JOC The Journal of Organic Chemistry

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Silver-Catalyzed Tandem Synthesis of Naphthyridines and Thienopyridines via Three-Component Reaction

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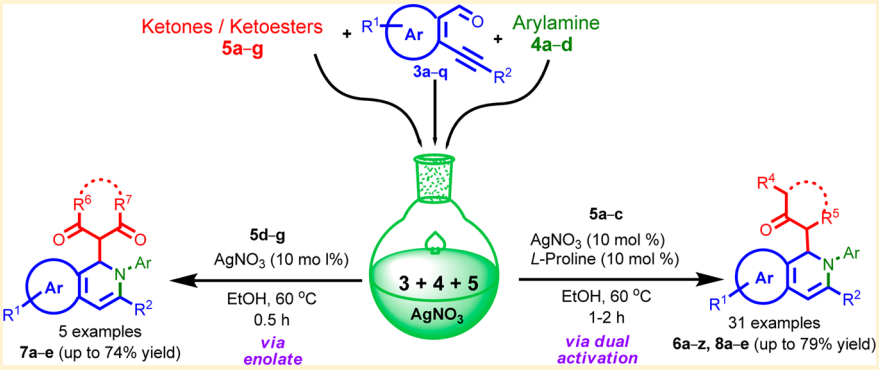
Supporting Information



ABSTRACT: An efficient approach for the silver-catalyzed regioselective tandem synthesis of highly functionalized 1,2-dihydrobenzo[1,6]naphthyridines **6a−z** and **7a−e** by the reaction of *ortho*-alkynylaldehydes **3a−n** with amines **4a−d** and ketones **5a−c**/active methylene compounds **5d−g**, under mild reaction conditions, is described. The scope of the developed chemistry was successfully extended for the direct synthesis of 1,2-dihydrobenzo[4,5]thieno[2,3-*c*]pyridines **8a−e**, which is known as the sulfur analogue of *β*-carbolines. Naphthyridines **6a−z** and thienopyridines **8a−e** were obtained via dual activation concept using L-proline as organocatalyst; however, naphthyridines **7a−e** were synthesized without using organocatalyst. The reaction shows selective N−C bond formation on the more electrophilic alkynyl carbon, resulting in the regioselective 6-*endo*-*dig*-cyclized products. Reactivity behavior of electron-deficient and electron-rich *ortho*-alkynylaldehydes in the synthesis of naphthyridines and thienopyridine by three-component reaction is supported by the control experiment.

INTRODUCTION

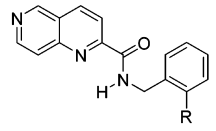
Rapid advances in medicinal chemistry continue to underscore the need of practical routes for the synthesis of heterocycles, as a majority of drug-like compounds and natural products contains a heterocyclic nucleus at their core.[1] In recent years, transition-metal-catalyzed reactions provided a promising algorithm to this urge, which enables the efficient conversion of simple starting materials to complex molecules in an iterative manner.[2] Among the various transition metals, silver-catalyzed tandem sequences have gained considerable attention because of their ability to activate various *π*-systems in mild conditions and at low-catalyst loading.[3]

Among various *N*-heterocycles, naphthyridines and thieno-[2,3-*c*]pyridine occur widely among natural products and are known to exert significant biological activity in many active pharmaceutical ingredients.[4] Marine sponges are proving to be productive sources of many interesting series of naphthyridine alkaloids (Figure 1ii,iii).[5] Naphthyridines have attracted considerable interest due to their interesting biological activities, such as anti-HIV-1, anticancer, antimicrobial and antifungal properties (Figure 1i).[6] The bronchodilator drug *benafentrine* has been developed on the basis of the derivatives of partially hydrogenated benzo[*c*][1,6]naphthyridines, which are phosphodiesterase III/IV inhibitors.[7] Benzothieno[2,3-*c*]pyridines (*S-analogues* of *β*-carbolines) have been found as appetite-depressants and anxiolytics (Figure 1iv).[8] In contrast to the naphthyridines, synthesis of benzothieno[2,3-*c*]pyridine has not been explored. Despite the various synthetic protocols available for the synthesis of naphthyridines[9] and thieno[2,3-*c*]pyridine,[10] a need for atom-economic efficient methodologies starting from inexpesive and readily available starting materials for their synthesis attracts the interest of synthetic chemists.

In the past two decades, construction of small molecules, heterocycles and natural-product-like compounds via tandem/three-component reactions (TCRs) has attracted growing interest in organic synthesis due to their high degree of atom economy, convergence, productivity, selectivity, and broad applications in combinatorial chemistry.[11] The variation of two or more reactants of the reaction can lead a large number of

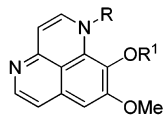
Received: February 23, 2013
Published: April 8, 2013

   dx.doi.org/10.1021/jo400400c | *J. Org. Chem.* 2013, 78, 4386−4401

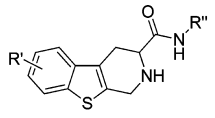


R : OCF_3, OMe, Me

i. 1,6-Naphthyridine: HCMV-inhibitors (synthetic compound)



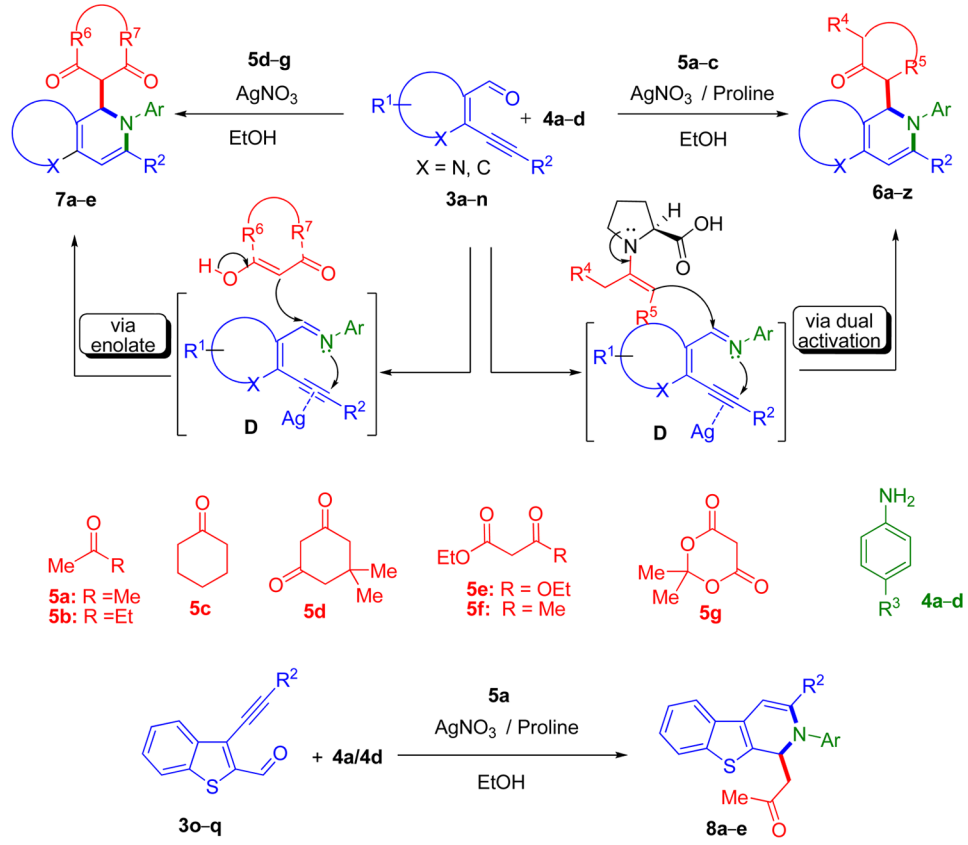
ii. Aaptamine (R = H, R^1 = Me)
iii. Isoaptamine: R = Me, R^1 = H
(Marine natural product)



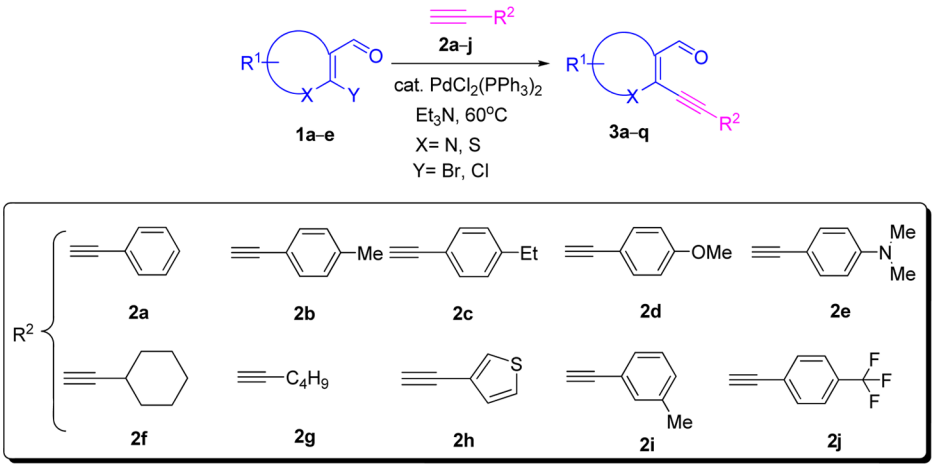
iv. Thienopyridine: appetite depressant, anxiolytics (synthetic compound)

Figure 1. Significant examples of biologically active naphthyridines and thienopyridines.

Scheme 1. Designed Tandem Strategy for the Synthesis of Naphthyridines and Thienopyridines via Three-Component Reaction



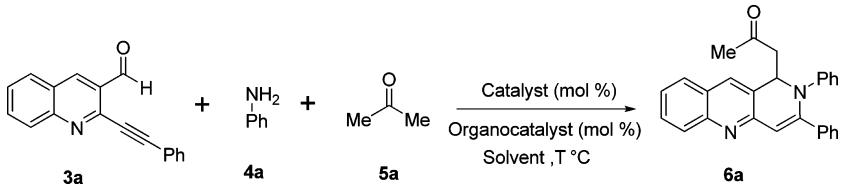
Scheme 2. Preparation of *o*-Alkynylaldehydes



molecules and increase the chemical diversity. Considerable progress has been made for the tandem synthesis of nitrogen heterocycles from *ortho*-alkynylaldehydes using dual activation concept. Dual-activation concept involves combination of two

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386–4401

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	organocatalyst	solvent	time (h)	yield (%)
1	AgOTf	L-proline	EtOH	6	50
2	AgOTf	L-proline	EtOH	12	52
3	AgOTf[b]	L-proline	EtOH	6	58
4	AgOTf[b]	L-proline	EtOH	12	57
5	AgOTf	L-proline	EDC	6	42
6	AgOTf[b]	L-proline	EDC	6	45
7	$AgNO_3$	L-proline	EtOH	6	68
8	$AgNO_3$	L-proline	EtOH	3	68
9	**$AgNO_3$**	**L-proline**	**EtOH**	**1**	**70**
10	$AgNO_3$	L-proline	EtOH	0.5	65
11	$AgNO_3$[c]	L-proline	EtOH	3	50
12	$AgNO_3$[b]	L-proline	EtOH	1	69
13	$AgNO_3$	L-proline[d]	EtOH	1	70
14	$AgNO_3$	–	EtOH	10	10
15	$AgNO_3$	L-proline	MeOH	1	68
16	$AgNO_3$	L-proline	H_2O	12	nr
17	$AgNO_3$	L-proline	EDC	6	35
18	$AgNO_3$	L-proline	toluene	12	25
19	$AgNO_3$	L-proline	THF	12	35
20	$AgNO_3$	piperidine	EtOH	6	10
21	AgOAc	L-proline	EtOH	6	30
22	$PdCl_2$	L-proline	EtOH	6	10
23	$Pd(OAc)_2$	L-proline	EtOH	6	15

[a]Reaction was performed using **3a** (70 mg, 1 equiv), **4a** (1 equiv) and 5 equiv of **5a** in 2 mL of EtOH at 60 °C, unless otherwise noted. [b]20 mol % of catalyst was loaded. [c]5 mol % of catalyst was employed. [d]20 mol % L-proline was used.

separate catalysts in one catalytic system.[12] Yamamoto proposed a concept called "designer acids" to form a combination of acids with higher reactivity, selectivity, and versatility than the individual.[13]

Ding et al. reported the synthesis of isoquinolines by three-component reaction from *ortho*-alkynylaldehydes, and later Larock and co-workers reported the synthesis of a library of isoquinolines using dual activation concept.[14,15] Hecht and co-workers have found that introduction of nitrogen in camptothecin ring system made significant improvement in antitumor activity.[16] Recently, we have successfully synthesized variety of nitrogen heterocycles using 2-(arylethynyl)quinoline-3-carbaldehydes.[17,18] Encouraged by the above observation of Hecht and co-workers and our ongoing work on the synthesis of heterocycles by tandem reactions/electrophilic cyclization of alkynes,[19] herein we report the synthesis of highly functionalized 1,2-dihydrobenzo[1,6]naphthyridines **6a–z**, **7a–e** and 1,2-dihydrobenzo[4,5]thieno[2,3-*c*]pyridines **8a–e** by the reaction of *ortho*-alkynylaldehydes **3a–q** with amines **4a–d** and ketones **5a–c** /active methylene compounds **5d–g** in moderate to good yields, by three-component reaction under mild reaction conditions (Scheme 1).

