PHYSICAL SCIENCES

In situ generation of N-unsubstituted imines from alkyl azides and their applications for imine transfer via copper catalysis

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Although azides have been widely used in nitrene transfer reactions, in situ generation of N-H imines from azides for downstream transformations has rarely been explored. We report copper-mediated formation of N-unsubstituted aliphatic imines from easily available aliphatic azides using a customized phenanthroline-based ligand (L_1*). Through trapping in situ–generated N-H imines, multisubstituted pyridines or indoles were readily synthesized. ^{13}C-labeled azide was used as part of an isotope labeling study, which suggests that the construction of pyridine derivatives involves a three-component dehydrogenative condensation. The construction of 2,3,5-triaryl pyridines using this method provided evidence supporting a proposed pathway involving both imine formation and abnormal Chichibabin pyridine synthesis. The generation of N-unsubstituted imine intermediates was also confirmed by formation of indole derivatives from alkyl azides.

INTRODUCTION

Organic azides (*1*, *2*) have shown great potential in C–N bond formations catalyzed by transition metals, such as Rh (*3*, *4*), Fe (*5*, *6*), Cu (*7*–*9*), Ir (*10*), Co (*11*), and Ru (*12*) (Fig. 1A), because of their notable features as follows: (i) facile accessibility; (ii) environmental friendliness (only releasing an equivalent of nitrogen as byproduct); and (iii) not requiring the use of external oxidants because nitrene species can serve as internal oxidants. Mechanistic studies indicated that C–N bond–forming reactions using azides as the nitrogen source have predominantly involved nitrene species (*13*–*16*).

Unfortunately, the reactivity of azides has been nearly limited to nitrene transfer reactions, despite the knowledge that N-H imines could be derived from the 1,2-hydrogen shift of alkyl azide–derived nitrenes. In synthetic chemistry, it is desirable to direct the reactivities of multifunctional active intermediates toward divergent downstream transformations, preferably via catalyst modulation. Thus, it would be fascinating to achieve chemoselective catalytic transformations of azides to participate in nitrene transfer or imine chemistry. Although imines and their derivatives are among the most prevalent synthons (*17*–*22*), the use of imines suffers from the preformation of protected imines and subsequent removal of the protecting group (*23*–*28*). Instead, alkyl azide–derived nitrene isomerization would provide an attractive alternative for in situ generation of N-H imines. To date,

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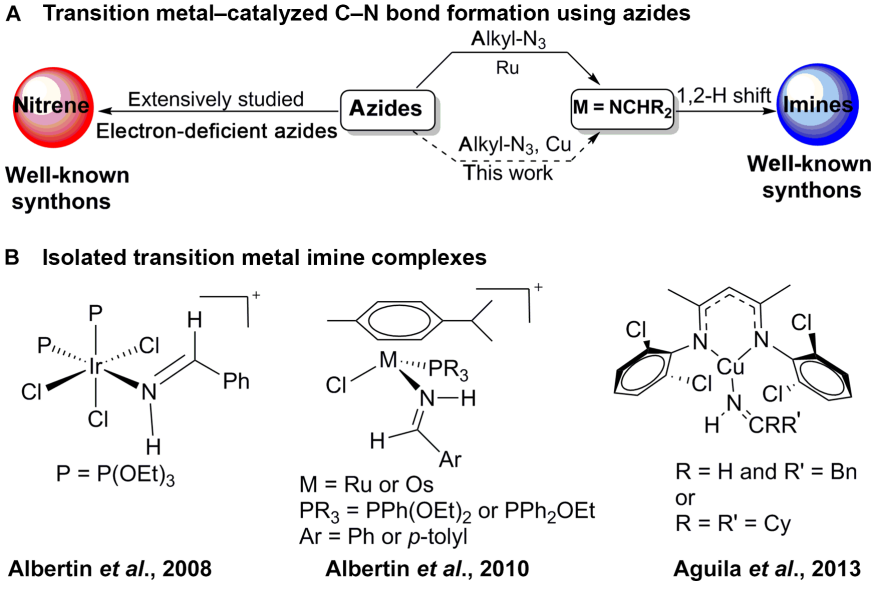


Fig. 1. Azides derived synthons and transition metal imine complexes. (**A**) Transition metal–catalyzed C–N bond formation from azides. (**B**) Isolated transition metal imine complexes.

alkyl azides have been relatively underexplored in nitrene transfer reactions (*6*, *8*, *9*), compared to azides substituted with an electron-withdrawing group (Fig. 1A). It is more difficult for an alkyl azide to release N_2 to generate nitrenes. Unsurprisingly, there have been few examples of obtaining N-unsubstituted imines directly from azides. Recently, Albertin *et al.* (*29*, *30*) reported the preparations of metal/imine complexes from benzyl azides (Fig. 1B). Further improvement of this scheme was reported by Park and Rhee and coworkers (*31*–*34*), who accomplished the generation of N-H imines using a Ru catalyst and then trapping them with various reagents. However, they required the use of noble metal and often need light assistance. Although Chiba *et al.* (*35*) achieved generation of N-unsubstituted imines from α-azido-*N*-arylamides with an inexpensive copper catalyst, the reaction scope was quite limited. In 2013, Aguila *et al.* (*15*) reported that unprotected aliphatic imines could be obtained using a Cu-based catalyst (Fig. 1B). Unfortunately, the coordination of the generated imines to [Cu] reduced the effectiveness of the catalyst, hindering further transformations.

