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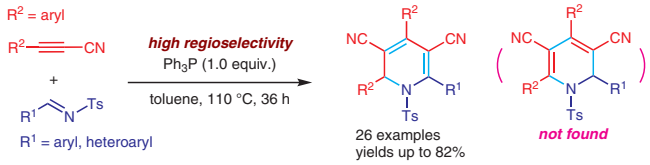
Highly Regioselective Phosphine-Promoted [2+2+2] Annulations of Cyanoacetylenes and *N*-Tosylimines to 1,2-Dihydropyridine-3,5-dicarbonitrile Derivatives

Jinfeng Zhang
Qi Zhang
Xin Ji
Ling-Guo Meng*

Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, P. R. of China
milig@126.com



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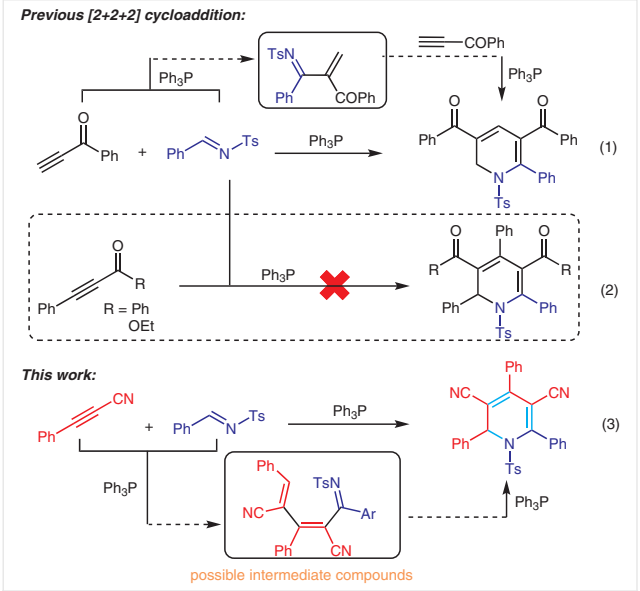
Abstract A series of fully functionalized dihydropyridine-3,5-dicarbonitrile derivatives were easily prepared through [2+2+2] annulations of cyanoacetylenes and *N*-tosylimines in the presence of tertiary phosphine. The scope of the cyclization reaction was investigated, and the high regioselectivity was explained by a rational reaction mechanism.

Key words phosphine, annulations, cyanoacetylenes, *N*-tosylimines, regioselectivity

Dihydropyridines and its derivatives are among the most prevalent heterocyclic structural units, and these molecules have attracted much attention from organic chemists, as they widely exist in pharmaceutical targets, natural products, bioactive molecules, as well as in functional materials.[1] Among them, cyano-substituted dihydropyridines are corrosion inhibitors, show anti-inflammatory and fluorescence behavior, and are used as antioxidant and coenzyme inhibitors;[2] and their derivatives have also been used as dyes for synthetic fabrics[3] and in security paper.[4] However, only a few reports are related to the synthesis of cyano-substituted dihydropyridines or its derivatives because of the difficulty to directly introduce a cyano group into a nitrogen-containing heterocycle.[5] Thus, to find a new and facile method to efficiently construct cyano-substituted dihydropyridines is a significant research task in organic synthesis task in organic synthesis.[6]

In the past decades, tertiary phosphine, with a comparatively strong and readily tunable nucleophilicity, induced various annulation reactions based on the active alkynes or allenes and had been certified as efficient synthetic method to obtain multifunctional cyclic compounds under simple reaction conditions.[7] Among various electrophiles used in phosphine-promoted cycloadditions, *N*-tosylimines are one kind of the most important precursor and are widely used as substrate for the synthesis of various nitrogen-containing cyclic compounds through different cycloaddition reactions, such as [2+2],[8] [2+3],[9] [2+4],[10] [4+1],[11] and [4+2][12] annulations. Apart from the above reactions, sequential [3+2]/[2+3],[13] [2+3]/[2+3],[14] and [4+2]/[2+3][15] annulations were also reported. Nevertheless, there are a few reports about multicomponent cycloaddition reactions in which *N*-tosylimines were used as a precursor in the presence of organic base.[8a,b] Recently, the [2+2+2] cycloaddition of active alkynes with *N*-tosylimines was developed by Tong's group and represented a convenient access to functionalized 1,2-dihydropyridines (Scheme 1, eq. 1).[16] Unfortunately, these



