc)_2$	PIDA	21	
8	$Zn(OAc)_2$	PIDA	26	
9	$Co(OAc)_2$	PIDA	46	
10[d]	$Co(OAc)_2$	PIDA	50	
11[d]	$Co(OAc)_2$	$PhI(OPiv)_2$	25	
12[d]	$Co(OAc)_2$	PIFA	<10	<10
13[d]	$Co(OAc)_2$	O_2		47
14[d,e]	$Co(OAc)_2$	PIDA	45	
15[d,f]	$Co(OAc)_2$	PIDA	43	
16[d,g]	$Co(OAc)_2$	PIDA	59	
17[d,g,h]	$Co(OAc)_2$	PIDA	70	
18[d,g,h,i]	$Co(OAc)_2$	PIDA	20	
19[d,g,h,j]	$Co(OAc)_2$	PIDA	30	

[a]Unless specified, **1a** (0.15 mmol), cat. (10 mol %), oxidant (0.75 mmol), CsF (0.6 mmol), and $TMSCF_3$ (0.6 mmol) in 1.5 mL of CH_3CN was stirred at 80 °C for 12 h. [b]Isolated yield. [c]Toluene was used as solvent. [d]Lewis acid (20 mol %) was used. [e]PIDA (4 equiv) was used. [f]PIDA (6 equiv) was used. [g]The reaction was performed at rt. [h]DCM was used as solvent. [i]KF (4 equiv) instead of CsF was used. [j]AgF (4 equiv) instead of CsF was used.

Unfortunately, only the commonly observed imidazopyridine product **3a** was obtained. However, to our delight, in the presence of oxidant PIDA (5 equiv), the reaction course was altered (entry 2). A new, major, 1,8-naphthyridine product **2a** was detected with a trace amount of **3a**. When the reaction medium was changed to MeCN, **2a** was isolated in 41% yield (entry 3). Importantly, the production of **3a** was completely suppressed. The yield decreased sharply (18%) when $Cu(OAc)_2$ was removed, indicative of the indispensable role of Lewis acid in the 6-membered cyclization (entry 4). More commonly used Lewis acids, such as $Pd(OAc)_2$, $Fe(OAc)_2$, $Ni(OAc)_2$, and $Zn(OAc)_2$ were probed but resulted in lower yields (entries 5–8). Encouragingly, the isolated yield could be elevated to 46% by use of $Co(OAc)_2$ (entry 9). Elevating the catalyst loading to 20 mol % led to a slight growth in the yield to 50% (entry 10). Various oxidants were examined subsequently. $PhI(OPiv)_2$ delivered a lower yield of 25% (entry 11). The stronger oxidant PIFA only generated a trace amount of **2a** along with **3a** (entry 12). The combination of O_2 and $Co(OAc)_2$ failed to promote the cyclization (entry 13). Neither reducing nor increasing amount of the PIDA was beneficial (entries 14 and 15). The reaction carried out at room temperature resulted in marginal improvement (59%, entry 16). Moreover, our screening of solvents including EtOAc, toluene, $CHCl_3$, THF, and DMF led to DCM being selected as the best choice (70% yield, entry 17).[13] Substitution of CsF by KF and AgF afforded **2a** in lower yields (entries 18 and 19). Finally, different ligands were also examined and gave inferior outcomes.[14] These investigations revealed the ligand sensitivity of the coordination of the pyridine "N" with $Co(OAc)_2$.[15]

With the optimized reaction conditions in hand, the substrate scope of this new cascade reaction was investigated (Scheme 2).

Scheme 2. Scope of Pyridines[a]



[a]Unless otherwise specified, **1** (0.15 mmol), $Co(OAc)_2$ (20 mol %), PIDA (0.75 mmol), CsF (0.6 mmol), and $TMSCF_3$ (0.6 mmol) in 1.5 mL of DCM was stirred for 12 h at rt. Isolated yields.