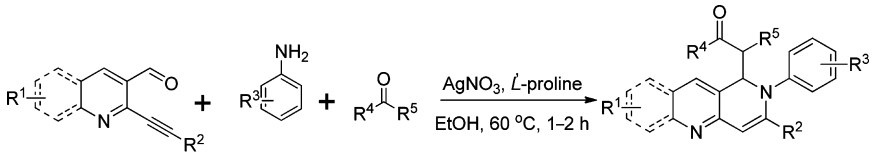
RESULTS AND DISCUSSION

Preparation of *o*-Alkynylaldehydes. Starting substrates *o*-alkynylaldehydes **3a–q** required for examining the scope and generality of this chemistry were readily prepared by the standard Sonogashira coupling of *o*-haloarylaldehydes **1a–e** with commercially available terminal alkynes **2a–j** (Scheme 2).[17]

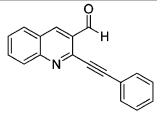
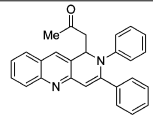
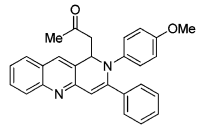
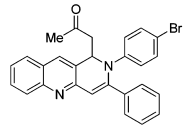
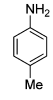
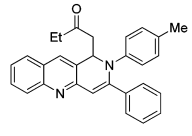
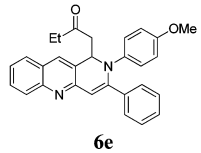
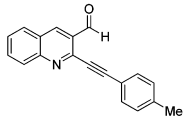
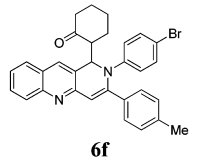
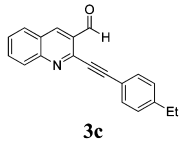
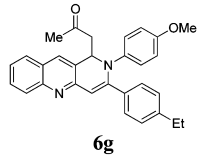
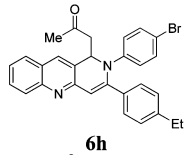
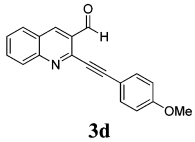
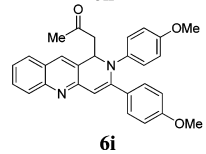
To identify the optimal conditions for the reaction, we examined the reaction of 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) with aniline (**4a**) and acetone (**5a**) using 10 mol % of AgOTf, 10 mol % of L-proline in 2 mL of EtOH at 60 °C for 6 h; the desired product **6a** was obtained in 50% yield (entry 1). When the reaction was further allowed to run for 12 h, no significant change in the yield of the product was observed (entry 2). Increasing the catalyst loading from 10 to 20 mol % made no significant improvement in the yield of the product **6a** (entries 3 and 4). When reaction was carried out in EDC, the product **6a** was obtained in 42 and 45% yields, respectively (entries 5 and 6). Reaction using 10 mol % of $AgNO_3$ in ethanol at 60 °C for 6 h afforded the desired product **6a** in 68% (entry 7). Decreasing the reaction time from 6 to 3 h made no significant change in the yield (entry 8). Further decreasing the reaction time to 1 h and then to 30 min afforded the desired product **6a** in 70 and 65% yield, respectively (entries 9 and 10). However, decreasing the catalyst loading from 10 to 5 mol % afforded the product **6a** in only 50% yield (entry 11), whereas the increase of catalyst loading from 10 to 20 mol % made no significant change in the yield (entry 12). Increase of the loading of L-proline from 10 to 20 mol % made no improvement in the yield of the product (entry 13). However, in absence of L-proline, the desired product **6a** was obtained in

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386–4401

Table 2. Synthesis of 1,2-Dihydrobenzo[1,6]naphthyridine[a]

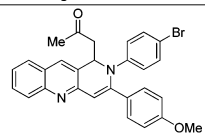
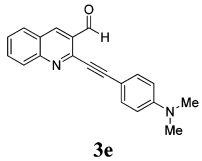
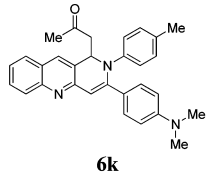
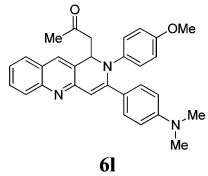
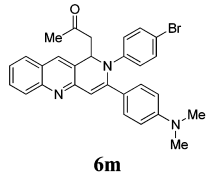
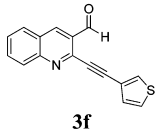
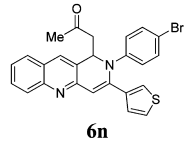
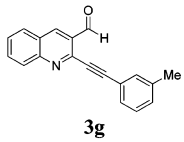
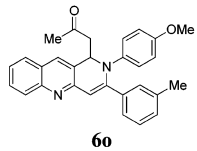
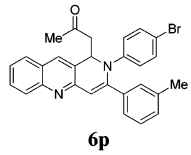
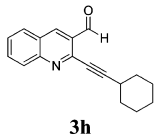
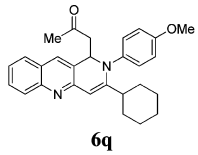
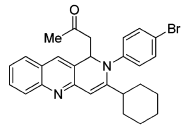
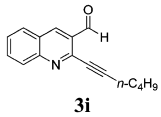
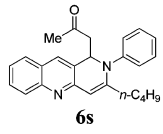


3a–m **4a–f** **5a–c** **6a–z**

entry	substrate	amine	ketone	product	yield (%)[b]
1	 **3a**	 **4a**	 **5a**	 **6a**	70
2	**3a**	 **4b**	**5a**	 **6b**	75
3	**3a**	 **4c**	**5a**	 **6c**	69
4	**3a**	 **4d**	 **5b**	 **6d**	55
5	**3a**	**4b**	**5b**	 **6e**	60
6	 **3b**	**4c**	 **5c**	 **6f**	50
7	 **3c**	**4b**	**5a**	 **6g**	78
8	**3c**	**4c**	**5a**	 **6h**	74
9	 **3d**	**4b**	**5a**	 **6i**	79

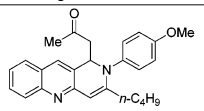
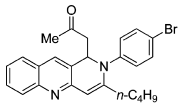
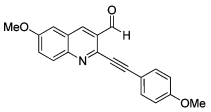
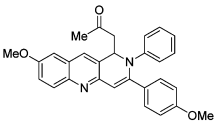
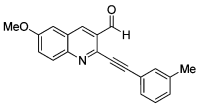
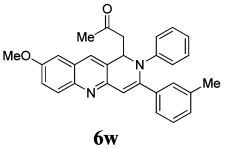
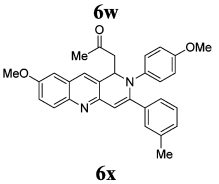
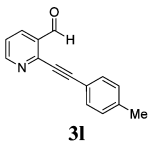
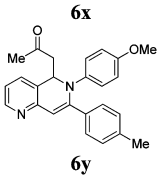
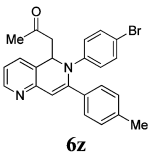
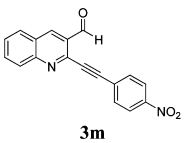
dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386−4401

Table 2. continued

entry	substrate	amine	ketone	product	yield (%)[b]
10	**3d**	**4c**	**5a**	 **6j**	75
11	 **3e**	**4d**	**5a**	 **6k**	78
12	**3e**	**4b**	**5a**	 **6l**	79
13	**3e**	**4c**	**5a**	 **6m**	75
14	 **3f**	**4c**	**5a**	 **6n**	76
15	 **3g**	**4b**	**5a**	 **6o**	72
16	**3g**	**4c**	**5a**	 **6p**	72
17	 **3h**	**4b**	**5a**	 **6q**	69[c]
18	**3h**	**4c**	**5a**	 **6r**	68[c]
19	 **3i**	**4a**	**5a**	 **6s**	68[c]

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386−4401

Table 2. continued

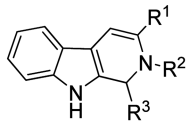
entry	substrate	amine	ketone	product	yield (%)[b]
20	**3i**	**4b**	**5a**	 **6t**	70[c]
21	**3i**	**4c**	**5a**	 **6u**	68[c]
22	 **3j**	**4a**	**5a**	 **6v**	78
23	 **3k**	**4a**	**5a**	 **6w**	71
24	**3k**	**4b**	**5a**	 **6x**	74
25	 **3l**	**4b**	**5a**	 **6y**	79
26	**3l**	**4c**	**5a**	 **6z**	74
27	**3a**	 **4e**	**5a**	-	-[d]
28	**3a**	 **4f**	**5a**	-	-[d]
29	 **3m**	**4a**	**5a**	-	-[d]

[a]Reactions were performed using *o*-alkynylaldehyde **3** (70 mg, 1 equiv), amine **4** (1 equiv) and 5 equiv of **5**, L-proline (10 mol %) and $AgNO_3$ (10 mol %) in 2 mL of EtOH at 60 °C for 1 h. [b]Yields. [c]Reaction was run for 1−2 h. [d]Inseparable complex mixtures.

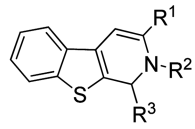
only 10% yield (entry 14). After the optimization of reaction time, we screened the effect of solvents. Different solvents like EtOH, EDC, MeOH, H_2O, toluene and THF were screened to find out an appropriate solvent for the reaction (entries 15−19). It is clear from Table 1 that EtOH and MeOH at 60 °C were found to be suitable solvents for the reaction (entries 9 and 15). When piperidine was used instead of L-proline, the product **6a** was obtained in 20% yield (entry 20). Use of other catalysts such as AgOAc, $PdCl_2$ and $Pd(OAc)_2$ were found inferior and afforded the product **6a** in lower yield (entries 21−23), respectively.

Synthesis of 1,2-Dihydrobenzo[1,6]naphthyridine. After optimizing the reaction conditions, we then examined the scope and generality of the reaction by employing variety of *ortho*-alkynylaldehyde **3a−m** with substituted amines **4a−f** and ketones **5a−c**. A diverse library of 1,2-dihydrobenzo[1,6]-naphthyridine **6a−z** was synthesized in good yields (Table 2, entries 1−29).

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386−4401



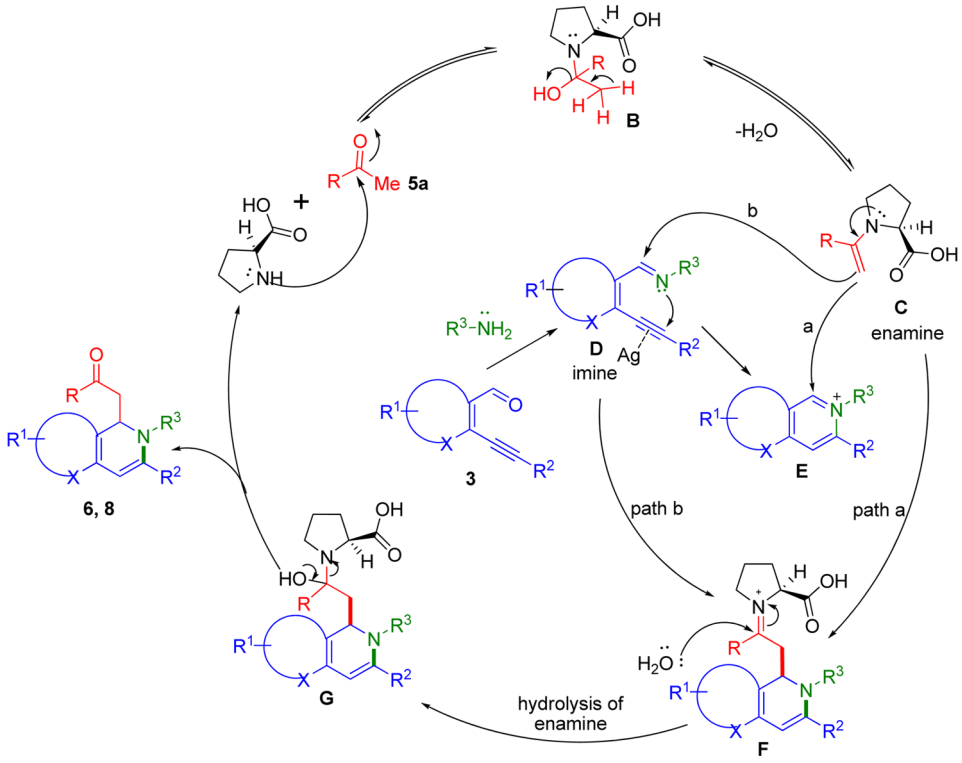
1,2-dihydro-β-carboline



1,2-dihydrobenzo-thienopyridine

Figure 2. Analogue of *β*-carbolines.