Scheme 1 Phosphine-driven [2+2+2] cycloadditions with different reaction procedures

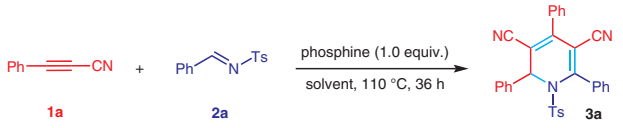
synthetic methods were unworkable to construct fully substituted 1,2-dihydropyridine compounds when β-substituted alkyne ketones or esters participated in the above reaction through our test (Scheme 1, eq. 2). Cyanoacetylene was often a neglected activated alkyne[17] and had a better potential nucleophilicity in the presence of tertiary phosphine due to the much stronger electron-withdrawing property of the cyano group.

To our delight, cyanoacetylene could be employed to overcome the above-mentioned problems, and fully substituted 1,2-dihydropyridine-3,5-dicarbonitrile derivatives were obtained with high regioselectivity (Scheme 1, eq. 3) and compared to previous reports. These new protocols proceeded in different reaction mechanism and had the advantages of easily controlled reaction conditions, which afforded the desired adducts with improved functional group tolerance, broaden scope of the substrate, and diversity of 1,2-dihydropyridine species. Herein, we report our efforts in the development of this annulation process, and such studies would be of benefit in expanding the diversity of cyano-substituted 1,2-dihydropyridine derivatives in synthetic chemistry.

In the initial exploration of the [2+2+2] annulation reaction of cyanoacetylenes and *N*-tosylimines, 3-phenylpropiolonitrile (**1a**) and *N*-tosyl benzaldimine (**2a**) were chosen as model substrates for our investigation, and the results are summarized in Table 1. The reaction of **1a** with **2a** in the presence of Ph_3P (1.0 equiv.) at 110 °C in toluene for 36 h afforded the annulation product **3a** as a white solid in 82% yield (Table 1, entry 1). The amount of Ph_3P had an obvious effect on this annulation reaction. When 0.5 equiv. of Ph_3P were used, the desired product **3a** was isolated in 55% yield, and the yield of **3a** was not improved by further increasing the amount of Ph_3P (Table 1, entries 2 and 3). Further, the yield of **3a** was not successfully improved when the reaction was conducted at room temperature, 80 °C, or 130 °C. (Table 1, entries 4–6). Then in toluene solvent and 110 °C, several tertiary phosphines were screened as promoter. It was found that various aromatic phosphines, such as (4-$CH_3C_6H_4)_3P$, (4-$CH_3OC_6H_4)_3P$, (4- $FC_6H_4)_3P$, and (4-$ClC_6H_4)_3P$ (Table 1, entries 7–10), could all promote the reaction, but no one gave a better yield than that of using Ph_3P. Meanwhile, alternative promoters such as Ph_2MeP, 1,2-bis(diphenylphosphino)ethane (DPPE), $PhMe_2P$, Bn_3P, $^nBu_3P$, and 2-(diphenylphosphino)pyridine (DPPPy) resulted in relatively lower yields (Table 1, entries 11–16). Choosing Ph_3P as the optimized promoter and after testing various common solvents, toluene was found to be the best one. THF was inferior and afforded only 41% yield of **3a**. When the solvent was switched to CH_3CN, only a trace amount of **3a** was detected. No desired product was detected when DMF and DMSO were used as solvent (Table 1, entries 17–20).