It is still quite challenging to develop versatile and applicable methods to transfer N-H imines from alkyl azides using a nonprecious metal-based catalyst. Here, we describe the copper-catalyzed formation of aliphatic imines from easily available aliphatic azides using a specially designed phenanthroline-based ligand (L_1*). We also report our investigation of the reactivities of aliphatic N-H imines generated from azides in situ and further unusual constructions of multisubstituted pyridines or indole derivatives.

RESULTS

Ligand design

We started our investigation searching for catalyst/ligand systems suitable for cascade reactions involving imines generated from azides. We anticipated that these systems should meet two requirements: (i) a metal-based catalytic system enabling the release of molecular nitrogen to give N-H imines, and (ii) that imines must exhibit a weak binding affinity to the metal catalyst, allowing facile release for subsequent transformation (Fig. 2A). To date, phenanthroline-based ligands are widely used in a variety of copper-mediated reactions (*36*–*38*), and a typical modification on these ligands is installing small alkyl or methoxy groups at different positions. Although the structures of 2,9-diaryl-1,10-phenanthrolines had been reported (*39*), interest on these ligands was mainly focused on supramolecular chemistry and material chemistry. Considering that a sterically hindered ligand would less likely inhibit the reactivity of an N-H imine due to weakened imine-metal coordination, we designed and prepared a sterically hindered phenanthroline-based ligand (L_1*) (Fig. 2B). With this customized ligand in hand, we strived to test our original hypothesis for imine transfer chemistry.

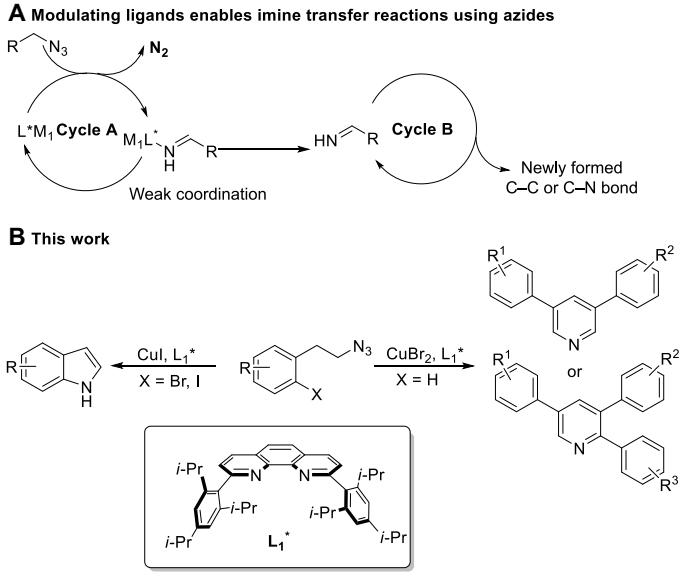
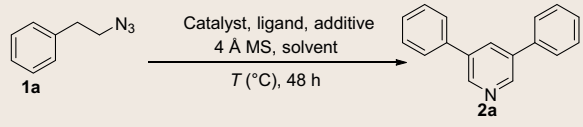


Fig. 2. The construction of C–N bonds through imine transfer reactions using azides as nitrogen source. (**A**) Modulating ligands enables imine transfer reactions using azides. (**B**) This work.

Construction of pyridines

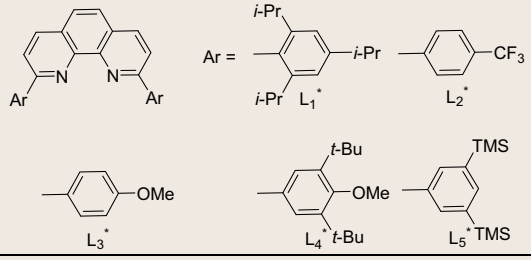
3,5-Diaryl derivatives of pyridines are structural subunits in many biologically active molecules (*40*, *41*); however, there are very few effective methods available for their synthesis (*42*–*48*). To the best of our knowledge, the construction of 3,5-diaryl pyridines from alkyl azides has not been achieved yet. Therefore, we initiated our synthesis of

Table 1. Optimization of reaction conditions for the construction of 3,5-diaryl pyridines. Reaction conditions: **1a** (0.1 mmol, 1 equiv.), catalyst (0.01 mmol, 0.1 equiv.), ligand (0.01 mmol, 0.1 equiv.), and additive (0.02 mmol, 0.2 equiv.) in solvent (1.0 ml) at *T* (°C) for 48 hours. MS, molecular sieves; phen, 1,10-phenanthroline; bpy, bipyridine; THF, tetrahydrofuran; n.r., no reaction.



Entry	Catalyst	Ligand	Additive	Solvent	*T* (°C)	Yield (%)
1*	CuI	L_1*	$AgSbF_6$	HFIP	80°C	44†
2*	CuI	—	$AgSbF_6$	HFIP	80°C	n.r.
3	CuI	L_1*	—	HFIP	80°C	n.r.
4*	CuI	L_2*	$AgSbF_6$	HFIP	80°C	14†
5*	CuI	L_3*	$AgSbF_6$	HFIP	80°C	17†
6*	CuI	Phen	$AgSbF_6$	HFIP	80°C	n.r.
7*	CuI	Bpy	$AgSbF_6$	HFIP	80°C	n.r.
8	$CuBr_2$	L_1*	$AgSbF_6$	HFIP	80°C	60†
9	$CuBr_2$	L_1*	$AgSbF_6$	HFIP	100°C	74†
10	$CuBr_2$	L_1*	$AgSbF_6$	HFIP	120°C	75†
11	$CuBr_2$	L_4*	$AgSbF_6$	HFIP	100°C	45†
12	$CuBr_2$	L_5*	$AgSbF_6$	HFIP	100°C	41†
13	$CuBr_2$	L_1*	$AgPF_6$	HFIP	100°C	66†
14	$CuBr_2$	L_1*	$AgBF_6$	HFIP	100°C	65†
15	$CuBr_2$	L_1*	Ag_2CO_3	HFIP	100°C	69†
16	$CuBr_2$	L_1*	$AgSbF_6$	Dioxane	100°C	n.r.
17	$CuBr_2$	L_1*	$AgSbF_6$	THF	100°C	20†
18	$CuBr_2$	L_1*	$AgSbF_6$	Toluene	100°C	24†

*Reaction was conducted with additive (0.01 mmol, 0.1 equiv.). †Yield was determined by ^{1}H NMR using 2,4,6-trimethoxybenzene as an internal standard.