Scheme 3. Plausible Mechanistic Pathway by Dual Activation Using L-Proline



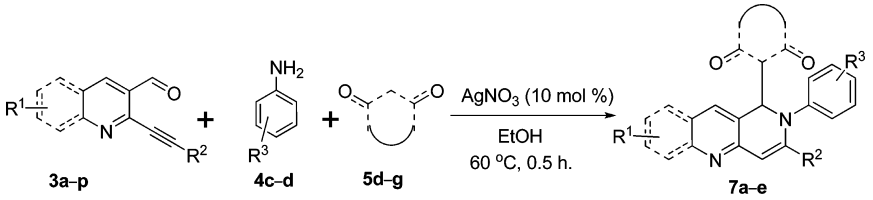
The reaction of 2-(phenylethynyl)quinoline-3-carbaldehyde (**3a**) and anilines **4a**−**c** with acetone (**5a**) afforded the desired products **6a**−**c** in 70, 75, and 69% yields, respectively (entries 1−3). Products **6d**,**e** were obtained in lower yields when ketone **5a** was replaced with unsymmetrical 2-butanone (**5b**) (entries 4 and 5). Reaction of 2-(*p*-tolylethynyl)quinoline-3-carbaldehyde (**3b**) with amine **4c** and cyclohexanone (**5c**) afforded the desired product **6f** in 50% yield (entry 6). The substrates **3c**−**e** bearing electron-donating substituent such as Et, OMe and NMe_2 *para* to the triple bond of the phenyl ring showed the capability to trigger the 6-*endo*-*dig* cyclization and provided the respective desired products **6g**−**m** in good yields (entries 7−13). 2-(Thiophen-3-ylethynyl)quinoline-3-carbaldehyde (**3f**) bearing an electron-rich heterocycle thiophene on reaction with amine **4c** and ketone **5a** proved to be favorable for the reaction and afforded the desired product **6n** in 76% yield (entry 14). *ortho*-Alkynylaldehyde **3g**, bearing substitution at the *meta* position of the phenyl ring afforded the desired products comparatively in lower yields (entries 15−16). Substrates **3h**,**i** bearing a cyclohexyl and *n*-butyl group provided the desired products **6q**−**u** in 68−70% yields (entries 17−21). Reaction of 6-methoxy substituted *o*-alkynylaldehydes **3j**,**k** with anilines **4a**,**b** and **5a** afforded the desired product **6v**−**x** in 71−78% yields (entries 22−24). Further exploring the reaction of 2-(*p*-tolylethynyl)nicotinaldehyde (**3l**) with anilines **4b**,**c** and acetone **5a** provided the desired products **6y** and **6z** in 79 and 74% yields, respectively (entries 25 and 26). However, reaction of substrate **3a** with cyclohexylamine (**4e**) and *n*-butylamine (**4f**) provided an inseparable, unidentified complex mixture (entries 27 and 28). Reaction of 2-((4-nitrophenyl)ethynyl)-quinoline-3-carbaldehyde (**3m**) bearing an electron-withdrawing nitro group at 4-position of the phenyl ring fails to afford the desired product.

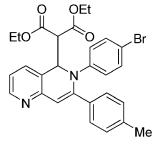
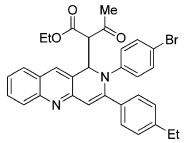
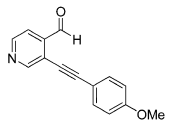
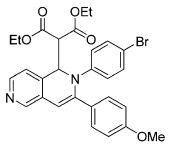
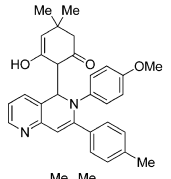
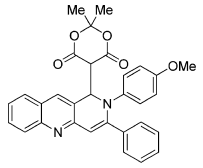
All the synthesized products **6a**−**z** were fully characterized by ^{1}H NMR, ^{13}C NMR, HRMS and X-ray crystallographic analysis[20] (Figure 2). Products were obtained as racemic mixtures, and chiral-HPLC analysis of products **6h**, **6i**, **6k** and **6v** supports the formation of racemic products.

The possible mechanism for the formation of 1,2-dihydrobenzo[1,6]naphthyridines **6a**−**z** and 1,2-dihydrobenzo-[4,5]thieno[2,3-*c*]pyridines **8a**−**e** via three-component reaction is shown in Scheme 3. It is proposed that generation of key intermediates imine **D** (generated by the reaction of *o*-alkynylealdehyde **3** with aniline) and enamine **C** (generated by the reaction of L-proline and ketone) takes place simultaneously. Under silver catalysis imine **D** is susceptible to attack by the nucleophile. Intermolecular attack of enamine **C** on imine carbon of intermediate **D** and subsequent intramolecular attack of nitrogen on alkyne form **F** (path a). Intermediate **F** can also be obtained by the attack of **C** on

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386−4401

Table 3. Synthesis of 1,2-Dihydrobenzo[1,6]naphthyridine Using Reactive Methylene Compounds and Cyclic 1,3-Diketones and Ketoesters[a]



entry	substrate	amine	ketoester/diketone		product		yield (%)
1	**3l**	**4c**		**5e**		**7a**	70
2	**3c**	**4c**		**5f**		**7b**	62
3	 **3n**	**4c**		**5e**		**7c**	74
4	**3l**	**4b**		**5d**		**7d**	72
5	**3a**	**4b**		**5g**		**7e**	74

[a]Reactions were performed using *o*-alkynylaldehyde **3** (70 mg, 1 equiv), amine **4** (1 equiv), 5 equiv of **5**, and AgNO3 (10 mol %) in 2 mL of EtOH at 60 °C for 0.5 h.

possible isoquinolinium intermediate **E** (path b). **F** on hydrolysis results in the formation of the products **6**, **8** and regenerates L-proline.

Encouraged by the above results, we further explored the scope of the reaction with a wide range of readily accessible reactive methylene compounds and "1,3-dione" substrates, by replacing one of the reactants of the three-component reaction. Under the optimized reaction conditions (Table 1, entry 9), reaction of *o*-alkynylaldehydes **3a**, **3c**, **3l** and **3n**, arylamines **4b–c** with dimedone (**5d**), diethylmalonate (**5e**), ethylacetoacetate (**5f**), and meldrum's acid (**5g**) afforded the desired products **7a–e** in 62–74% yields (Table 3, entries 1–5). We observed that reaction with reactive dicarbonyl compounds/esters was faster and completed within 30 min (compare reaction times of Table 2 and /table 3). It is interesting to note that synthesis of naphthyridines **7a–e** proceeds without using organocatalyst L-proline.

The possible mechanism for the formation of naphthyridines **7a–e** via three-component reaction is shown in Scheme 4. The proposed mechanism for products **7a–e** does not involve the enamine formation, as this reaction proceeds without use of L-proline. Intermolecular attack of enolate on imine carbon of intermediate **D** and subsequent intramolecular attack of nitrogen on alkyne result in the formation of the products **7**.

We further extended the scope of the developed chemistry for the synthesis of another very important class of hetrocyclic scaffold 1,2-dihydrobenzo[4,5]thieno[2,3-*c*]pyridines **8a–e**, which is known as sulfur analogue of the *β*-carbolines (Figure 2). Using the optimized reaction conditions (Table 1, entry 9), reaction of 3-(arylethynyl)benzo[*b*]thiophene-2-carbaldehydes **3o–q** with acetone (**5a**) and aniline **4a**, **4d** provided the thienopyridines **8a–e**, along with uncyclized imine **9a–e** (Table 4, entries 1–5).

With the above results, we investigated further structural elaboration of the bromo-substituted naphthyridines via palladium-catalyzed cross-coupling reactions. To this end, compound **6j** was functionalized by applying palladium-catalyzed Suzuki[21] and Heck[21] coupling reactions using 2-(1-benzotriazolyl)pyridine (BtPy) as a ligand to afford the corresponding products **11** and **13** in 72 and 70% yields, respectively (Scheme 5).

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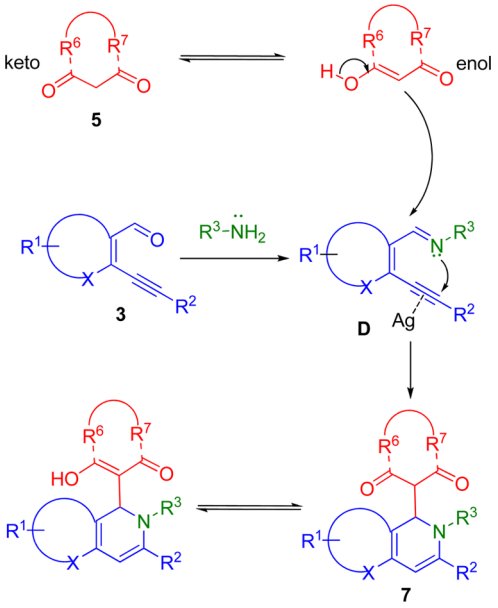
Scheme 4. Plausible Mechanistic Pathway without Using L-Proline



Study of the Reactivity Behavior of the Electron-Deficient and Electron-Rich *ortho*-Alkynylaldehydes. Naphthyridines **6a−z** and **7a−e** synthesized from 2-(arylethynyl)quinoline-3-carbaldehyde) **3a−n** were obtained in good yields and required less reaction time; however, thienopyridines **8a−e** synthesized by using 3-(arylethynyl)-benzo[*b*]thiophene-2-carbaldehydes **3o−q** were obtained in lower yield and required longer reaction time in comparison to naphthyridines (compare Tables 2, 3 with Table 4). The above observation could be explained on the basis of reactivity behavior of *o*-alkynylaldehydes. In case of 2-(arylethynyl)-quinoline-3-carbaldehydes (**3a−n**), presence of electron-deficient pyridine ring system (-I and -R effect) increases the reactivity of the aldehydic group, which facilitates the formation of the key intermediate imine, whereas in the case of 3-(arylethynyl)benzo[*b*]thiophene-2-carbaldehydes (**3o−q**), presence of electron-rich thiophene ring system (+R effect) decreases the reactivity of the aldehydic group as well as intramolecular attack of imine on alkyne (Figure 3).

To validate the reactivity behavior of the electron-deficient, electron-rich *ortho*-alkynylaldehydes, we performed a control experiment. We carried out the reaction of **3a** (1 equiv), **3o** (1 equiv), with amine **4a** (1 equiv) and ketone **5a** (5 equiv) using 10 mol % of $AgNO_3$ and 10 mol % L-proline in 2 mL of EtOH at 60 °C for 2 h (Scheme 6). The results demonstrate that the product **6a** was obtained in 63% yield, whereas product **9a** was formed only in 6% yield. This clearly reveals that *o*-alkynylaldehydes **3a−n** is more reactive because of the presence of electron-withdrawing pyridine ring and afforded the products in good yields. However, *o*-alkynylaldehydes **3o−q** bearing an electron-rich thiophene ring provided the products in lower yields along with unreacted imines.

CONCLUSION

In conclusion, we have demonstrated a direct one pot approach for the silver-catalyzed tandem synthesis of highly functionalized 1,2-dihydrobenzo[1,6]naphthyridines via three-component reaction using readily available starting materials in good yields with high regioselectivity under mild reaction conditions. Application of the developed chemistry has been successfully extended for the another important class of hetrocyclic scaffold 1,2-dihydrobenzo[4,5]thieno[2,3-*c*]pyridines, which is known as sulfur analogue of the *β*-carbolines. Naphthyridines **6a−z** and thienopyridines **8a−e** were obtained via dual activation concept using L-proline as organocatalyst; however, naphthyridines **7a−e** were synthesized via enolate chemistry (without using organocatalyst). Reactivity behavior of the electron-deficient and electron-rich *ortho*-alkynylaldehydes in the synthesis of variety of heterocyclic compounds by three-component reaction is described and validated by the control experiment. From a synthetic point of view, the net transformation involves a one-step conversion of simple, inexpensive and readily available starting materials into an interesting class of fused heterocyclic scaffolds. This chemistry is expected to find application in organic synthesis in general and in the construction of a variety of heterocyclic compounds.

