JOC The Journal of Organic Chemistry
Article
pubs.acs.org/joc

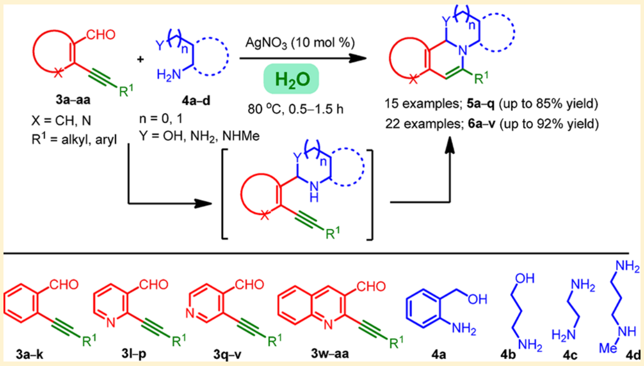
On Water: Silver-Catalyzed Domino Approach for the Synthesis of Benzoxazine/Oxazine-Fused Isoquinolines and Naphthyridines from *o*-Alkynyl Aldehydes

Akhilesh K. Verma,*[,†] Deepak Choudhary,[†] Rakesh K. Saunthwal,[†] Vineeta Rustagi,[†] Monika Patel,[†] and Rakesh K. Tiwari[‡]

[†]Synthetic Organic Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110007, India
[‡]Department of Life Sciences, School of Natural Sciences, Shiv Nadar University, Gautam Budh Nagar 203207, India

Supporting Information

ABSTRACT: An operationally simple domino approach for the silver-catalyzed synthesis of oxazine/benzoxazine-fused isoquinolines **5a−q** and naphthyridines **6a−v** by the reaction of *o*-alkynyl aldehydes **3a−aa** with amines having embedded nucleophiles **4a−d** under mild reaction condition in water is described. The reaction shows selective C−N bond formation on the more electrophilic alkynyl carbon resulting in the formation of 6-*endo-dig* cyclized product. The competitive experiments show the viability of an intramolecular nucleophilic attack over an intermolecular attack of the external nucleophile. This methodology accommodates wide functional group variation, which proves to be useful for structural and biological assessment.



INTRODUCTION

The increasing significance of synthetic organic chemistry in pharmaceutical sciences demands the development of new strategies to synthesize a collection of natural-product-like compounds.[1] For several decades, a large effort has been devoted to the development of new, efficient catalytic transformations to achieve high molecular complexity from simple starting materials. Domino reactions are one of the attractive processes that enhance the synthetic efficiency by using more than two reactants to create complex products with an optimal number of new bonds and functionalities.[1a,2a] Among the various catalysts used, transition-metal-catalyzed domino processes have shown to affect the efficient conversion from simple starting materials to complex molecules in a stepwise manner.[2b−f] Particularly, silver-catalyzed cyclizations have acquired tremendous success due to their cost and capability to activate alkyne, alkene, and allene functionalities at a low catalyst loading under mild reaction conditions.[3]

As a privileged fragment, a 1,2-dihydroisoquinoline skeleton is an important substructure that occurs in both natural products and therapeutic agents and has wide applications in pharmaceutical research.[4] Functionalized benzoxazines have attracted considerable attention due to their prominent biological activities. They are known to act as antidepressant, anti-inflammatory, antitumor,[5a−d] and antimalarial agents[6] (Figure 1A). They also act as phosphatidylinositol-3-kinase (PI3K) inhibitors,[7] neuroprotective antioxidants,[8] 5-HT1A/B/D receptor antagonists,[9] antiarrhythmics against ischemia-reperfusion injury,[10] and intermediates for the synthesis of various natural products such as glyantrypine, fumiquinazoline F, fumiquinazoline G, and fiscalin B.[11] Their analogues exhibit high selectivity as competitive antagonists for the M4 receptor and Parkinsonism.[12] Their derivatives have shown thrombin inhibitory and glycoprotein IIb/IIIa receptor antagonistic activity[13] and were evaluated as progesterone receptor (PR) antagonists[14] (Figure 1B).

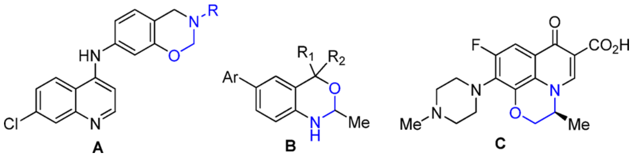


Figure 1. Significant examples of biologically active benzoxazine cores.