Alternation of substituents on the pyridine ring was first probed. The results show that the process serves as a general approach to 1,8-naphthyridines. It appears that the electronic effect has impact on the reaction. The pyridine rings bearing an electron-donating group afforded the desired products (**2b** and **2c**) with lower yields, while electron-withdrawing groups delivered the corresponding naphthyridine products (**2d–g**) with higher efficiency. Pyrazine **1h** worked smoothly with the protocol as well (**2h**). The structure of the products was determined by the single-crystal X-ray diffraction analysis of **2a** (Figure S1).[16]

Next, the structural variation of the alkyne components (e.g., R′ and R′′, respectively) was examined according to Scheme 3. Probing R^1 revealed that a wide range of structures tolerated the protocol. They include aryl (**2i–o**), heteroaromatic (**2p**), and alkyl (**2q**) structures. Furthermore, arene rings bearing electron-neutral (**2a**), -donating (**2i** and **2j**), and -withdrawing (**2k–o**) groups have limited influence on the reaction. Finally, we examined the R′′ component. Similarly, both electron-donating (4-Me) and electron-withdrawing groups (3-Br and 2-Cl) worked smoothly to give the desired products (**2r–2t**).

1,2,3,4-Tetrahydronaphthyridines (THNADs) are an important class of framework, exhibiting diversely attractive biological activities.[17] In addition, they are also versatile building blocks in synthesis.[18] The 1,8-naphthyridine products **2** could serve as the precursors for the synthesis of unique trifluoromethylated THNADs. We identified the reaction conditions with 10 mol % of PtO_2 under 1 atm of H_2 pressure at rt for 24 h, enabling selective reduction of the unsubstituted pyridine ring to deliver THNAD **4** in 71% yield (Scheme 4).

To gain a preliminary understanding of the mechanistic aspect of the new reaction, several experiments were carried out (Scheme 5). In the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.5 equiv), the formation of product **2a** was suppressed along with a trace amount of **3a** detected (Scheme 5, eq 1). A new TEMPO–CF_3 adduct **5** was observed in 29% yield by NMR analysis. In addition, the reactions of TEMPO carried

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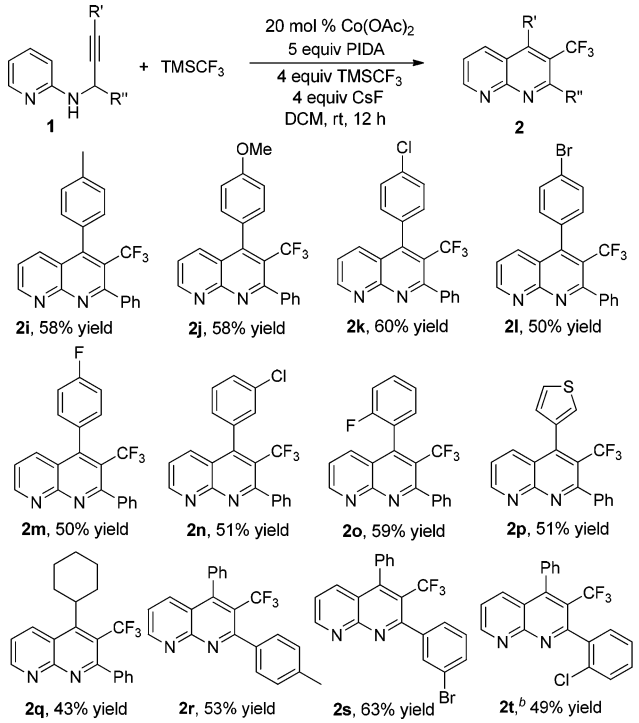
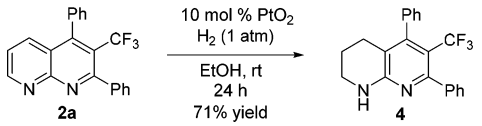
Scheme 3. Scope of Substituents on Alkynes[a]