EXPERIMENTAL SECTION

General Information and Methods. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants in Hertz, and integration. High-resolution mass spectra were recorded with q-TOF electrospray mass spectrometer . TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates and visualized by either UV irradiation or by staining with I_2. All purchased chemicals were used as received. All melting points are uncorrected.

The starting materials **3** were prepared by Sonogashira coupling using the reported procedure.[17] The structure and purity of known starting materials **3a**,**b**,**d**,**f**,**h**,[17b] and **3g**,**i**,[17a] were confirmed by comparison of their physical and spectral data (^{1}H NMR and ^{13}C NMR) with those reported in literature.

*2-((4-Ethylphenyl)ethynyl)quinoline-3-carbaldehyde (**3c**).* This compound was obtained as a light brown solid (1.04 g, 70%): mp 114−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.71 (s, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 7.3 Hz, 1H), 7.61−7.57 (m, 3H), 7.25−7.21 (m, 2H), 2.67 (q, J = 7.3 Hz, 2H), 1.24 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 150.1, 146.5, 144.1, 137.0, 132.9, 132.3, 129.6, 129.2, 128.7, 128.14, 128.06, 126.3, 118.4, 96.0, 85.0, 28.9, 15.2; HRMS (ESI) $[M]^+$ Calcd for $[C_{20}H_{15}NO]$ 285.1154, found 285.1154.

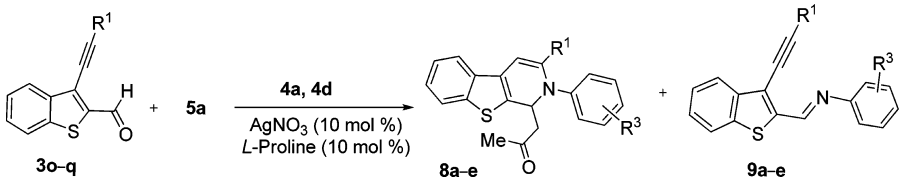
*2-((4-(Dimethylamino)phenyl)ethynyl)quinoline-3-carbaldehyde (**3e**).* This compound was obtained as dark brown solid (1.17 g, 75%): mp 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.8 (s, 1H), 8.68 (s, 1H), 8.13−8.10 (m, 1H), 7.92−7.90 (m, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.58−7.54 (m, 3H), 6.66 (d, J = 8.8 Hz, 2H), 3.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 151.0, 150.2, 144.8, 136.8, 133.7, 132.8, 129.6, 129.0, 128.4, 127.6, 126.0, 111.6, 107.3, 98.4, 84.6, 40.0; HRMS (ESI) $[M]^+$ Calcd for $[C_{20}H_{16}N_2O]$ 300.1263, found 300.1263.

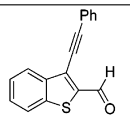
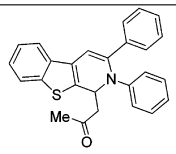
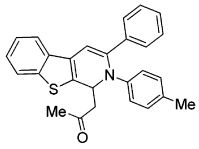
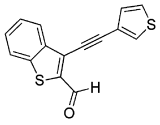
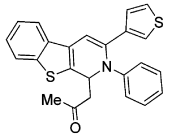
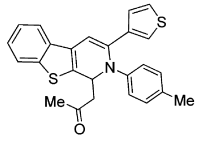
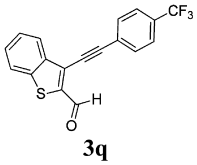
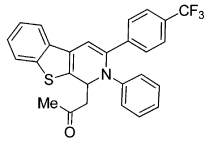
*6-Methoxy-2-((4-methoxyphenyl)ethynyl)quinoline-3-carbaldehyde (**3j**).* This compound was obtained as a dark brown solid (1.10 g, 77%): mp 142−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.74 (s, 1H), 8.56 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.60−7.58 (m, 2H), 7.47−7.44 (m, 1H), 7.12 (d, J = 2.9, 1H), 6.90−6.88 (m, 2H), 3.92 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 160.7, 158.8, 146.5, 141.8, 135.3, 133.8, 130.6, 128.9, 127.5, 126.2, 114.2, 113.5, 106.2, 95.2, 84.6, 55.7, 55.3; HRMS (ESI) $[M]^+$ Calcd for $[C_{20}H_{15}NO_3]$ 317.1052, found 317.1052.

*6-Methoxy-2-(m-tolylethynyl)quinoline-3-carbaldehyde (**3k**).* This compound was obtained as a yellow solid (0.97 g, 72%): mp 138−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.61 (s, 1H), 8.07 (d, J = 9.5 Hz, 1H), 7.51−7.47 (m, 3H), 7.30−7.24 (m, 2H), 7.16 (d, J = 2.2, 1H), 3.95 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 159.5, 146.4, 141.5, 138.3, 135.4, 132.8, 130.6,

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386−4401

Table 4. Synthesis of 1,2-Dihydrobenzo[4,5]thieno[2,3-*c*]pyridine[a]



entry	substrate	amine	product		yield(%) (**8**:**9**)
1	 **3o**	**4a**		**8a**	65:15
2	**3o**	**4d**		**8b**	60:20
3	 **3p**	**4a**		**8c**	65:20
4	**3p**	**4d**		**8d**	60:22
5	 **3q**	**4a**		**8e**	30:50

[a]Reactions were performed using *o*-alkynylaldehyde **3** (70 mg, 1 equiv), amine **4** (1 equiv), 5 equiv of **5**, L-proline (10 mol %) and AgNO3 (10 mol %) in 2 mL of EtOH at 60 °C for 2 h.

129.3, 128.4, 127.8, 126.4, 121.1, 106.2, 85.1, 55.8, 21.2; HRMS (ESI) $[M]^+$ Calcd for $[C_{20}H_{15}NO_2]$ 301.1103, found 301.1103.

*2-(p-Tolylethynyl)nicotinaldehyde (**3l**).* This compound was obtained as an orange solid (0.80 g, 68%): mp 96−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.82 (dd, J = 2.2, 5.1 Hz, 1H), 8.21 (dd, J = 1.4, 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.41−7.38 (m, 1H), 7.21 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 154.5, 146.4, 140.4, 134.8, 132.1, 131.7, 129.4, 123.0, 118.6, 96.9, 83.6, 21.7; HRMS (ESI) $[M]^+$ Calcd for $[C_{15}H_{11}NO]$ 221.0841, found 221.0841.

*2-((4-Nitrophenyl)ethynyl)quinoline-3-carbaldehyde (**3m**).* The product was obtained as a yellow solid (0.80 g, 65%): mp 164−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.76 (s, 1H), 8.26 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.91−7.87 (m, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.66 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 150.0, 147.9, 142.4, 137.9, 133.4, 133.1, 132.6, 129.6, 129.4, 128.9, 128.8, 128.1, 126.6, 123.8, 92.3, 89.8; HRMS (ESI) calcd for $[C_{18}H_{10}N_2O_3]$ requires $[M]^+$ 302.0691, found 302.0692.

*3-((4-Methoxyphenyl)ethynyl)isonicotinaldehyde (**3n**).* This compound was obtained as an orange solid (0.91 g, 72%): mp 55−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.94 (s, 1H), 8.69 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 5.1 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 160.6, 154.5, 148.7, 140.2, 133.5, 121.9, 119.2, 114.5, 114.0, 113.6, 99.4, 80.9, 55.3; HRMS (ESI) $[M]^+$ Calcd for $[C_{15}H_{11}NO_2]$ 237.0790, found 237.0790.

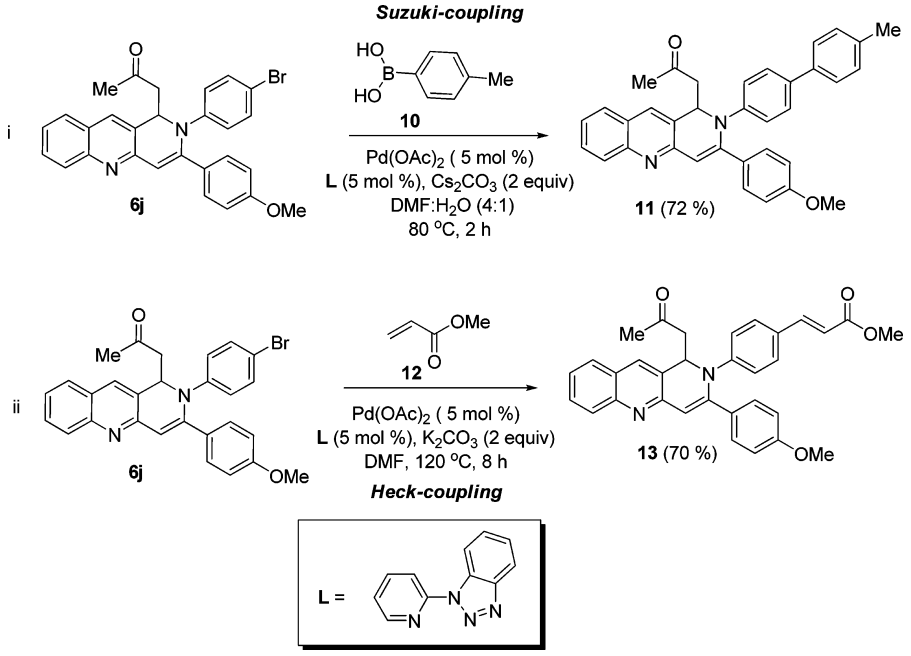
*3-(Phenylethynyl)benzo[b]thiophene-2-carbaldehyde (**3o**).* This compound was obtained as a yellow brown solid (0.38 g, 70%): mp 104−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.10−8.08 (m, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.59−7.56 (m, 2H), 7.51−7.43 (m, 2H), 7.37−7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 139.9, 137.5, 135.8, 128.4, 126.0, 125.3, 125.1, 124.2, 122.1, 121.5, 119.8, 118.3, 95.5, 77.0; HRMS (ESI) $[M]^+$ Calcd for $[C_{17}H_{10}OS]$ 262.0452, found 262.0451.

*3-(Thiophen-3-ylethynyl)benzo[b]thiophene-2-carbaldehyde (**3p**).* This compound was obtained as yellow solid (0.41 g, 75%): mp 68−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.12−8.10 (m, 1H), 7.86−7.84 (m, 1H), 7.69−7.67 (m, 1H), 7.53−7.48 (m, 2H), 7.37−7.35 (m, 1H), 7.28−7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 143.0, 140.5, 138.9, 130.2, 129.3, 128.3, 127.0, 125.6, 125.1, 124.5, 122.8, 120.5, 93.6, 79.7; HRMS (ESI) $[M]^+$ Calcd for $[C_{15}H_8OS_2]$ 268.0017, found 268.0017.

*3-((4-(Trifluoromethyl)phenyl)ethynyl)benzo[b]thiophene-2-carbaldehyde (**3q**).* This compound was obtained as a dark brown solid

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386−4401

Scheme 5. Pd-Catalyzed Synthetic Elaboration



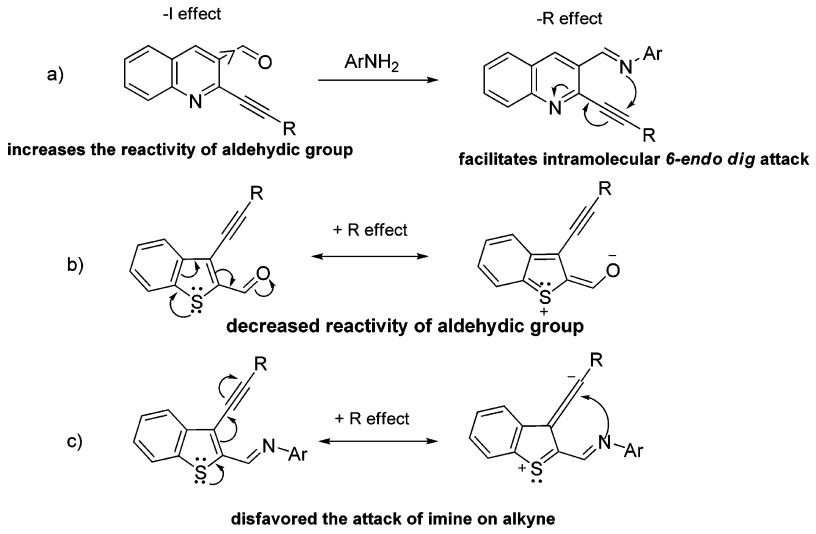
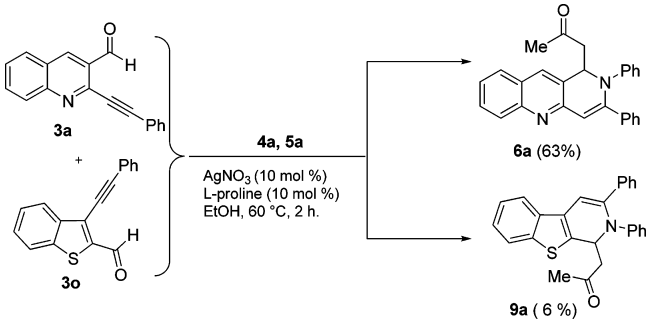


Figure 3. Reactivity behavior of the electron-deficient, electron-rich *ortho*-alkynylaldehydes.