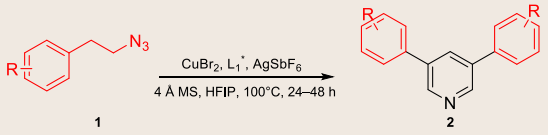


pyridines using alkyl azide **1a** (Table 1) in the presence of $AgSbF_6$ and the [Cu] catalyst/ligand as a model system. Hexafluoroisopropanol (HFIP) was selected as the solvent because we considered that HFIP's acidity could be useful to stabilize N-unsubstituted imine intermediates (*49*, *50*).

In our initial survey, a series of neutral, sterically hindered L_1*, L_2*, and L_3* were attempted (entries 1, 4, and 5). As anticipated, sterically more hindered and neutral L_1* favored the reaction, and the reactions conducted with commonly used 1,10-phenanthroline and bipyridine ligands resulted in no desired product **2a** (entries 6 and 7). The control experiments showed that both L_1* and additive $AgSbF_6$ were essential to the reaction (entries 2 and 3) probably because Ag^+ is needed to capture I^- or Br^-, liberating the reactive coordination site. Replacing CuI with $CuBr_2$ improved the reaction yield (entry 8). Increasing the temperature from 80° to 100°C resulted in higher yields; however, no improvement was observed at temperatures above 100°C (entries 8 to 10). Further reactions using L_4* and L_5* afforded products in much lower yields (entries 11 and 12) than the one using the L_1* ligand (entry 9). Screening of different additives indicated that $AgSbF_6$ was the most favored in this transformation (entries 9 and 13 to 15). The reactions conducted in toluene or tetrahydrofuran resulted in lower yields of pyridine **2a** (entries 17 and 18), whereas no desired product was formed when reactions were carried out in dioxane (entry 16), indicating that HFIP is crucial as a solvent for the reaction.

With the optimized reaction conditions in hand, we explored the use of the optimized reaction scheme for obtaining pyridines via N-unsubstituted imines from various azides (Table 2). (2-Azidoethyl) benzene **1**, containing a variety of functional groups, underwent this transformation to form the desired products **2** in moderate to high yields. Electron-donating, electron-neutral, and electron-withdrawing substituents were all well tolerated (**2a** to **2g** and **2j** to **2l**). The reaction

Table 2. Substrate scope for the construction of 3,5-diaryl pyridines. Reaction conditions: **1** (0.5 mmol, 1 equiv.), $CuBr_2$ (0.05 mmol, 0.1 equiv.), L_1* (0.05 mmol, 0.1 equiv.), $AgSbF_6$ (0.01 mmol, 0.2 equiv.), 4 Å MS (150 mg), and HFIP (5.0 ml). Yields were that of isolated products.



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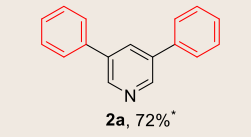
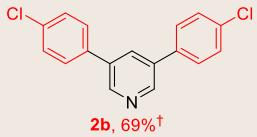
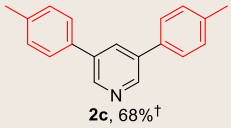
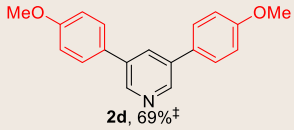
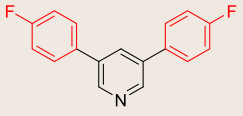
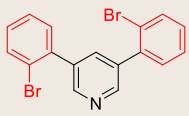

2a, 72%*

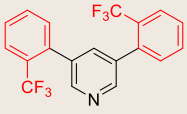

2b, 69%†

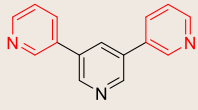

2c, 68%†

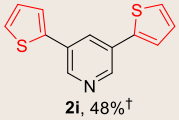

2d, 69%‡

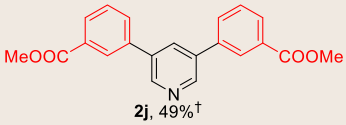

2e, 56%*

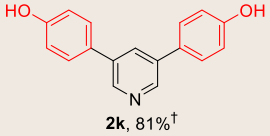

2f, 54%†

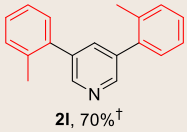

2g, 62%†


2h, 65%†,§


2i, 48%†

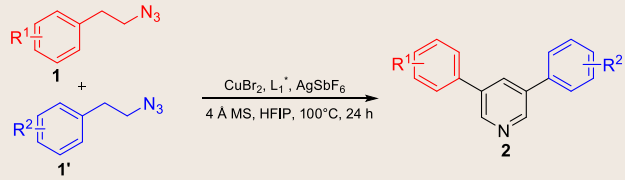

2j, 49%†


2k, 81%†

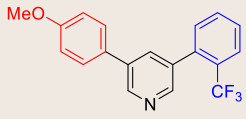

2l, 70%†

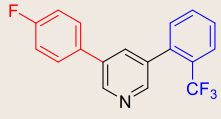
*48 h. †24 h. ‡28 h. §Reaction was conducted at 120°C.