Under the preferred conditions (1.0 equiv. of Ph_3P was used as the promoter in refluxing toluene at 110 °C for 36 h), the substrate scope and limitations for the annulations of 3-phenylpropiolonitrile (**1a**) and *N*-tosylimines **2** were studied (Scheme 2). For a wide range of aromatic *N*-tosylimines with either relatively electron-poor or electron-rich aryl groups, their corresponding [2+2+2] annulations with **1a** readily proceeded, giving fully substituted 1,2-dihydropyridine **3** with high regioselectivity, and the representative results are shown in Scheme 2. But the efficiency of this reaction was relatively sensitive to changes in the aryl substituents when different aromatic imines **2** were tested. The substrate with an electron-donating group on the aromatic ring gave a better yield than that with an electron-withdrawing group on the aromatic ring. The substrate containing an electron-donating group, such as me-

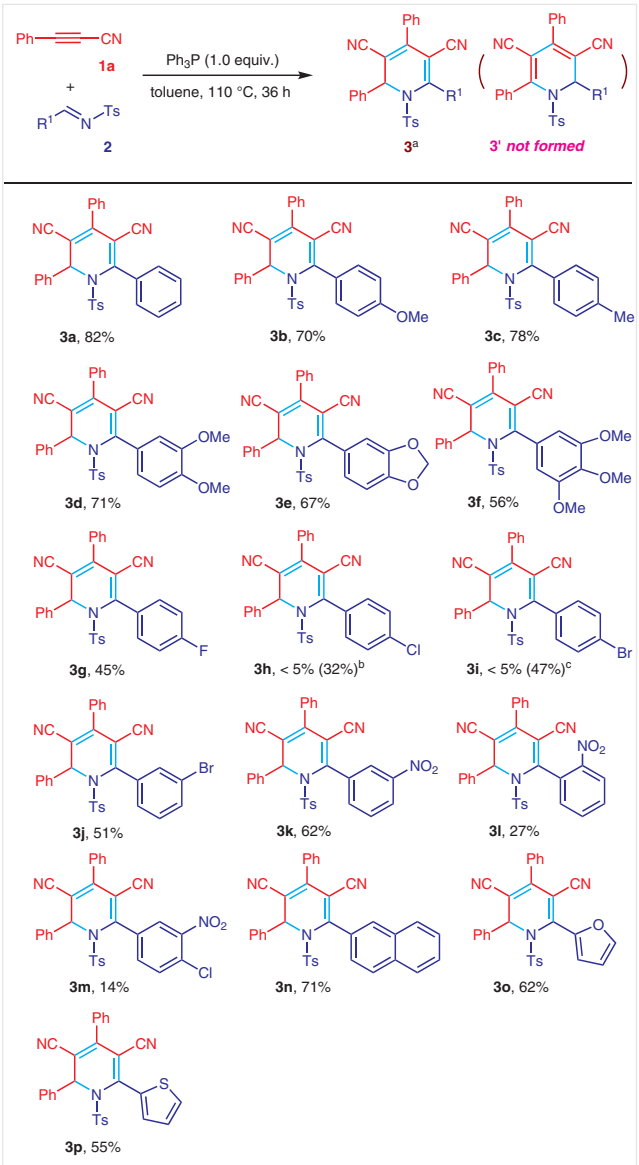
Table 1 Optimization of the Reaction Conditions[a]



Entry	Phosphine	Solvent	Yield (%)[b]
1	Ph_3P	toluene	82
2	Ph_3P	toluene	55[c]
3	Ph_3P	toluene	73[d]
4	Ph_3P	toluene	35[e]
5	Ph_3P	toluene	60[f]
6	Ph_3P	toluene	76[g]
7	$(4\text{-}CH_3C6H_4)_3P$	toluene	60
8	$(4\text{-}CH_3OC_6H_4)_3P$	toluene	58
9	$(4\text{-}FC_6H_4)_3P$	toluene	46
10	$(4\text{-}ClC_6H_4)_3P$	toluene	42
11	Ph_2MeP	toluene	40
12	DPPE[h]	toluene	33
13	$PhMe_2P$	toluene	25
14	Bn_3P	toluene	18
15	$^nBu_3P$	toluene	<10
16	DPPPy[i]	toluene	<10
17	Ph_3P	THF	41
18	Ph_3P	CH_3CN	<10
19	Ph_3P	DMF	ND[j]
20	Ph_3P	DMSO	ND[j]