Scheme 6. Experimental Support on the Reactivity of *o*-Alkynylaldehydes



(0.42 g, 68%): mp 92–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.09–8.07 (m, 1H), 7.84 (d, J = 7.3 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.53–7.45 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 144.2, 141.0, 139.2, 132.2, 129.0, 126.6, 125.8, 125.60, 125.57, 124.9, 123.4, 97.1, 82.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{18}H_9F_3OS]$ 330.0326, found 330.0326.

General Procedure for Synthesis of 1,2-Dihydrobenzo[1,6]-naphthyridine. A solution of *o*-alkynylaldehyde **3a–m** (70 mg, 1 equiv), amine **4a–f** (1 equiv), ketones **5a–c** (5 equiv), $AgNO_3$ (10 mol %), L-proline (10 mol %) in C_2H_5OH (2 mL) was stirred at 60 °C for a period of 1–2 h. After completion of the reaction as indicated by TLC, the solvent was evaporated and then quenched with water (10 mL), extracted with EtOAc (3 × 10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding products **6a–z**.

*1-(2,3-Diphenyl-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)-propan-2-one (**6a**).* This compound was obtained as a yellow solid (74 mg, 70%): mp 120–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 1H), 7.76 (s, 1H), 7.64–7.56 (m, 2H), 7.53–7.51 (m, 2H), 7.33 (t, J = 7.1 Hz, 1H), 7.23–7.19 (m, 4H), 7.05–6.97 (m, 4H), 6.81 (t, J = 7.0 Hz, 1H), 5.70 (t, J= 6.9 Hz, 1H), 3.32 (dd, J = 7.3, 17.6 Hz, 1H), 2.81 (dd, J = 5.8, 16.8 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 151.5, 148.3, 147.8, 146.6, 137.7, 132.3, 129.5,

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386–4401

129.1, 128.8, 128.6, 128.2, 127.8, 127.6, 127.5, 127.2, 125.3, 123.13, 123.09, 112.4, 61.0, 47.8, 31.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{27}H_{22}N_2O]$ 390.1732, found 390.1731.

*1-(2-(4-Methoxyphenyl)-3-phenyl-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)propan-2-one (**6b**).* This compound was obtained as orange solid (85 mg, 75%): mp 136−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 1H), 7.80 (s, 1H), 7.69−7.62 (m, 2H), 7.58−7.55 (m, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.27−7.24 (m, 4H), 7.00−6.96 (m, 2H), 6.62 (d, J = 8.8 Hz, 2H), 5.62 (t, J = 7.0 Hz, 1H), 3.63 (s, 3H), 3.36 (dd, J = 7.3, 16.8 Hz, 1H), 2.79 (dd, J = 7.3, 18.3 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 155.9, 151.6, 148.9, 147.7, 140.2, 136.8, 132.3, 129.5, 129.1, 128.5, 128.1, 128.0, 127.6, 127.5, 126.8, 125.2, 124.9, 114.1, 111.3, 61.6, 55.3, 47.9, 31.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{28}H_{24}N_2O_2]$ 420.1838, found 420.1837.

*1-(2-(4-Bromophenyl)-3-phenyl-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)propan-2-one (**6c**).* This compound was obtained as a yellow solid (87 mg, 69%): mp 178−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 1H), 7.75 (s, 1H), 7.64−7.57 (m, 2H), 7.49−7.47 (m, 2H), 7.35 (t, J = 7.3 Hz, 1H), 7.23−7.22 (m, 3H), 7.13 (d, J = 8.8 Hz, 2H), 7.01 (s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 5.65−5.61 (m, 1H), 3.35 (dd, J = 8.1, 17.6 Hz, 1H), 2.70 (dd, J = 5.8, 17.5 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 151.3, 147.5, 145.8, 139.1, 136.3, 132.8, 132.1, 132.0, 131.8, 131.0, 129.7, 129.3, 129.0, 128.8, 128.3, 127.7, 127.5, 127.0, 126.4, 125.6, 124.6, 116.1, 113.3, 61.0, 47.6, 31.5; HRMS (ESI) $[M]^+$ Calcd for $[C_{27}H_{21}BrN_2O]$ 468.0837, found 468.0837.

*1-(3-Phenyl-2-(p-tolyl)-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)butan-2-one (**6d**).* This compound was obtained as a yellow solid (62 mg, 55%): mp 80−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 1H), 7.71 (s, 1H), 7.62−7.55 (m, 2H), 7.51−7.49 (m, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.21−7.18 (m, 3H), 6.94 (s, 1H), 6.85 (q, J = 8.8 Hz, 4H), 5.65 (t, J = 6.9 Hz, 1H), 3.28 (dd, J = 7.3, 16.1 Hz, 1H), 2.72 (dd, J = 5.8, 16.8 Hz, 1H), 2.37−2.26 (m, 1H), 2.24−2.19 (m, 1H), 2.09 (s, 3H), 0.96 (t, J = 7.3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 151.8, 148.3, 147.9, 144.2, 136.9, 132.8, 132.0, 129.4, 129.3, 129.0, 128.6, 128.4, 127.8, 127.6, 127.5, 127.1 125.2, 123.1, 112.3, 61.5, 46.7, 37.7, 20.7, 7.5; HRMS (ESI) $[M]^+$ Calcd for $[C_{29}H_{26}N_2O]$ 418.2045, found 418.2045.

*1-(2-(4-Methoxyphenyl)-3-phenyl-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)butan-2-one (**6e**).* This compound was obtained as an orange solid (70 mg, 60%): mp 68−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 1H), 7.73 (s, 1H), 7.63−7.58 (m, 2H), 7.51−7.49 (m, 2H), 7.33 (t, J = 7.7 Hz, 1H), 7.21−7.19 (m, 3H), 6.97 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 5.60−5.57 (m, 1H), 3.58 (s, 3H), 3.30 (dd, J = 8.0, 16.9 Hz, 1H), 2.69 (dd, J = 6.6, 17.6 Hz, 1H), 2.42−219 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 155.9, 151.5, 140.2, 132.5, 129.6, 129.1, 128.5, 128.0, 127.8, 127.6, 127.5, 126.9, 125.2, 124.9, 114.1, 61.8, 55.3, 46.7, 37.7, 31.9; HRMS (ESI) $[M]^+$ Calcd for $[C_{29}H_{26}N_2O_2]$ 434.1994, found 434.1994.

*2-(2-(4-Bromophenyl)-3-(p-tolyl)-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)cyclohexanone (**6f**).* This compound was obtained as a brown solid (67 mg, 50%): mp 180−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4H), 7.43 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.8 Hz, 1H), 7.24 (s, 1H), 7.13−7.07 (m, 4H), 6.78 (d, J = 8.8 Hz, 1H), 6.35 (d, J = 8.8 Hz, 1H), 5.49 (d, J = 8.8 Hz, 1H), 3.24−3.17 (m, 1H), 2.51 (d, J = 13.2 Hz, 1H), 2.43−2.35(m, 1H), 2.32 (m, 1H), 2.29 (s, 3H), 2.08−2.02 (m, 1H), 1.70−1.60 (m, 3H), 1.46−1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 152.0, 149.6, 148.7, 147.9, 146.7, 146.2, 139.5, 133.7, 133.2, 131.9, 131.6, 129.5, 128.3, 127.6, 127.1, 125.3, 124.9, 124.7, 121.2, 120.7, 115.8, 113.5, 64.1, 52.2, 43.2, 32.5, 28.7, 25.1, 21.2; HRMS (ESI) $[M]^+$ Calcd for $[C_{31}H_{27}BrN_2O]$ 522.1307, found 522.1307.

*1-(3-(4-Ethylphenyl)-2-(4-methoxyphenyl)-1,2-dihydrobenzo[b]-[1,6]naphthyridin-1-yl)propan-2-one (**6g**).* This compound was obtained as a yellow solid (85 mg, 78%): mp 116−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.1 Hz, 1H), 7.77 (s, 1H), 7.67−7.61 (m, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.37 (t, J = 6.6 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.99−6.97 (m, 3H), 6.62 (d, J = 8.8 Hz, 2H), 5.61−5.58 (m, 1H), 3.63 (s, 3H), 3.37 (dd, J = 8.1, 17.6 Hz, 1H), 2.75 (dd, J = 7.3, 18.3 Hz, 1H), 2.58 (q, J = 7.3 Hz, 2H), 2.12 (s, 3H), 1.17 (t, J = 8.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 155.8, 151.8, 148.9, 145.5, 140.4, 134.1, 132.1, 129.4, 128.2, 128.1, 128.0, 127.6, 127.4, 126.9, 125.1, 124.8, 114.1, 111.1, 61.7, 55.2, 47.8, 31.7, 28.5 15.2; HRMS (ESI) $[M]^+$ Calcd for $[C_{30}H_{28}N_2O_2]$ 448.2151, found 448.2151.

*1-(2-(4-Bromophenyl)-3-(4-ethylphenyl)-1,2-dihydrobenzo[b]-[1,6]naphthyridin-1-yl)propan-2-one (**6h**).* This compound was obtained as a yellow solid (90 mg, 74%): mp 134−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H), 7.69−7.62 (m, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 7.05 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 5.68−5.65 (m, 1H), 3.40 (dd, J = 8.8, 17.6 Hz, 1H), 2.72 (dd, J = 5.8, 17.6 Hz, 1H), 2.60 (q, J = 8.0 Hz, 2H), 2.12 (s, 3H), 1.19 (t, J = 8.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 151.5, 148.0, 147.6, 145.9, 145.8, 133.7, 131.9, 131.8, 129.6, 128.4, 128.3, 127.6, 127.4, 127.1, 125.4, 124.6, 115.9, 112.9, 61.0, 47.5, 31.5, 28.6 15.2; HRMS (ESI) $[M]^+$ Calcd for $[C_{29}H_{25}BrN_2O]$ 496.1150, found 496.1151.

*1-(2,3-Bis(4-methoxyphenyl)-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)propan-2-one (**6i**).* This compound was obtained as a brown solid (86 mg, 79%): mp 136−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 1H), 7.67 (s, 1H), 7.59−7.53 (m, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 9.5 Hz, 2H), 6.86 (s, 1H), 6.71 (d, J = 8.8 Hz, 2H), 6.55 (d, J = 8.8 Hz, 2H), 5.52−5.49 (m, 1H), 3.67 (s, 3H), 3.56 (s, 3H), 3.31 (dd, J = 8.8, 17.6 Hz, 1H), 2.66 (dd, J = 5.8, 16.9 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 160.2, 155.7, 151.8, 148.6, 147.7, 140.3, 133.7, 132.1, 129.3, 129.0, 127.9, 127.5, 127.3, 126.7, 124.9, 124.8, 114.1, 113.9, 110.0, 61.6, 55.13, 55.09, 47.7, 31.5; HRMS (ESI) $[M]^+$ Calcd for $[C_{29}H_{26}N_2O_3]$ 450.1943, found 450.1943.

*1-(2-(4-Bromophenyl)-3-(4-methoxyphenyl)-1,2-dihydrobenzo-[b][1,6]naphthyridin-1-yl)propan-2-one (**6j**).* This compound was obtained as a light brown solid (0.260 g, 75%): mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.63−7.56 (m, 2H), 7.43−7.40 (m, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.14−7.12 (m, 2H), 6.94−6.89 (m, 3H), 6.75 (d, J = 8.8 Hz, 2H), 5.61−5.58 (m, 1H), 3.71 (s, 3H), 3.34 (dd, J = 8.0, 16.8 Hz, 1H), 2.67 (dd, J = 5.8, 17.6 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 160.5, 151.6, 148.0, 147.3, 146.0, 131.9, 131.8, 129.5, 129.1, 128.6, 128.3, 127.6, 127.3, 127.0, 125.3, 124.7, 116.0, 114.2, 112.0, 61.1, 55.3, 47.5, 31.5; HRMS (ESI) $[M]^+$ Calcd for $[C_{28}H_{23}BrN_2O_2]$ 498.0943, found 498.0943.