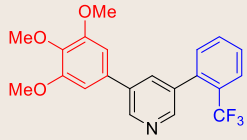
Table 3. Substrate molecules for the construction of unsymmetrical 3,5-diaryl pyridines. Reaction conditions: **1** (0.2 mmol, 1 equiv.), **1'** (0.8 mmol, 4 equiv.), $CuBr_2$ (0.04 mmol, 0.2 equiv.), L_1* (0.04 mmol, 0.2 equiv.), $AgSbF_6$ (0.08 mmol, 0.4 equiv.), 4 Å MS (60 mg), and HFIP (2.0 ml). Yields were that of isolated products.

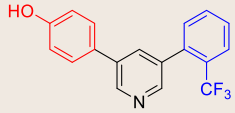


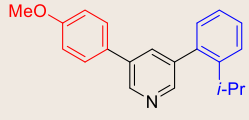
1 1' 2

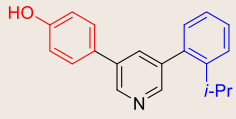

2dg, 60%

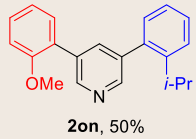

2eg, 42%

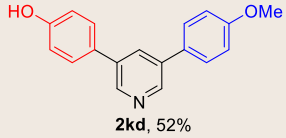

2mg, 53%

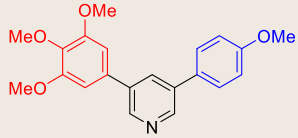

2kg, 64%

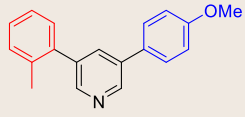

2dn, 51%


2kn, 51%


2on, 50%


2kd, 52%

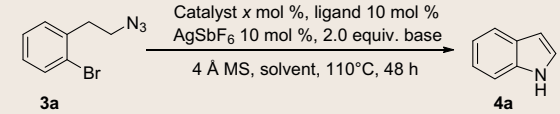

2md, 49%


2ld, 49%

conditions were also compatible with heteroarenes, such as pyridine and thiophene (**2h** and **2i**). It is noteworthy that the reaction with the azide compound bearing a hydroxyl group proceeded in the highest yield among the attempted reactions (**2k**). The bromo substituent was tolerated, considering that the substrate containing the bromo substituent could potentially undergo the copper-catalyzed Ullmann reaction (**2f**) (*51*).

Furthermore, unsymmetrical 3,5-disubstituted pyridines were also constructed through the N-unsubstituted imines (Table 3). The reaction of 1-(2-azidoethyl)-4-methoxybenzene **1d** with 1-(2-azidoethyl)-2-(trifluoromethyl)benzene **1g** (4 equiv.) gave the corresponding unsymmetrical pyridine **2dg** in 60% yield. Notably, the substrate bearing the hydroxyl group **1k** was also able to react with **1g**, forming the desired product **2kg** in 64% yield. Reaction of an electron-withdrawing group containing azide **1e** with **1g** displayed slightly lower selectivity (**2eg**). The alkyl azides **1d** and **1o** reacted with **1n** to form the desired products **2dn** and **2on**, respectively, in comparable yields. These data suggested that the substituents at the ortho and para positions on the aryl ring indistinctively influence selectivity. Traditionally, the synthesis of unsymmetrical 3,5-diaryl pyridines involves palladium-catalyzed Suzuki-Miyaura cross-coupling reactions (*52*–*55*), which suffers from multistep preparation and uses an expensive Pd catalyst. It is noteworthy that these unsymmetrical pyridines could not be prepared by the typical abnormal Chichibabin pyridine synthesis (*45*, *46*). Thus, this method showed great potential to access these pyridines through an alternative method.

Table 4. Optimization of reaction conditions for the construction of indoles. Reaction conditions: **3a** (0.1 mmol, 1 equiv.), catalyst [*x* mole percent (mol %)], ligand (0.01 mmol, 0.1 equiv.), $AgSbF_6$ (0.01 mmol, 0.1 equiv.), 4 Å MS (30 mg), and base (0.2 mmol, 2.0 equiv.) in solvent (1.0 ml) for 48 hours at 110°C. DME, dimethoxyethane; NMP, *N*-methyl-2-pyrrolidone.