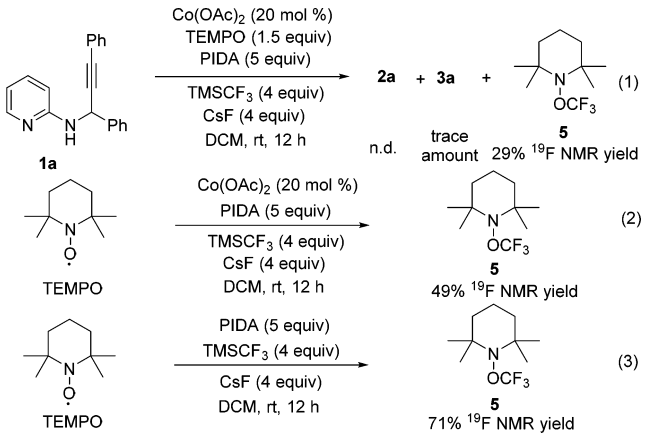


[a]Unless otherwise specified,**1** (0.15 mmol), $Co(OAc)_2$ (20 mol %), PIDA (0.75 mmol), CsF (0.6 mmol), and $TMSCF_3$ (0.6 mmol) in 1.5 mL of DCM were stirred at room temperature for 12 h. Isolated yields. [b]The reaction mixture was stirred for 4 d.

Scheme 4. Selective Reduction of Pyridine Rings



Scheme 5. Control Experiments with TEMPO



out under the standard conditions with and without $Co(OAc)_2$, respectively, led to 49% and 71% yields of TEMPO−CF_3 adduct **5** (Scheme 5, eqs 2 and 3). When other radical scavengers (butylated hydroxytoluene (BHT) and galvinyoxy) were added into the reaction mixture under the standard conditions, the formation of product **2a** was suppressed completely as well (Supporting Information). These results suggest that the reaction proceeds via a plausible radical process initiated by $CF_3^{\bullet}$ radical produced from the combination of PIDA, $TMSCF_3$, and CsF.[10,11] To understand the fact that the reaction takes places at C(3) rather than on the often observed N of the pyridine ring, ^{1}H NMR studies were performed in DMSO-d_6 by using 2-(methylamino)pyridine **6** as substrate and HOTf instead of $Co(OAc)_2$ due to its electron paramagnetic effect. As shown in Figure 1, C(3) in **6** has higher electron density than that of

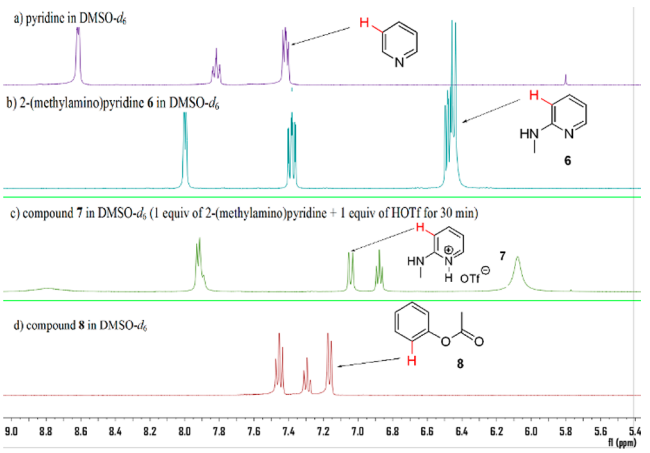
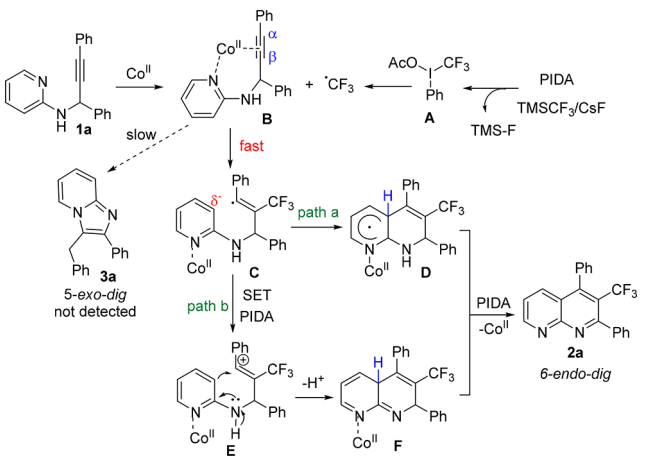