*1-(3-(4-(Dimethylamino)phenyl)-2-(p-tolyl)-1,2-dihydrobenzo[b]-[1,6]naphthyridin-1-yl)propan-2-one (**6k**).* This compound was obtained as a brown solid (81 mg, 78%): mp 128−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 10.6 Hz, 1H), 7.72 (s, 1H), 7.65−7.62 (m, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.33 (t, J = 9.5 Hz, 1H), 6.96−6.94 (m, 2 H), 6.92−6.87 (m, 3H), 6.57 (d, J = 9.5 Hz, 2H), 5.65−5.60 (m, 1H), 3.38 (dd, J = 8.8, 17.6 Hz, 1H), 2.92 (s, 6H), 2.73 (dd, J = 6.6, 17.6 Hz, 1H), 2.15 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 152.3, 150.8, 149.0, 147.9, 145.0, 132.4, 131.9, 129.4, 129.2, 129.0, 128.0, 127.5, 127.2, 124.7, 124.0, 123.2, 115.9, 111.7, 61.5, 47.6, 40.1, 31.7, 20.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{30}H_{29}N_3O]$ 447.2311, found 447.2311.

*1-(3-(4-(Dimethylamino)phenyl)-2-(4-methoxyphenyl)-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)propan-2-one (**6l**).* This compound was obtained as an orange semisolid (85 mg, 79%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 10.1 Hz, 1H), 7.68 (s, 1H), 7.60−7.52 (m, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 9.5 Hz, 2H), 6.86 (s, 1H), 6.57 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 8.8 Hz, 2H), 5.52−5.48 (m, 1H), 3.58 (s, 3H), 3.34 (dd, J = 8.8, 17.6 Hz, 1H), 2.87 (s, 6H), 2.63 (dd, J = 5.9, 16.8 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 155.6, 150.9, 140.9, 129.5, 129.2, 128.8, 127.6, 127.2, 127.0, 124.9, 124.8, 124.0, 123.9, 115.9, 114.1, 111.7, 61.8, 55.3, 47.7, 40.1, 31.8; HRMS (ESI) $[M]^+$ Calcd for $[C_{30}H_{29}N_3O_2]$ 463.2260, found 463.2260.

*1-(2-(4-Bromophenyl)-3-(4-(dimethylamino)phenyl)-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)propan-2-one (**6m**).* This

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386−4401

compound was obtained as an orange solid (89 mg, 75%): mp 76−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.66−7.60 (m, 2H), 7.42−7.34 (m, 3H), 7.18 (d, J = 8.8 Hz, 2H), 6.99−6.96 (m, 3H), 6.57 (d, J = 8.8 Hz, 2H), 5.65−5.61 (m, 1H), 3.41 (dd, J = 8.0, 17.6 Hz, 1H), 2.93 (s, 6H), 2.67 (dd, J = 5.9, 17.6 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 151.8, 151.0, 148.5, 147.5, 146.4, 139.2, 132.0, 131.7, 129.6, 128.9, 127.8, 127.5, 127.2, 127.1, 125.1, 124.7, 123.2, 115.7, 111.8, 61.1, 47.3, 40.1, 31.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{29}H_{26}BrN_3O]$ 511.1259, found 511.1259.

*1-(2-(4-Bromophenyl)-3-(thiophen-3-yl)-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)propan-2-one (**6n**).* This compound was obtained as a pale white solid (95 mg, 76%): mp 168−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.70−7.63 (m, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.33 (s, 1H), 7.25−7.21 (m, 4H), 7.07 (s, 1H), 6.98−6.96 (m, 2H), 5.63−5.60 (m, 1H), 3.39 (dd, J = 8.0, 17.6 Hz, 1H), 2.72 (dd, J = 5.8, 17.5 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 151.2, 147.8, 146.1, 142.7, 138.5, 132.1, 131.9, 129.7, 128.3, 127.6, 127.4, 126.9, 126.4, 126.3, 125.6, 125.3, 124.4, 116.3, 112.4, 61.2, 47.6, 31.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{25}H_{19}BrN_2OS]$ 474.0401, found 474.0402.

*1-(2-(4-Methoxyphenyl)-3-m-tolyl-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)propan-2-one (**6o**).* This compound was obtained as orange solid (81 mg, 72%): mp 66−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H), 7.60−7.53 (m, 2H), 7.38 (s, 1H), 7.31−7.23 (m, 2H), 7.05 (t, J = 7.3 Hz, 1H), 6.98 (d, J = 7.4 Hz, 1H), 6.92−6.90 (m, 3H), 6.55 (d, J = 8.8 Hz, 2H), 5.53 (t, J = 7.3 Hz, 1H), 3.55 (s, 3H), 3.30 (dd, J = 7.4, 16.9 Hz, 1H), 2.69 (dd, J = 5.9, 17.6 Hz, 1H), 2.21 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 155.8, 151.8, 149.0, 147.9, 140.3, 138.0, 136.8, 132.1, 129.8, 129.3, 128.6, 128.3, 128.2, 127.5, 126.8, 125.2, 125.0, 124.8, 114.0, 111.5, 61.7, 55.1, 47.8, 31.5, 22.5; HRMS (ESI) $[M]^+$ Calcd for $[C_{29}H_{26}N_2O_2]$ 434.1994, found 434.1994.

*1-(2-(4-Bromophenyl)-3-m-tolyl-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)propan-2-one (**6p**).* This compound was obtained as yellow solid (89 mg, 72%): mp 54−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 1H), 7.66 (s, 1H), 7.57−7.50 (m, 2H), 7.32−7.25 (m, 2H), 7.16 (d, J = 7.3 Hz, 1H), 7.09−7.02 (m, 3H), 6.98−6.96 (m, 2H), 6.88−6.85 (d, J = 8.8 Hz, 2H), 5.59−5.56 (m, 1H), 3.29 (dd, J = 8.1, 17.6 Hz, 1H), 2.63 (dd, J = 5.1, 17.6 Hz, 1H), 2.19 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 151.2, 147.8, 147.7, 145.8, 138.3, 136.2, 132.0, 131.7, 130.1, 129.5, 128.5, 128.2, 127.5, 127.4, 127.0, 125.4, 124.8, 124.5, 115.9, 113.8, 60.9, 47.4, 31.3, 21.3; HRMS (ESI) $[M]^+$ Calcd for $[C_{28}H_{23}BrN_2O]$ 482.0994, found 482.0994.

*1-(3-Cyclohexyl-2-(4-methoxyphenyl)-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)propan-2-one (**6q**).* This compound was obtained as a yellowish semisolid (77 mg, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.60−7.52 (m, 2H), 7.48(t, J = 7.3 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 6.35 (s, 1H), 5.26 (t, J = 6.6 Hz, 1H), 3.69 (s, 3H), 3.05 (dd, J = 6.6, 16.8 Hz, 1H), 2.73 (dd, J = 6.6, 17.5 Hz, 1H), 1.98 (s, 3H), 1.93−1.81 (m, 3H), 1.68−1.62 (m, 3H), 1.54−1.47 (m, 3H), 1.46−1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 151.7, 147.1, 141.5, 139.5, 137.4, 132.5, 132.1, 129.5, 129.2, 128.7, 127.7, 127.5, 127.2, 127.0, 126.0, 125.5, 124.5, 61.2, 55.4, 48.1, 31.3, 26.7, 26.2, 26.1, 25.7, 24.8; HRMS (ESI) $[M]^+$ Calcd for $[C_{28}H_{30}N_2O_2]$ 426.2307, found 426.2307.

*1-(2-(4-Bromophenyl)-3-cyclohexyl-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)propan-2-one (**6r**).* This compound was obtained as a dark brown liquid (85 mg, 68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 1H), 7.63 (s, 1H), 7.59−7.49 (m, 2H), 7.32−7.28 (m, 3H), 6.93 (d, J = 8.8 Hz, 2H), 6.54 (s, 1H), 5.36 (t, J = 6.6 Hz, 1H), 3.15 (dd, J = 7.4, 17.6 Hz, 1H), 2.65 (dd, J = 5.8, 17.6 Hz, 1H), 2.02 (s, 3H), 1.97−1.95 (m, 1H), 1.93−1.74 (m, 5H), 1.65−1.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 152.8, 151.1, 145.6, 139.2, 135.3 132.1, 129.5, 127.9, 127.5, 127.3, 125.9, 125.3, 123.9, 123.3, 60.8, 48.0, 40.6, 31.6, 31.1, 30.3, 29.3, 26.7, 26.2, 26.1; HRMS (ESI) $[M]^+$ Calcd for $[C_{27}H_{27}BrN_2O]$ 474.1307, found 474.1307.

*1-(3-Butyl-2-phenyl-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)-propan-2-one (**6s**).* This compound was obtained as a brown liquid (74 mg, 68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.8 Hz, 1H), 7.64 (s, 1H), 7.58−7.50 (m, 2H), 7.29−7.18 (m, 3H), 7.06−7.02 (m, 3H), 6.33 (s, 1H), 5.40−5.37 (m, 1H), 3.04 (dd, J = 5.8, 16.8 Hz, 1H), 2.93 (dd, J = 7.3, 16.8 Hz, 1H), 2.34−2.28 (m, 1H), 2.21−2.16 (m, 1H), 1.98 (s, 3H), 1.25−1.15 (m, 4H), 0.80−0.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 152.2, 151.5, 147.5, 145.5, 132.2, 129.4, 129.1, 127.8, 127.6, 127.1, 125.7, 124.7, 124.6, 108.4, 61.0, 48.1, 33.3, 31.5, 30.4, 22.2, 13.8; HRMS (ESI) $[M]^+$ Calcd for $[C_{25}H_{26}N_2O]$ 370.2045, found 370.2045.

*1-(3-Butyl-2-(4-methoxyphenyl)-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)propan-2-one (**6t**).* This compound was obtained as a brown liquid (82 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 1H), 7.64 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 6.6 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 6.22 (s, 1H), 5.29 (t, J = 7.3 Hz, 1H), 3.74 (s, 3H), 3.05 (dd, J = 6.5, 17.5 Hz, 1H), 2.92 (dd, J = 7.3, 17.6 Hz, 1H), 2.24−2.11 (m, 2H), 1.99 (s, 3H), 1.44−1.39 (m, 2H), 1.29−1.20 (m, 2H), 0.83−0.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 157.2, 152.6, 151.9, 147.9, 138.7, 131.8, 129.6, 129.2, 128.8, 127.9, 127.5, 127.1, 126.8, 125.3, 124.3, 114.3, 106.6, 61.4, 55.0, 48.0, 33.3, 31.4, 30.3, 22.2, 13.8 ; HRMS (ESI) $[M]^+$ Calcd for $[C_{26}H_{28}N_2O_2]$ 400.2151, found 400.2151.

*1-(2-(4-Bromophenyl)-3-butyl-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)propan-2-one (**6u**).* This compound was obtained as a brownish liquid (89 mg, 68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.8 Hz, 1H), 7.56−7.44 (m, 3H), 7.26−7.19 (m, 3H), 6.89 (d, J = 8.7 Hz, 2H), 6.36 (s, 1H), 5.28 (t, J = 6.6 Hz, 1H), 3.06 (dd, J = 6.6, 17.6 Hz, 1H), 2.70 (dd, J = 6.6 Hz, 17.5, 1H), 1.94 (s, 3H), 1.38−1.25 (m, 3H), 1.18−1.10 (m, 3H), 0.76−0.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 151.2, 151.1, 147.5, 144.7, 132.04, 131.97, 129.4, 127.9, 127.5, 127.1, 125.7, 125.6, 124.9, 117.4, 110.4, 60.9, 47.9, 33.1, 31.2, 30.4, 22.2, 13.7; HRMS (ESI) $[M]^+$ Calcd for $[C_{25}H_{25}BrN_2O]$ 448.1150, found 448.1150.

*1-(8-Methoxy-3-(4-methoxyphenyl)-2-phenyl-1,2-dihydrobenzo-[b][1,6]naphthyridin-1-yl)propan-2-one (**6v**).* This compound was obtained as an orange solid (77 mg, 78%): mp 170−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 9.5 Hz, 1H), 7.63(s, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.24−7.21 (m, 1H), 7.05−6.96 (m, 4H), 6.91−6.89 (m, 2H), 6.80 (t, J = 7.3 Hz, 1H), 6.72 (d, J = 8.0 Hz, 2H), 5.64 (t, J = 6.6 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.29 (dd, J = 7.3, 16.8 Hz, 1H), 2.76 (dd, J = 5.8, 16.8 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 160.2, 156.9, 149.9, 146.9, 146.5, 143.8, 131.0, 129.6, 129.2, 129.0, 128.8, 128.2, 127.5, 123.0, 122.9, 121.9, 114.0, 111.5, 105.5, 61.1, 55.5, 55.2, 47.8, 31.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{29}H_{26}N_2O_3]$ 450.1943, found 450.1943.