3a **4a**

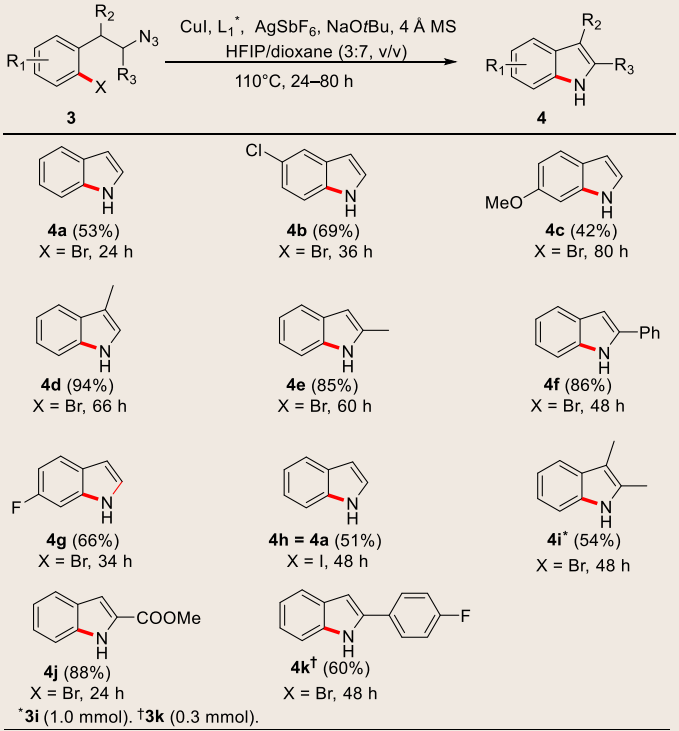
Entry	Catalyst (*x*)	Ligand	Base	Solvent	Yield (%)
1	CuI (20)	L_1^*	K_3PO_4	HFIP	0
2	CuI (20)	L_1^*	K_3PO_4	THF	0
3	CuI (20)	L_1^*	K_3PO_4	DME	0
4	CuI (20)	L_1^*	K_3PO_4	NMP	0
5	CuI (20)	L_1^*	K_3PO_4	Dioxane	Trace
6	CuI (20)	L_2^*	K_3PO_4	Dioxane	0
7	CuI (20)	L_3^*	K_3PO_4	Dioxane	0
8	$CuBr_2$ (20)	L_1^*	K_3PO_4	Dioxane	0
9	CuI (20)	L_1^*	K_3PO_4	50% HFIP/dioxane	0
10	CuI (20)	L_1^*	K_3PO_4	75% HFIP/dioxane	0
11	CuI (20)	L_1^*	K_3PO_4	25% HFIP/dioxane	28*
12	CuI (20)	L_1^*	K_3PO_4	40% HFIP/dioxane	11*
13	CuI (20)	L_1^*	K_3PO_4	30% HFIP/dioxane	31*
14	CuI (20)	—	K_3PO_4	30% HFIP/dioxane	0
15	CuI (20)	L_1^*	K_2CO_3	30% HFIP/dioxane	29*
16	CuI (20)	L_1^*	NaOAc	30% HFIP/dioxane	5*
17	CuI (20)	L_1^*	NaO*t*Bu	30% HFIP/dioxane	41*
18	CuI (30)	L_1^*	NaO*t*Bu	30% HFIP/dioxane	47*
19	CuI (40)	L_1^*	NaO*t*Bu	30% HFIP/dioxane	56*
20	CuI (50)	L_1^*	NaO*t*Bu	30% HFIP/dioxane	57*

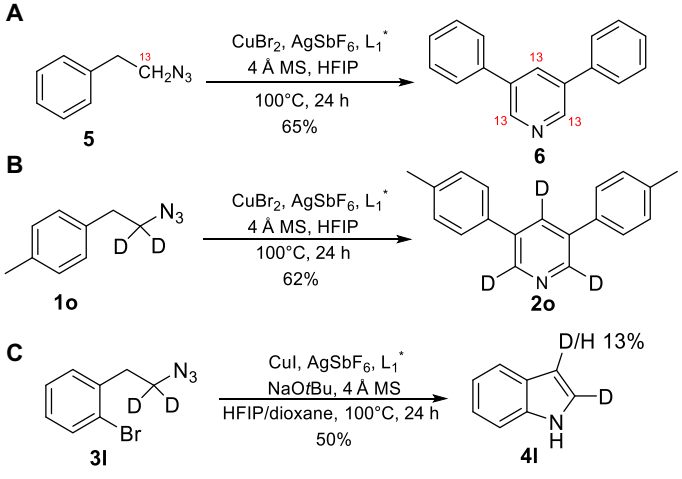
*Yield was determined by ^{1}H NMR using 2,4,6-trimethoxybenzene as an internal standard.

Construction of N-H indoles

To further demonstrate the potential application of in situ–generated N-unsubstituted imines, we decided to explore the possibility of transferring these imines to indoles. It is well known that indole derivatives are among the most abundant naturally occurring heterocyclic