[a] Reaction conditions: **1a** (0.40 mmol), **2a** (0.20 mmol), phosphine (0.2 mmol), solvent (2.0 mL), 110 °C, in sealed tube, 36 h.
[b] Isolated yield.
[c] 0.5 equiv. of Ph_3P was used.
[d] 2.0 equiv. of Ph_3P was used.
[e] At room temperature.
[f] At 80 °C.
[g] At 130 °C.
[h] 1,2-Bis(diphenylphosphino)ethane.
[i] 2-(Diphenylphosphino)pyridine.
[j] ND: No product was detected.

thoxy and methyl, on its phenyl ring, the corresponding products were isolated in 70% and 78% yields, respectively. Substrate **2** containing multiple electron-donating groups could also give the desired annulation products **3d–f**) in 56–71% yields. The reaction was difficult to manipulate when electron-withdrawing group are introduced in the substrate.

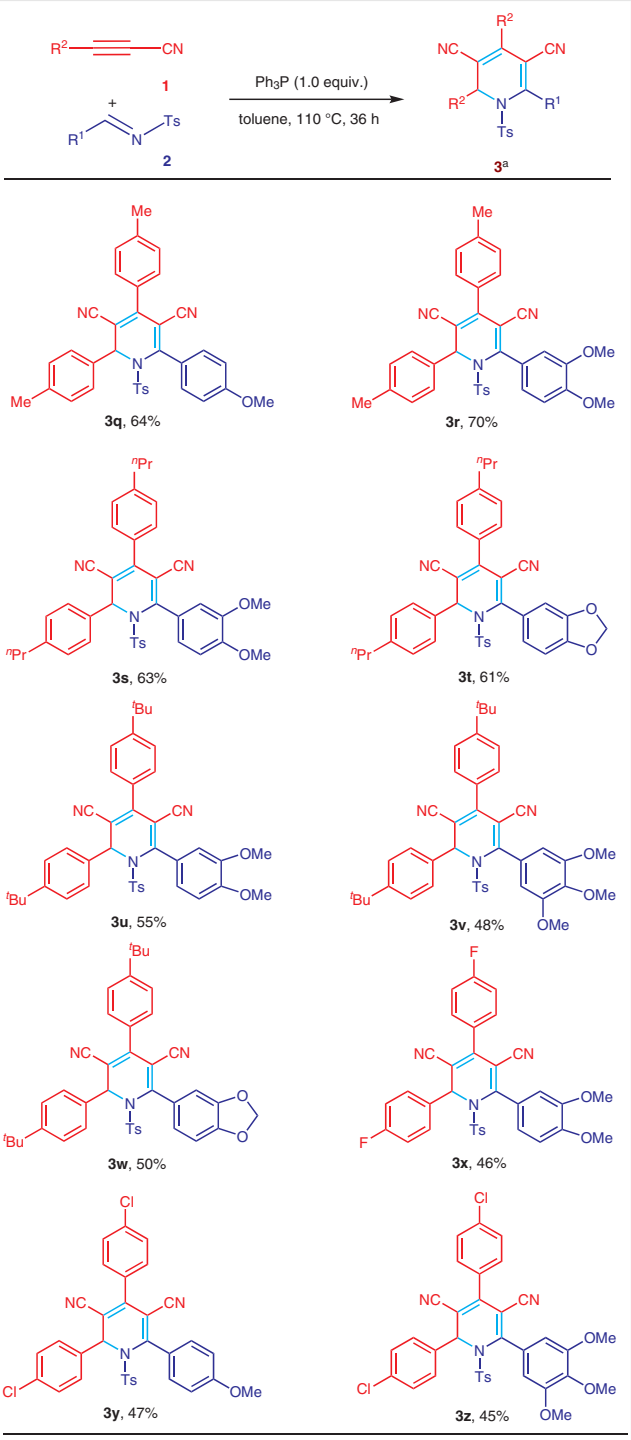


Scheme 2 Ph_3P-mediated formal [2+2+2] cycloadditions of 3-phenylpropiolonitrile (**1a**) with *N*-tosylimines. Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), Ph_3P (0.20 mmol), toluene (2.0 mL), 110 °C, in sealed tube, 36 h.[a] Isolated yields. [b] 1.0 equiv. of $^nBu_3P$ was used.[c]1.0 equiv. of $(4\text{-}ClC_6H_4)_3P$ was used.