Substituted benzoxazines such as levofloxacin are known to act as antibacterial agents (Figure 1C).[15] 1,3-Benzoxazines have been used as herbicides and agricultural microbiocides as well as bactericides and fungicides.[5a−d,16a] Further, *N*-haloacetyl derivatives of benzoxazines inhibit methane production in ruminants.[16b] As a privileged fragment, an oxazine core is also found in many natural products exhibiting remarkable bio-

Received: May 3, 2013
Revised: June 11, 2013
Accepted: June 12, 2013
Published: June 12, 2013

dx.doi.org/10.1021/jo4009639 | *J. Org. Chem.* 2013, 78, 6657−6669

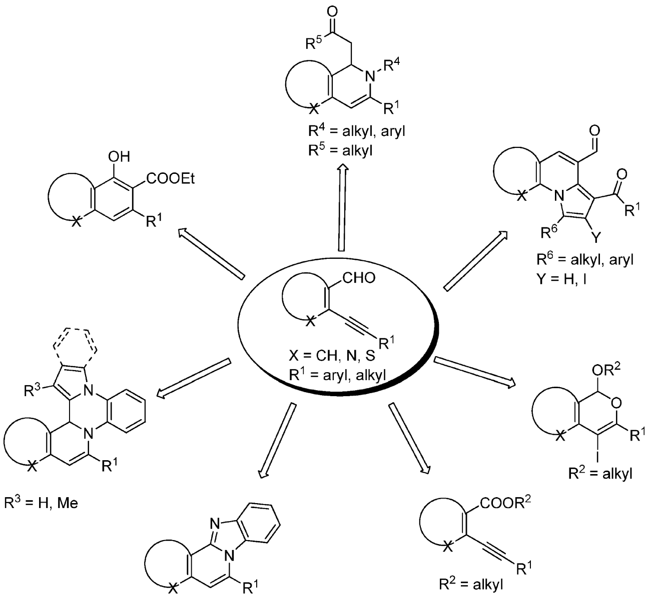
logical activities[17a−f] and also acts as a synthetic intermediate in synthesis.[18] Because of the enriched biological profile these compounds, significant efforts are being continued and are still required for the development of efficient ecofriendly methods for their construction.

Using cascade addition of nucleophiles[19a] and cyclization,[19b−l] various reports have been presented in the literature showing the syntheses of fused 1,2-dihydroisoquinolines[20−22]/isoquinolines[23] and naphthyridines[23g,h,24] in the presence or even absence of various transition-metal catalysts.[25] Moreover, 1,3-benzoxazines were synthesized using 2-(allyloxy)-benzylamines with syngas in the presence of a rhodium(I) catalyst.[26a,b] Their syntheses have been reported using metal catalysts such as Au[26c] and $Cu(OTf)_2$[26d] and also in the absence of metal.[26e,f] Some polymeric 1,3-benzoxazines were also synthesized without using a catalyst.[26g,h] Similarly, synthesis of substituted 1,3-oxazine has been reported with both metal[26e,f] and nonmetal catalysts.[26j]

Development of new and efficient synthetic strategies is as important as offering a reduced environmental impact. Therefore, many reactions are being carried out in ecofriendly conditions. Thus, reactions of water-insoluble organic compounds taking place in an aqueous suspension are becoming prominent and proceeding with high efficiency, and the synthetic protocols are becoming feasible.[27] Water is an ideal solvent because it fulfils many criteria; it is nontoxic, nonflammable, and abundantly available and inexpensive.[27] Use of water often imparts a significant effect on the both rate and selectivity of organic reactions through hydrophobic interactions and the enrichment of organic substrates in a local hydrophobic environment.[28]

Motivated by the importance of biological activity and as a part of our ongoing efforts to synthesize N-heterocycles by the activation of alkynes (Scheme 1),[29] and also on the basis of our recent preliminary reports regarding the synthesis of fused polyheterocyclic quinoxalines and benzimidazoles,[23g,h] we thought that *o*-alkynyl aldehydes could further be used to synthesize fused isoquinolines/naphthyridines with a new heterocyclic frame. We thereby envisaged that reactions of *o*-alkynyl aldehydes **3a**−**aa** and amines that have embedded nucleophiles **4a**−**d** through intermolecular condensation would provide the corresponding imines, which in the presence of the appropriate alkyne activators would afford fused isoquinolines/naphthyridines in an apparently simple way. The designed retrosynthetic pathway is shown in Scheme 2. This cascade strategy would involve the formation of two new C−N bonds and one new C−Y bond, thereby leading to the formation of two heterocyclic rings in a one-pot synthesis. This has prompted us to explore and develop a convergent domino strategy for the divergent preparation of the fused array of isoquinolines while keeping in mind the environmental considerations. Herein, we present our recent efforts for the silver-catalyzed regioselective domino synthesis of benzoxazine/oxazine-fused isoquinolines and naphthyridines in water.