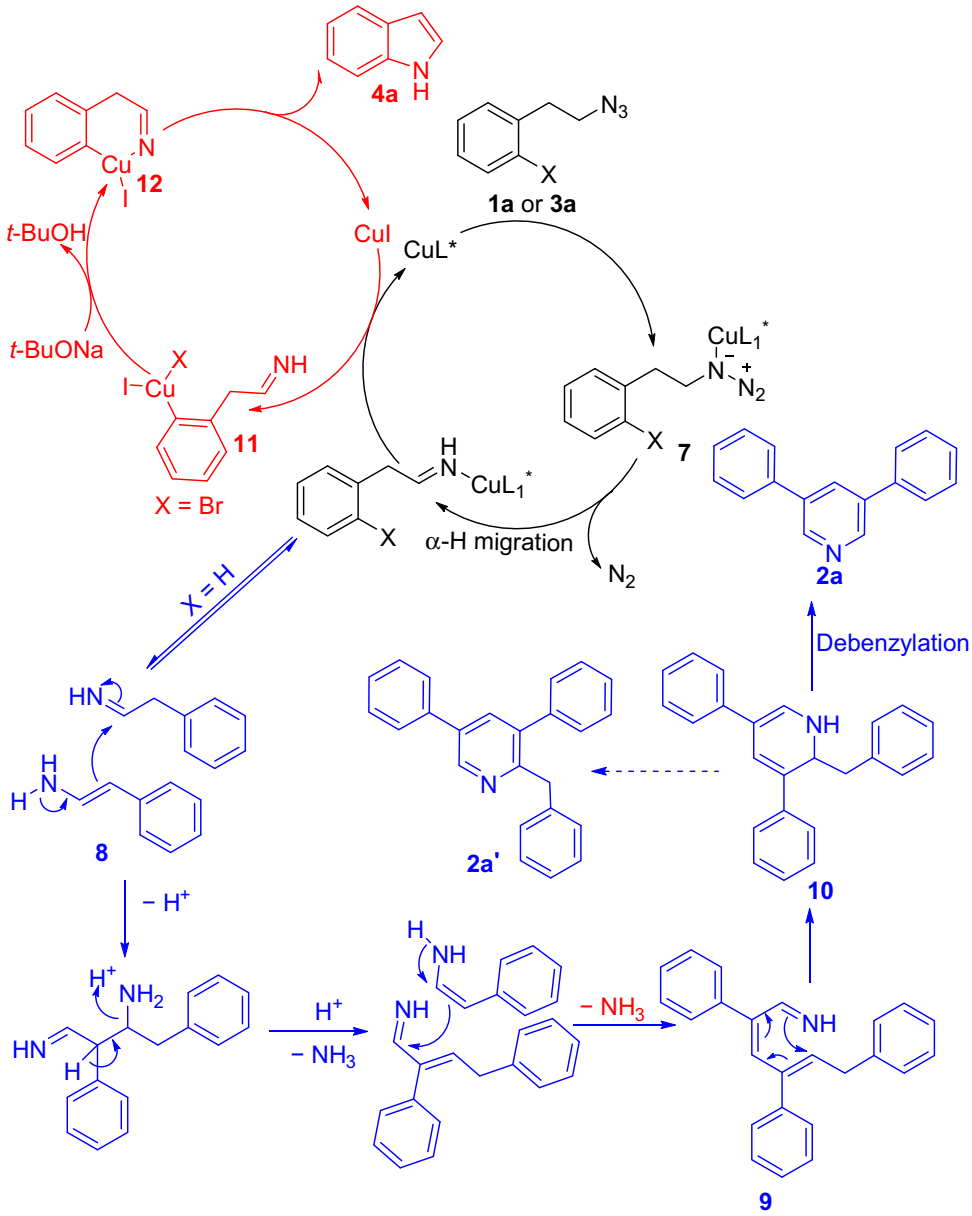
Table 5. Substrate scope for the construction of indoles. Reaction conditions: **3** (0.5 mmol, 1 equiv.), CuI (0.2 mmol, 0.4 equiv.), L_1* (0.05 mmol, 0.1 equiv.), $AgSbF_6$ (0.05 mmol, 0.1 equiv.), 4 Å MS (150 mg), and NaO*t*Bu (0.1 mmol, 2.0 equiv.) in HFIP/dioxane [3:7 (v/v), 5.0 ml] for 24 to 80 hours at 110°C. Yields were that of isolated products.





Scheme 1. Isotope study. (**A**) Carbon-13 labeling experiment. (**B**) Deuterium-labeling experiment in the synthesis of pyridine. (**C**) Deuterium-labeling experiment in the synthesis of indole.

compounds, and many of them have been shown to be important pharmaceutical agents (*55*, *56*). An important strategy for indole synthesis is palladium-catalyzed cyclization of *N*-aryl enamines or imines (*57*–*59*). We hypothesized that the active imines generated from copper-catalyzed processes could further undergo cyclization to afford N-unsubstituted indoles without using a palladium catalyst, if the copper-catalyzed imine formation is incorporated with Ullmann chemistry. Azide **3a** was chosen as the model substrate to study for optimized reaction conditions (Table 4). When the reaction of **3a** was carried out in HFIP, no desired indole product **4a** was observed; the corresponding pyridine **2f** was formed as the major product (entry 1). We then searched for a solvent to block the pathway to form pyridine **2**, forcing the reaction to proceed in a route toward indole **4** (entries 2 to 5). Trace amounts of **4a** were obtained using dioxane as a solvent, whereas gas chromatography–mass spectrometry analysis indicated that **3a** remained largely unreacted (entry 5). When L_2* or L_3* was used as ligand, no desired product was formed (entries 6 and 7). CuI was a superior catalyst to $CuBr_2$, and the reaction catalyzed by $CuBr_2$ resulted in no desired product (entry 8). Success in this reaction would rely on two factors: in situ generation of N-H imine and copper-mediated cyclization. Because HFIP would favor N-H imine generation process and N-H imine cyclization could occur in dioxane, we decided to use a mixed solvent of dioxane and HFIP to study the model reaction. As expected, the reaction yield was improved by using a mixed solvent (entries 9 to 13). The reaction conducted without L_1* gave no indole product **4a** (entry 14), indicating that L_1* is indispensable for the reaction. Sodium *tert*-butoxide (NaO*t*Bu) worked best among the three bases attempted (entries 15 to 17). Increasing the ratio of catalyst



Scheme 2. Proposed mechanism.

CuI to substrate improved the reaction yield until this ratio surpassed 0.4:1 (entries 18 to 20).