For example, the substituent was a phenyl group bearing a fluoro group that could be converted into the desired product in 45% yield under optimized conditions. However, when the substituents were phenyl bearing a chloro or bromo group, $^nBu_3P$ and $(4\text{-}ClC_6H_4)_3P$ are needed to trigger the annulation, respectively. Treatment of *N*-tosylimines **2**, containing 3-bromo- or 3-nitrophenyl groups, with **1a** also afforded the desired products **3j** and **3k** in 51% and 62% yields, respectively. However, when a nitro group was located at the *ortho*-position of its benzene ring, the corresponding product **3l** was obtained in only 27% yield, which might be ascribed to steric hindrance. Furthermore, multiple electron-withdrawing groups introduced in the imine **2** also could be converted to corresponding product, albeit the yield was so low. In addition, *N*-tosylimines **2** containing 2-naphthyl or heteroaryl groups (such as furyl, thienyl) could also be used in the reaction. On the other hand, no desired product was detected when aliphatic *N*-tosylimine was submitted to this reaction. It should be noted that the products 1,2-dihydropyridine **3** were isolated as single diastereomers in all tested cases, which were analyzed through ^1H NMR and ^{13}C NMR spectroscopy. Its analogues **3′** could not be formed.[18]

To evaluate the scope of this reaction further, various cyanoacetylenes were also tested under the standard conditions, and the results are summarized in Scheme 3. Various aromatic cyanoacetylenes bearing different substituents afforded the corresponding products **3** in moderate to good yields. Moreover, the substrate with an electron-donating group on the aromatic ring gave a better yield than that with an electron-withdrawing group. For example, cyanoacetylenes with electron-donating functionalities, such as methyl, propyl, *tert*-butyl groups, reacted with different *N*-tosylimines to afford the corresponding products **3q–w** in 48–70% yields. While electron-withdrawing functionalities, such as fluoro and chloro groups, introduced in substrate **1**, the yields of products **3x–z** were decreased to 45–47%. Notably, the bulk of the substituents in **1** had slight effect on the yield of this annulation (**3r** *vs* **3s** *vs* **3u**; **3t** *vs* **3w**). Furthermore, aliphatic cyanoacetylene was in place of aromatic cyanoacetylene, the reaction was disordered, and the desired product cannot be detected. The structures of compound **3** were identified by ^1H NMR and ^{13}C NMR spectroscopy and HRMS analysis.

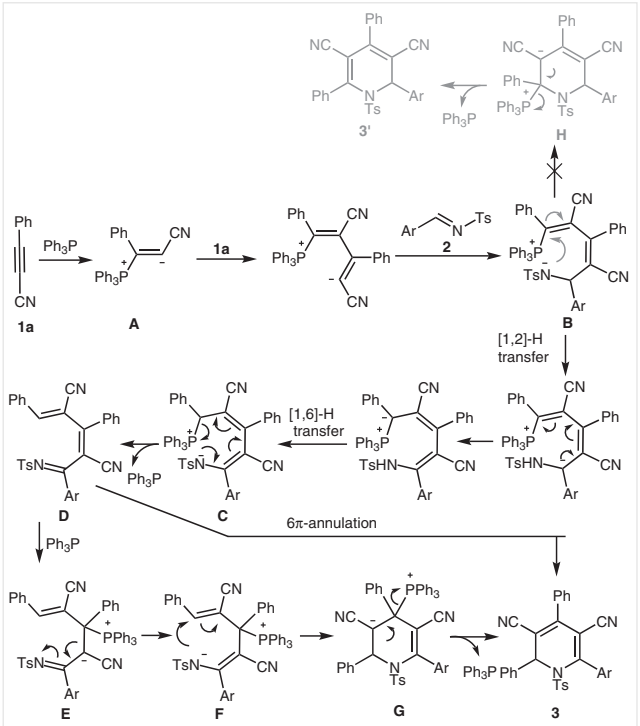
X-ray crystallographic analysis for representative compound **3q** provided unequivocal evidence for the position of double bond in the structure of the annulation product, and the corresponding CIF data were presented in the Supporting Information. Furthermore, with the obtained fully functionalized 1,2-dihydropyridine-3,5-dicarbonitrile derivatives in hand, their further transformation into pyridine-3,5-dicarbonitrile derivatives is desirable. When typical 1,2-dihydropyridine-3,5-dicarbonitrile derivative **3a** or **3j** was solved into DMF, and the mixture was performed at 140 °C for 12 h, the corresponding pyridine-3,5-dicarbonitrile products **4a** and **4b** were obtained in 96% and 92% yields, respectively.