*1-(8-Methoxy-2-phenyl-3-(m-tolyl)-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)propan-2-one (**6w**).* This compound was obtained as a yellow solid (71 mg, 71%): mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.8 Hz, 1H), 7.61 (s, 1H), 7.35 (s, 1H), 7.22−7.16 (m, 2H), 7.05−6.89 (m, 8H), 6.78−6.75 (m, 1H), 5.64 (t, J = 6.6 Hz, 1H), 3.77 (s, 3H), 3.27 (dd, J = 7.3, 17.5 Hz, 1H), 2.77 (dd, J = 6.5, 17.5 Hz, 1H), 2.20 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 157.0, 149.4, 147.1, 146.8, 143.8, 138.1, 136.8, 131.0, 129.7, 129.6, 128.7, 128.3, 128.2, 127.5, 124.8, 122.8, 122.0, 112.6, 105.5, 60.9, 55.4, 47.7, 31.6, 21.3; HRMS (ESI) $[M]^+$ Calcd for $[C_{29}H_{26}N_2O_2]$ 434.1994, found 434.1994.

*1-(8-Methoxy-2-(4-methoxyphenyl)-3-(m-tolyl)-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)propan-2-one (**6x**).* This compound was obtained as an orange solid (79 mg, 74%): mp 136−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 9.5 Hz, 1H), 7.60 (s, 1H), 7.38 (s, 1H), 7.26−7.20 (m, 2H), 7.06 (t, J = 7.3 Hz, 1H), 6.99−6.96 (m, 1H), 6.92−6.89 (m, 4H), 6.55 (t, J = 9.5, 2H), 5.51 (t, J = 6.6, 1H), 3.79 (s, 3H), 3.56 (s, 3H), 3.29 (dd, J = 7.3, 16.8 Hz, 1H), 2.70 (dd, J = 5.8, 16.8 Hz, 1H), 2.22 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 156.9, 155.7, 149.6, 147.7, 143.8, 140.4, 138.0, 136.9, 129.7, 129.6, 128.4, 128.3, 127.1, 125.0, 124.6, 121.9, 114.0, 111.7, 105.5, 61.6, 55.5, 55.2, 47.9, 31.6, 21.4;

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386−4401

HRMS (ESI) $[M]^+$ Calcd for $[C_{30}H_{28}N_2O_3]$ 464.2100, found 464.2100.

*1-(6-(4-Methoxyphenyl)-7-(p-tolyl)-5,6-dihydro-1,6-naphthyridin-5-yl)propan-2-one (**6y**).* This compound was obtained as a yellow solid (95 mg, 79%): mp 114−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35−8.34 (m, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 7.32 Hz, 1H), 6.99−6.87 (m, 3H), 6.76 (s, 3H), 6.54 (d, J = 8.8 Hz, 2H), 5.38−5.34 (m, 1H), 3.54 (s, 3H), 3.19 (dd, J = 8.1, 16.9 Hz, 1H), 2.59 (dd, J = 5.9, 16.8 Hz, 1H), 2.19 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 155.5, 151.1, 148.3, 146.1, 140.0, 138.7, 133.8, 133.1, 129.1, 127.6, 125.8, 124.5, 121.0, 113.9, 110.5, 61.2, 55.1, 47.1, 29.6, 21.1; HRMS (ESI) $[M]^+$ Calcd for $[C_{25}H_{24}N_2O_2$] 384.1838, found 384.1838.

*1-(6-(4-Bromophenyl)-7-(p-tolyl)-5,6-dihydro-1,6-naphthyridin-5-yl)propan-2-one (**6z**).* This compound was obtained as a yellow solid (101 mg, 74%): mp 114−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 3.6 Hz, 1H), 7.44−7.39 (m, 3H), 7.23 (d, J = 8.0 Hz, 2H), 7.13−7.08 (m, 3H), 7.00−6.95 (m, 3H), 5.57−5.54 (m, 1H), 3.38−3.31 (m, 1H), 2.70 (dd, J = 5.8, 17.6 Hz, 1H), 2.34 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 150.8, 148.5, 145.6, 145.0, 139.1, 133.3, 133.0, 131.6, 129.4, 127.4, 126.5, 124.4, 121.3, 115.7, 112.2, 60.4, 46.7, 29.5, 21.1; HRMS (ESI) $[M]^+$ Calcd for $[C_{24}H_{21}BrN_2O$] 432.0837, found 432.0837.

General Procedure for Synthesis of 1,2-Dihydrobenzo[1,6]-naphthyridines (Table 3). A solution of *o*-alkynylaldehydes **3** (70 mg, 1 equiv), amine **4b,c** (1 equiv), **5d−g** (5 equiv) and $AgNO_3$ (10 mol %), in C_2H_5OH (2 mL) was stirred at 60 °C for a period of 0.5 h. After completion of the reaction as indicated by TLC, the solvent was evaporated and then quenched with water (10 mL), extracted with EtOAc (3 × 10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding products **7a−e**. (Table 3, entries 1−5).

*Diethyl 2-(6-(4-bromophenyl)-7-(p-tolyl)-5,6-dihydro-1,6-naphthyridin-5-yl)malonate (**7a**).* This compound was obtained as a yellow solid (118 mg, 70%): mp 114−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 5.12 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 7.01−6.96 (m, 4H), 6.92 (d, J = 8.8 Hz, 2H), 5.59 (d, J = 11.0 Hz, 1H), 4.30−4.18 (m, 2H), 3.99−3.87 (m, 3H), 2.22 (s, 3H), 1.22−1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 166.6, 151.0, 149.2, 145.2, 139.3, 134.7, 132.6, 131.7, 129.2, 127.5, 124.8, 123.1, 121.1, 116.4, 112.9, 64.2, 62.0, 61.6, 54.3, 21.2, 13.9, 13.8; HRMS (ESI) $[M]^+$ Calcd for $[C_{28}H_{27}BrN_2O_4]$ 534.1154, found 534.1154.

*Ethyl 2-(2-(4-bromophenyl)-3-(4-ethylphenyl)-1,2-dihydrobenzo-[b][1,6]naphthyridin-1-yl)-3-oxobutanoate (**7b**).* This compound was obtained as a yellow solid (78 mg, 62%): mp 72−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, J = 7.3 Hz, 1H), 7.86 (d, J = 15.4 Hz, 2H), 7.68−7.61 (m, 2H), 7.45−7.42 (m, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.26 (s, 1H), 7.21 (s, 1H), 7.15 (d, J = 8.9 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 5.86 (d, J = 11 Hz, 1H), 5.23 (s, 1H), 4.46−4.41 (m, 2H), 2.60−2.54 (m, 2H), 2.30 (s, 3H), 1.28−1.22 (m, 3H), 1.16 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 200.2, 167.1, 166.2, 151.1, 147.7, 146.0, 145.4, 134.6, 134.1, 132.8, 131.8, 130.0, 128.4, 128.1, 127.6, 127.0, 125.6, 124.8, 123.8, 116.7, 112.9, 63.8, 62.1, 60.4, 29.6, 28.5, 14.0, 13.7; HRMS (ESI) $[M]^+$ Calcd for $[C_{32}H_{29}BrN_2O_3]$568.1362, found 568.1363.

*Diethyl 2-(2-(4-bromophenyl)-3-(4-methoxyphenyl)-1,2-dihydro-2,6-naphthyridin-1-yl)malonate (**7c**).* This compound was obtained as a brown solid (119 mg, 74%): mp 150−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.34−8.32 (m, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.06−7.05 (m, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.80−6.75 (m, 3H), 5.62 (d, J = 11.0 Hz, 1H), 4.36−4.20 (m, 2H), 4.07−3.94 (m, 2H), 3.88 (d, J=11.0 Hz, 1H), 3.75 (s, 3H), 1.24 (t, J = 7.32 Hz, 3H), 1.06 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 166.5, 160.3, 146.7, 145.2, 145.0, 142.4, 135.8, 131.8, 128.7, 128.2, 127.9, 124.7, 121.8, 116.5, 114.0, 107.6, 63.2, 62.1, 61.9, 55.3, 53.9, 14.0, 13.8; HRMS (ESI) $[M]^+$ Calcd for $[C_{28}H_{27}BrN_2O_5]$ 550.1103, found 550.1102.

*3-Hydroxy-2-(6-(4-methoxyphenyl)-7-(p-tolyl)-5,6-dihydro-1,6-naphthyridin-5-yl)-5,5-dimethylcyclohex-3-enone (**7d**).* This compound was obtained as a yellow semisolid (105 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.84 (s, 1H), 8.54 (d, J = 4.4 Hz, 1H), 7.31−7.26 (m, 3H), 7.11−7.06 (m, 5H), 6.71 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 8.8 Hz, 2H), 4.57 (d, J = 17.6 Hz, 1H), 4.25 (d, J = 16.8 Hz, 1H), 3.65 (s, 3H), 2.46 (s, 2H), 2.30 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 195.5, 169.7, 158.2, 151.6, 147.9, 139.3, 136.2, 135.8, 131.4, 129.9, 129.1, 126.7, 125.7, 115.9, 114.1, 114.0, 106.2, 55.2, 52.6, 52.1, 43.9, 31.6, 28.0, 24.6, 22.7; HRMS (ESI) $[M]^+$ Calcd for $[C_{30}H_{30}N_2O_3$]466.2256, found 466.2256.

*5-(2-(4-Methoxyphenyl)-3-phenyl-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**7e**).* This compound was obtained as a yellow solid (100 mg, 74%): mp 220−226 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 7.3 Hz, 1H), 7.68 (s, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.28−7.26 (m, 4H), 6.77 (d, J = 8.8 Hz, 2H), 6.67 (s, 2H), 6.44 (d, J = 8.8 Hz, 2H), 4.89 (d, J = 16.8 Hz, 1H), 4.39 (d, J = 16.9 Hz, 1H), 3.53 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 170.8, 167.3, 162.5, 158.2, 153.5, 151.6, 146.2, 139.3, 136.1, 134.5, 131.0, 130.3, 130.2, 129.5, 128.4, 127.8, 127.7, 126.8, 126.6, 126.3, 124.0, 123.5, 117.3, 114.8, 114.2, 103.3, 55.7, 55.2, 44.2, 26.8, 26.5; HRMS (ESI) $[M]^+$ Calcd for $[C_{31}H_{26}N_2O_5]$ 506.1842, found 506.1842.

General Procedure for the Synthesis of 1,2-Dihydrobenzo [4,5]thieno[2,3-*c*]pyridines (Table 4). A solution of *o*-alkynylaldehyde **3o−q** (70 mg, 1 equiv), amine **4a**/**4d** (1 equiv), acetone **5a** (5 equiv), $AgNO_3$ (10 mol %), L-proline (10 mol %) in C_2H_5OH (2 mL) was stirred at 60 °C for a period of 2 h. After completion of the reaction as indicated by TLC, the solvent was evaporated and then quenched with water (10 mL), extracted with EtOAc (3 × 10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding products **8a−e** along with imines **9a−e**, respectively (Table 4).

*1-(2,3-Diphenyl-1,2-dihydrobenzo[4,5]thieno[2,3-c]pyridin-1-yl)-propan-2-one (**8a**).* This compound was obtained as a brown solid (68 mg, 65%): mp 114−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7. 55−7.53 (m, 2H), 7.45−7.39 (m, 2H), 7.32−7.26 (m, 2H), 7.21−7.17 (m, 1H), 7.10−7.04 (m, 4H), 7.00 (s, 1 H), 6.85−6.81 (m, 1H), 5.77−5.73 (m, 1H), 3.24 (dd, J = 8.1, 17.6 Hz, 1H), 2.83 (dd, J = 5.1, 16.8 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 147.0, 141.7, 139.7, 138.6, 137.3, 134.6, 131.8, 128.7, 128.6, 128.4, 127.3, 127.0, 124.3, 123.9, 122.9, 122.53, 122.47, 122.3, 120.8, 106.4, 57.5, 47.3, 31.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{26}H_{21}NOS]$ 395.1344, found 395.1344.