Having identified the suitable reaction conditions for the construction of indoles, we investigated the scope of substrates (Table 5). Ortho-halogenated (2-azidoethyl)benzenes bearing a variety of functional groups were found to form their corresponding indoles in moderate to excellent yields. Reactions of substrates with electron-withdrawing groups attached to a phenyl ring proceeded in higher yields than those with an electron-donating group (**4b**, **4c**, and **4g**). Substituents on the alkyl chain were also well tolerated (**4e** to **4k**). The reaction conducted with *ortho*-iodo(2-azidoethyl)benzene **3h** also resulted in the formation of **4a**, but it required longer times to achieve yields similar to that of the reaction with ortho-bromo analog **3a.**

Mechanistic investigations

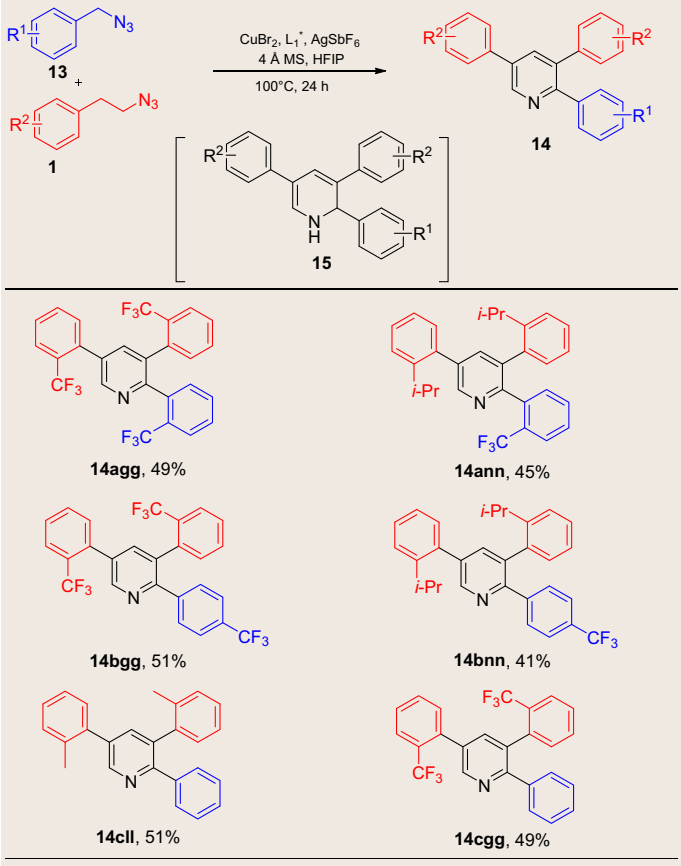
To shed light on the mechanism, several isotopic labeling experiments were conducted (Scheme 1). ^{13}C-labeled azide **5** was synthesized and subjected to the optimized reaction conditions in Table 1. The transformation produced a 2,4,6-^{13}C-labeled product (Scheme 1A). Reactions conducted with α-deuterated azide **1o** formed 2,4,6-deuterated pyridine **2o** (Scheme 1B). These results demonstrated that this reaction proceeds through a three-component transformation. Using α-deuterated azide **3l**, we observed a deuterium incorporation at the 3-position of indole **4l** (Scheme 1C), which suggested an equilibrium between imine and enamine. On the basis of the results of the isotope study, we proposed that the formation of both pyridines and indoles from imines, generated from alkyl azides, occurs via the mechanisms shown in Scheme 2. The initial step is the generation of an N-H imine through release of one molecular nitrogen from the starting alkyl azide (**1a** or **3a**). The sterically hindered ligand then allows the dissociation of the resulting imine from the copper complex, and the imine further undergoes a process similar to an abnormal Chichibabin reaction (*60*–*62*) to give intermediate **14.** This step is then followed by subsequent debenzylation (*45*–*47*), providing pyridine **2a.** In the construction of indole **4a** from the alkyl azide **3a**, the in situ–generated imine undergoes a classical Ullmann reaction (*63*, *64*) to afford the indole **4a.**

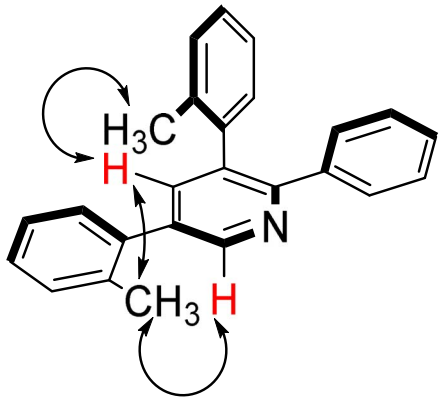
DISCUSSION

The construction of 3,5-diaryl pyridines and N-H indoles manifested the potential applications of the in situ–generated aliphatic N-H imines using our method. To the best of our knowledge, it is the first time alkyl azides were transformed to 3,5-diaryl pyridines and N-H indoles. It is noteworthy that the synthesis of unsymmetrical 3,5-diaryl pyridines traditionally involves two stepwise palladium-catalyzed Suzuki-Miyaura cross-coupling reactions and could not be also obtained by the typical abnormal Chichibabin pyridine synthesis (*45*, *46*). In addition, although it seems to require a highly excessive amount of azides **1′** (4 equiv.), azides **1′** (2 equiv.) theoretically reacted with azides **1** (1 equiv.) to afford unsymmetrical 3,5-diaryl pyridines. Thus, there was just onefold excess of alkyl azide **1′.** This method showed great potential to access these pyridines through a different route.