Scheme 3 Ph_3P-mediated formal [2+2+2] cycloaddition reactions of cyanoacetylenes **1** and *N*-tosylimines **2**. Reaction conditions: **1** (0.40 mmol), **2** (0.20 mmol), Ph_3P (0.20 mmol), toluene (2.0 mL), 110 °C, in sealed tube, 36 h. [a] Isolated yields.

Although the detailed reaction mechanism is not clear at the current stage, a rational reaction pathway is proposed and is different from Tong's mechanism (Scheme 4).

The reaction is believed to be initiated by the nucleophilic addition of Ph_3P to the 3-phenylpropiolonitrile (**1a**), thus giving the zwitterionic intermediate **A**, followed by two consecutive nucleophilic attacks of another molecular **1a** and *N*-tosylimines **2** to afford intermediate **B** to generate **C** through two consecutive proton-transfer steps. Then elimination of Ph_3P yields intermediate **D**. Our attempts to isolate **D** were not successful which might be ascribed to its unstable structure property, and **D** is rapidly reacted with Ph_3P to give **E**. Then electron-transfer-generated intermediate **F**, which undergoes an intramolecular nucleophilic attack of the nitrogen anion (TsN^-) to the double bond (Michael-type) to give intermediate **G**, followed by elimination of Ph_3P to afford the desired product **3**. On the other hand, intermediate **D** also might be converted into **3** through 6π-annulation mode. Meanwhile, it is worth noting that **3′** could not be formed because of the failed transformation of **B** into **H** due to the steric hindrance.



Scheme 4 Proposed reaction mechanism

In conclusion, an easy and facile protocol for the synthesis of fully functionalized 1,2-dihydropyridine-3,5-dicarbonitrile derivatives has been developed by [2+2+2] annulation of cyanoacetylene and *N*-tosylimine.[19] These nitrogen heterocyclic compounds prepared from the reactions are important compounds which exhibit interesting biological and pharmacological properties. A plausible mechanism has been proposed to explain this annulation with high regioselectivity. Further investigations using new phosphine-

mediated multicomponent cycloaddition reactions to the synthesis of other heterocycles are currently underway in our laboratory.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610708.

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(18) The X-ray crystal structure of **3q** data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures (CCDC 1025786).
(19) **Typical Procedure for the Highly Regioselective Annulations of Cyanoacetylenes and *N*-Tosylimines**
To a solution of cyanoacetylenes (0.4 mmol) with *N*-tosylimines (0.2 mmol) in toluene (2 mL) was added Ph_3P (0.2 mmol). The mixture was then stirred at 110 °C for 36 h in a reaction flask. Then the solvent was removed in vacuo, and residue was purified by column chromatography on silica gel to give the desired product **3a**. Yield 82%; yellow solid; mp 230–231 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.0 Hz, 2 H), 7.54–7.38 (m, 13 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.24–7.19 (m, 2 H), 6.46 (s, 1 H), 2.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 148.0, 145.8, 135.3, 134.1, 132.9, 132.4, 132.3, 130.8, 130.1, 130.0, 129.6, 129.3, 128.7, 128.5, 128.3, 127.1, 127.0, 116.0, 115.5, 102.1, 100.4, 58.7, 21.4. HRMS (ESI): *m/z* calcd for $C_{32}H_{24}N_3O_2S$ [M + H]$^+$: 514.1584; found: 514.1584.