*1-(3-Phenyl-2-(p-tolyl)-1,2-dihydrobenzo[4,5]thieno[2,3-c]-pyridin-1-yl)propan-2-one (**8b**).* This compound was obtained as a brown semisolid (65 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.50−7.47 (m, 2H), 7.38−7.34 (m, 1H), 7.26−7.14 (m, 5H), 6.91−6.88 (m, 3H), 6.81(d, J = 8.8 Hz, 1H), 5.65−5.61 (m, 1H), 3.17 (dd, J = 8.0, 16.8 Hz, 1H), 2.75 (dd, J = 5.1, 16.8 Hz, 1H), 2.11 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 145.0, 139.7, 138.7, 137.4, 135.6, 132.3, 129.5, 129.3, 128.5, 127.9, 127.0, 124.3, 124.2, 122.9, 122.4, 120.7, 113.7, 57.8, 47.4, 31.6, 20.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{27}H_{23}NOS]$ 409.1500, found 409.1501.

*1-(2-Phenyl-3-(thiophen-3-yl)-1,2-dihydrobenzo[4,5]thieno[2,3-c]pyridin-1-yl)propan-2-one (**8c**).* This compound was obtained as brown solid (68 mg, 65%): mp 92−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.45−7.43 (m, 2H), 7.34−7.28 (m, 3H), 7.25−7.20 (m, 1H), 7.13−7.08 (m, 2H), 7.02 (s, 1H), 6.90 (t, J = 6.6 Hz, 1H), 6.70−6.61 (m, 1H), 5.71−5.67 (m, 1H), 3.26 (dd, J = 11.0, 18.3 Hz, 1H), 2.79 (dd, J = 6.6, 16.8 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 147.3, 139.5, 135.6, 134.0, 129.9, 129.7, 128.8, 128.1, 126.0, 125.7, 124.4, 124.3, 122.9, 122.7, 122.1, 120.8, 114.1, 57.9, 47.2, 31.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{24}H_{19}NOS_2]$ 401.0908, found 401.0908.

*1-(3-(Thiophen-3-yl)-2-(p-tolyl)-1,2-dihydrobenzo[4,5]thieno[2,3-c]pyridin-1-yl)propan-2-one (**8d**).* This compound was obtained as brown solid (65 mg, 60%): mp 68−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.35−7.33

dx.doi.org/10.1021/jo400400c | J. Org. Chem. 2013, 78, 4386−4401

(m, 1H), 7.26−7.18 (m, 3H), 7.16−7.12 (m, 2H), 6.91−6.83 (m, 4H), 5.56−5.52 (m, 1H), 3.17 (dd, J = 8.1, 16.1 Hz, 1H), 2.69 (dd, J = 5.8, 16.8 Hz, 1H), 2.12 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 145.0, 139.6, 132.4, 129.4, 128.2, 126.1, 125.6, 124.3, 124.2, 123.9, 122.9, 122.8, 122.2, 120.7, 105.3, 58.2, 47.3, 31.6, 20.7; HRMS (ESI) $[M]^+$ Calcd for $[C_{25}H_{21}NOS_2]$ 415.1065, found 415.1065.

*1-(2-Phenyl-3-(4-(trifluoromethyl)phenyl)-1,2-dihydrobenzo[4,5]-thieno[2,3-c]pyridin-1-yl)propan-2-one (**8e**).* This compound was obtained as a brown semisolid (29 mg, 30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.61−7.57 (m, 2H), 7.45−7.43 (m, 2H), 7.39−7.36 (m, 1H), 7.28−7.25 (m, 1H), 7.06−6.98 (m, 5H), 6.82 (t, J = 6.6 Hz, 1H), 5.71−5.68 (m, 1H), 3.16 (dd, J = 8.0, 17.6 Hz, 1H), 2.76 (dd, J = 5.8, 17.6 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 146.7, 142.7, 140.9, 139.6, 137.2, 135.5, 131.9, 130.9, 128.9, 128.0, 127.0, 125.5, 124.6, 124.5, 123.02, 122.99, 122.3, 120.8, 116.0, 114.0, 107.9, 57.6, 47.4, 31.6; HRMS (ESI) $[M]^+$ Calcd for $[C_{27}H_{20}F_3NOS]$ 463.1218, found 463.1218.

*(E)-N-((3-(Phenylethynyl)benzo[b]thiophen-2-yl)methylene)-aniline (**9a**).* This compound was obtained as a yellow solid (14 mg, 15%): mp 116−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.00−7.98 (m, 1H), 7.82−7.77 (m, 1H), 7.58−7.54 (m, 3H), 7.47−7.32 (m, 8H), 7.28−7.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 151.0, 139.74, 139.67, 131.9, 131.8, 129.2, 128.6, 127.3, 126.7, 125.6, 125.1, 123.9, 123.7, 123.2, 122.6, 122.5, 121.3, 97.9, 81.5; HRMS (ESI) $[M]^+$ Calcd for $[C_{23}H_{15}NS]$ 337.0925, found 337.0925.

*(E)-4-Methyl-N-((3-(phenylethynyl)benzo[b]thiophen-2-yl)-methylene)aniline (**9b**).* This compound was obtained as a yellow solid (19 mg, 20%): mp 146−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.98−7.95 (m, 1H), 7.77−7.75 (m, 1H), 7.56−7.53 (m, 2H), 7.40−7.35 (m, 2H), 7.33−7.31 (m, 3H), 7.19−7.13 (m, 4H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 148.5, 144.9, 139.8, 139.5, 136.7, 131.9, 131.7, 129.8, 129.0, 128.9, 128.6, 128.5, 127.2, 125.0, 123.8, 122.8, 122.52, 122.45, 121.2, 97.7, 81.6, 21.1; HRMS (ESI) $[M]^+$ Calcd for $[C_{24}H_{17}NS]$ 351.1082, found 351.1082.

*(E)-N-((3-(Thiophen-3-ylethynyl)benzo[b]thiophen-2-yl)-methylene)aniline (**9c**).* This compound was obtained as a brown solid (18 mg, 20%): mp 99−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.95−7.92 (m, 1H), 7.78−7.73 (m, 1H), 7.56−7.55 (m, 1H), 7.47−7.41 (m, 1H), 7.37−7.35 (m, 2H), 7.30−7.25 (m, 1H), 7.21−7.18 (m, 1H), 7.16−7.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 151.9, 148.4, 144.8, 139.7, 139.5, 136.7, 130.5, 129.8, 128.8, 127.2, 126.0, 125.8, 125.0, 123.8, 122.8, 121.2, 115.9, 92.7, 81.2 ; HRMS (ESI) $[M]^+$ Calcd for $[C_{21}H_{13}NS_2]$ 343.0489, found 343.0490.

*(E)-4-Methyl-N-((3-(thiophen-3-ylethynyl)benzo[b]thiophen-2-yl)methylene)aniline (**9d**).* This compound was obtained as a brown solid (21 mg, 22%): mp 100−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.95−7.92 (m, 1H), 7.78−7.73 (m, 1H), 7.56−7.55 (m, 1H), 7.47−7.41 (m, 1H), 7.37−7.35 (m, 2H), 7.30−7.25 (m, 1H), 7.21−7.18 (m, 1H), 7.16−7.12 (m, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 151.9, 148.4, 144.8, 139.7, 139.5, 136.7, 130.5, 129.8, 128.8, 127.2, 126.0, 125.8, 125.0, 123.8, 122.8, 121.2, 115.9, 92.7, 81.2, 21.1; HRMS (ESI) $[M]^+$ Calcd for $[C_{22}H_{15}NS_2]$ 357.0645, found 357.0646.

*(E)-N-((3-((4-(Trifluoromethyl)phenyl)ethynyl)benzo[b]thiophen-2-yl)methylene)aniline (**9e**).* This compound was obtained as a yellow solid (42 mg, 50%): mp 124−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.97−7.95 (m, 1H), 7.80−7.77 (m, 1H), 7.65−7.57 (m, 5H), 7.45−7.33 (m, 3H), 7.26−7.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 150.9, 145.7, 139.6, 132.2, 132.0, 129.3, 128.9, 127.4, 126.9, 126.2, 125.49, 125.45, 125.2, 123.7, 123.4, 122.9, 121.9, 121.3, 96.1, 83.8; HRMS (ESI) $[M]^+$ Calcd for $[C_{24}H_{14}F_3NS]$ 405.0799, found 405.0798.

*1-(3-(4-Methoxyphenyl)-2-(4′-methyl-[1,1′-biphenyl]-4-yl)-1,2-dihydrobenzo[b][1,6] naphthyridin-1-yl)propan-2-one (**11**).* A solution of 1-(2-(4-bromophenyl)-3-(4-methoxyphenyl)-1,2-dihydrobenzo[b][1,6]naphthyridin-1-yl)propan-2-one **6j** (100 mg, 1 equiv), p-tolylboronic acid **10** (30 mg, 1.1 equiv) and Cs_2CO_3 (130 mg, 2 equiv), in 2 mL of DMF:H_2O (4:1) was purged under N_2 for 15−20 min, and then catalyst $Pd(OAc)_2$ (2.25 mg, 5 mol %) and **L** (2 mg, 5 mol %) were added under inert atmosphere and then heated to 80 °C for a period of 2 h. After completion of the reaction as indicated by TLC, reaction mixture was quenched with water (10 mL), extracted with EtOAc (3 × 10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **11**. This compound was obtained as an orange solid (73 mg, 72%): mp 50−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.69−7.61 (m, 2H), 7.52 (d, J = 6.6 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 4H), 7.14 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 9.9 Hz, 2H), 7.02 (s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 5.76 (t, J = 7.0 Hz, 1H), 3.76 (s, 3H), 3.39 (dd, J = 7.3, 17.6 Hz, 1H), 2.86 (dd, J = 6.6, 18.3 Hz, 1H), 2.31 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 160.4, 151.6, 148.2, 147.4, 145.8, 139.2, 137.4, 136.6, 135.7, 132.5, 130.0, 129.6, 129.4, 129.2, 129.0, 127.8, 127.6, 127.3, 127.2, 126.5, 125.2, 123.4, 115.4, 114.1, 110.7, 61.0, 55.2, 47.6, 30.3, 21.0; HRMS (ESI) $[M]^+$ Calcd for $[C_{35}H_{30}N_2O_2]$ 510.2307, found 510.2308.

*(E)-Methyl 3-(4-(3-(4-methoxyphenyl)-1-(2-oxopropyl)benzo[b]-[1,6]naphthyridin-2(1H)-yl)phenyl)acrylate (**13**).* A solution of 1-(2-(4-bromophenyl)-3-(4-methoxyphenyl)-1,2-dihydrobenzo[b][1,6]-naphthyridin-1-yl)propan-2-one **6j** (100 mg, 1 equiv), methyl acrylate **12** (18 mg, 1.1 equiv) and K_2CO_3 (60 mg, 2 equiv), in 2 mL of DMF was purged under N_2 for 15−20 min, and then catalyst $Pd(OAc)_2$ (2.25 mg, 5 mol %) and **L** (2 mg, 5 mol %) were added under inert atmosphere and then heated to 120 °C for a period of 8 h. After completion of the reaction as indicated by TLC, reaction mixture was quenched with water (10 mL), extracted with EtOAc (3 × 10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **13**. This compound was obtained as a yellow solid (70 mg, 70%): mp 148−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 1H), 7.78 (s, 1H), 7.64−7.56 (m, 2H), 7.47−7.41 (m, 3H), 7.34 (t, J = 8.8 Hz, 1H), 7.22−7.19 (m, 2H), 7.00 (d, J = 8.8 Hz, 3H), 6.76 (d, J = 8.8 Hz, 2H), 6.15 (d, J = 16.1 Hz, 1H), 5.73 (t, J = 7.3 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.33 (dd, J = 7.3, 16.8 Hz, 1H), 2.77 (dd, J = 5.9, 17.6 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 167.6, 160.6, 151.5, 148.5, 147.8, 147.6, 147.3, 147.1, 144.2, 139.3, 132.2, 129.7, 129.0, 128.8, 128.7, 128.6, 128.1, 127.6, 127.4, 127.3, 125.5, 123.9, 123.4, 122.7, 116.0, 114.2, 114.0, 112.0, 60.5, 55.3, 51.6, 47.4, 31.5; HRMS (ESI) $[M]^+$ Calcd for $[C_{32}H_{28}N_2O_4]$ 504.2049, found 504.2050.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and copies of ^{1}H NMR, ^{13}C NMR, HRMS and Chiral-HPLC (**6h**, **6i**, **6k**, and **6v**) spectra for all new compounds. CIF for compound **6z** (CCDC 886742). 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

We gratefully acknowledge the Department of Science and Technology (SR/S1/OC-66/2010) for financial support and USIC, University of Delhi, for providing instrumentation facilities. S.K.R.K., D.C., and M.P. are thankful to CSIR, DST for a fellowship.

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