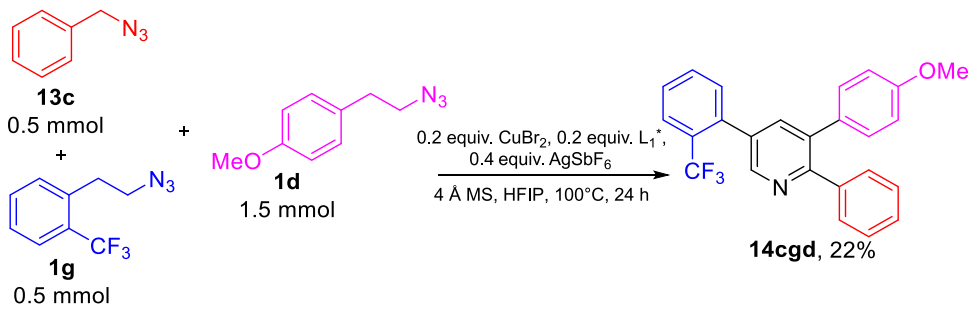
In our proposed mechanism, the putative intermediate 2,3,5-trisubstituted dihydropyridine **10** should predominantly undergo a debenzylation process to give 3,5-disubstitued pyridine **2a**, which is consistent with the observations of Burns and Baran (*47*) during their synthesis of 3,5-diarylpyridiniums. It was speculated that **2a′** has a destabilized structure, owing to the steric hindrance among the three substituents on the pyridine core. Thus, we hypothesized that 2,3,5-trisubstituted pyridines could be obtained if the benzyl group in the proposed intermediate **10** was replaced by an aryl group. On the basis of this hypothesis, reactions of different benzyl azides **13** with alkyl azides **1** were conducted under the reaction

Table 6. Construction of 2,3,5-triaryl pyridines. Reaction conditions: **13** (0.2 mmol, 1 equiv.), **1** (0.6 mmol, 3 equiv.), $CuBr_2$ (0.04 mmol, 0.2 equiv.), L_1* (0.04 mmol, 0.2 equiv.), $AgSbF_6$ (0.08 mmol, 0.4 equiv.), and 4 Å MS (60 mg) in HFIP (2.0 ml) for 24 hours at 100°C. Yields were that of isolated products.





Scheme 3. Key NOESY correlations of 14cll.



Scheme 4. Construction of unsymmetrical 2,3,5-triaryl pyridine 14cgd.

conditions outlined in Table 6. To our delight, 2,3,5-trisubstituted pyridines **14** were formed, presumably involving the formation of 2,3,5-trisubstituted dihydropyridine intermediates **15**, followed by an aromatization (Table 6). The positions of the two *o*-tolyl groups and the phenyl group on the pyridine ring in **14cll** were determined by nuclear Overhauser effect spectroscopy (NOESY) nuclear magnetic resonance (NMR) analysis (Scheme 3). These results also confirmed the mechanism proposed in Scheme 2. Inspired by these results, our curiosity led us to construct pyridines bearing three different substituents at each of the 2-, 3-, and 5-positions of the pyridine ring. Accordingly, a reaction conducted with three different benzyl azides, **13c**, **1g**, and **1d**, resulted in the predicted trisubstituted pyridine **14cgd**, albeit at low yield (Scheme 4). This represents a potential novel method to synthesize the 2,3,5-trisubstituted pyridines containing three distinct aryl substituents.

In summary, we have developed a method of generating N-unsubstituted aliphatic imines from easily available aliphatic azides using an inexpensive copper catalyst. By trapping the N-H imines generated in situ, multisubstituted pyridine and indole derivatives were synthesized. The described construction of 2,3,5-triaryl pyridines was carried out by coupling imine formation with a subsequent abnormal Chichibabin pyridine synthesis. This scheme provides a potential method for synthesizing the 2,3,5-trisubstituted pyridines containing three different aryl substituents. Further studies on the detailed mechanism and other potential applications of in situ–generated imines are ongoing in our laboratory.

MATERIALS AND METHODS

General procedure for the construction of 3,5-diaryl pyridines

In a glove box, a 48-ml sealed tube was charged with 4 Å molecular sieves (150 mg), $CuBr_2$ (0.100 equiv., 11.1 mg, 0.0500 mmol), L_1* (0.100 equiv., 29.2 mg, 0.0500 mmol), $AgSbF_6$ (0.200 equiv., 34.3 mg, 0.100 mmol), and HFIP (5.00 ml). Corresponding azides (1.00 equiv., 0.500 mmol) were added in the suspension and then stirred for 24 to 48 hours at 100°C. Then, the solvent was removed in vacuo. The residue was diluted with ethyl acetate and water, and ammonia was added (1 ml). The layers were separated and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give the products.

General procedure for the construction of unsymmetrical 3,5-diaryl pyridines

In a glove box, a 15-ml sealed tube was charged with 4 Å molecular sieves (60 mg), $CuBr_2$ (0.20 equiv., 8.9 mg, 0.040 mmol), L_1* (0.20 equiv., 23.2 mg, 0.040 mmol), $AgSbF_6$ (0.40 equiv., 27.4 mg, 0.080 mmol), and HFIP (2.0 ml). Azides **1** (1.0 equiv., 0.20 mmol) and azides **1′** (4.0 equiv., 0.80 mmol) were added in the suspension. Then, the mixture was stirred for 24 hours at 100°C. The reaction mixture was diluted with ethyl acetate and water, and ammonia was added (1.0 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give the products.

General procedure for the construction of N-H indoles

In a glove box, a 48-ml sealed tube was charged with 4 Å molecular sieves (150 mg), CuI (0.400 equiv., 38.1 mg, 0.200 mmol), L_1* (0.100 equiv., 29.2 mg, 0.0500 mmol), $AgSbF_6$ (0.100 equiv., 17.2 mg, 0.0500 mmol), NaO*t*Bu (2.00 equiv., 96.1 mg, 0.100 mmol), and 30% HFIP/dioxane (5.00 ml). Corresponding azides (1.00 equiv., 0.500 mmol) were added in the suspension and then stirred for 24 to 80 hours at 110°C. The reaction mixture was diluted with dichloromethane and water, and ammonia was then added (1.00 ml). The layers were separated and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give the products.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/8/e1700826/DC1
Supplementary Materials and Methods
Substrate structure
Experimental sections
NMR spectra
References (*65*–*77*)

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