Figure 1. ^{1}H NMR studies of different related species in DMSO-d_6: (a) spectrum of pyridine in DMSO-d_6; (b) spectrum of 2-(methylamino)-pyridine in DMSO-d_6; (c) spectrum of a mixture of 2-(methylamino)-pyridine and 1 equiv of HOTf for 30 min in DMSO-d_6; (d) spectrum of phenol acetate in DMSO-d_6.

pyridine due to the resonance effect of aminopyridine by comparison of their ^{1}H chemical shifts (panel a vs b).[19] Treatment of **6** with 1 equiv of HOTf in DMSO-d_6 led to a decrease of the C(3) electron density (panel b vs c). However, its electron density was still higher that of phenol acetate **8**, which has been used to construct trifluoromethylcoumarin via a similar radical mechanism (panel c vs d).[12a] Furthermore, it is believed that the complexation of the N of pyridine with Lewis acids can activate C−H bond and facilitates C−H bond cleavage.[19,20]

A plausible reaction mechanism is proposed (Scheme 6). An initial trifluoromethylated hypervalent iodine(III) species **A** was formed from the reaction of PIDA, $TMSCF_3$, and CsF, and this delivered an electrophilic $CF_3^{\bullet}$ radical via homolytic cleav-

Scheme 6. Proposed Mechanism



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age.[10,11,21] β-Selective addition of the radical to the Co(II) coordinated C≡C in intermediate **B**, generated from complexation of $Co(OAc)_2$ with the pyridine "N" and C≡C in **1a**, gave an electrophilic radical intermediate **C**. It is believed that the Co(II) chelation with "N" rendered the "N" electron deficient. A new 6-*endo-dig* pathway with the relatively electron-rich C(3) carbon then led to radical **C**. Two possible paths may account for the formation of the terminal product **2a**.[12a] In path a, cyclization of the radical with C(3) carbon gives the radical intermediate **D**. Alternatively (path b), the intermediate **C** undergoes a PIDA-mediated single-electron transfer (SET) oxidation to generate a cation **E**, followed by a Friedel−Crafts type reaction to deliver an intermediate **F**. Finally, under the influence of the Co(II) promoted C−H cleavage, the product **2a** is produced by PIDA oxidation and concurrent release of catalyst Co(II).

In summary, we have developed an unprecedented $Co(OAc)_2$-catalyzed trimethylation and subsequent C(3)-selective functionalization of pyridine derivatives. The process creates a distinct C−C bond-forming process for the assembly of the new pyridine frameworks of trifluoromethylated 1,8-naphthyridines instead of the well-documented imidazo[1,2-*a*]pyridines. The combination of $Co(OAc)_2$ as catalyst, PIDA as oxidant, and presence of $TMSCF_3$ and CsF changes the reaction course from a commonly observed 5-*exo-dig* cyclization involving "N" to an unusual 6-*endo-dig* with "C" atom of pyridines. The mild reaction conditions enable a broad scope of *N*-(prop-2-ynyl)pyridin-2-amine substrates to work smoothly in the protocol. Further exploration of this catalytic system in new organic transformations and studies into understanding its mechanistic aspects are being conducted in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02759.

Experimental procedures, characterization, and spectral data for all compounds (PDF)

Accession Codes

CCDC 1529108 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hli77@ecust.edu.cn.
*E-mail: wwang@unm.edu.

ORCID

Wei Wang: 0000-0001-6043-0860

Notes

The authors declare no competing financial interest.

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(14) The details of screening of ligands are provided in the Supporting Information.

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