Scheme 1. Heterocycles Synthesized in Our Laboratory Using *o*-Alkynyl Aldehydes



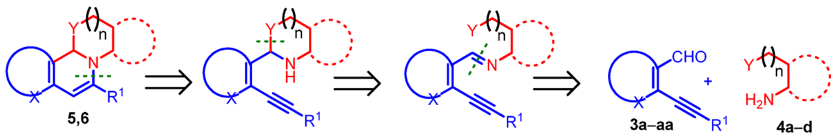
RESULTS AND DISCUSSION

Preparation of *o*-Alkynyl Aldehydes. To probe the viability of the designed domino strategy, *o*-alkynyl aldehydes **3a**−**aa** were readily prepared by a standard Sonogashira cross-coupling reaction of commercially available and readily accessible *o*-haloaldehydes **1a**−**d** with terminal alkynes **2a**−**n** (Scheme 3).[29b] This coupling procedure has readily accommodated a large variety of functional groups and provided the coupling products **3a**−**aa** in good to excellent yields.

In order to find an optimal reaction condition, we selected 2-(phenylethynyl)benzaldehyde (**3a**) and (2-aminophenyl)-methanol (**4a**) as model substrates (Table 1). Reaction of alkyne **3a** (0.5 mmol) with amine **4a** (1.1 equiv) using 5 mol % of $AgNO_3$ in 2.0 mL of CH_2Cl_2 at 25 °C for 4 h afforded the formation of the desired product **5a** in 38% yield (Table 1, entry 1). Increasing the amount of $AgNO_3$ from 5 to 10 mol % in CH_2Cl_2 afforded the product **5a** in 60% yield (entry 2). When different solvents such as THF, 1,2-dichloroethane (EDC), DMF, toluene, and ethanol were examined at elevated temperatures, it was observed that the reaction did not attain the desired levels of reactivity and provided the formation of product **5a** in 40−73% yield (entries 3−7). When water was employed as a solvent, the reaction proceeded to completion, and it provided the formation of the desired product **5a** in 81% yield in 1 h at 80 °C (entry 8). Other silver catalysts with different counteranions, such as AgOAc, AgOTf, and AgI, resulted in 71−76% yield of the desired product **5a** (entries 9−11). However, in the absence of a catalyst, the reactants remained almost unchanged during the course of reaction (entry 12). Transition metal catalysts other than silver, such as $PdCl_2$, $Pd(OAc)_2$, and CuI, afforded the formation of the desired product **5a** in lower yields (entries 13−15). A reaction with Lewis acid $AlCl_3$ fails to afford the desired product (entry 16). The formation of regioselective 6-*endo-dig* cyclized product **5a** was characterized by ^1H NMR, ^{13}C NMR, and mass spectroscopic data. Appearence of peaks at 5.95 ppm as a singlet and 5.26 and 5.09 ppm as diastereotopic doublets in ^1H NMR of **5a** and the disappearance of the two peaks of alkynyl carbons in its characteristic region in ^{13}C NMR spectrum suggested the formation of the desired cyclized product **5a**. X-ray crystallographic analysis of **5a** confirmed the formation of 6-*endo-dig* cyclized product (Supporting Information).

Synthesis of Benzoxazine/Oxazine-Fused Isoquinolines. Having demonstrated the viability of this domino strategy, we then investigated the generality and scope of the transformation under the optimized conditions. As shown in

Scheme 2. Designed Retrosynthetic Pathway for the Synthesis of Oxazine/Benzoxazine-Fused Isoquinolines and Naphthyridines



Scheme 3. Preparation of *o*-Alkynyl Aldehydes

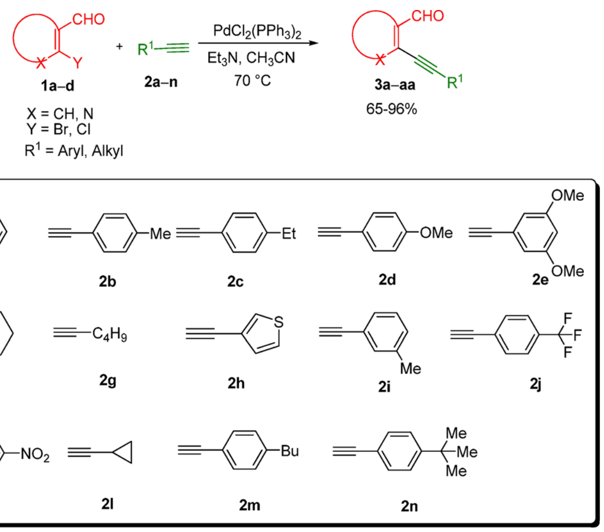
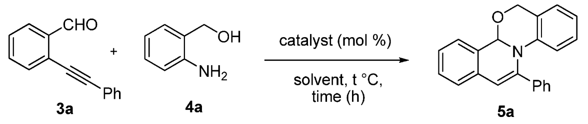


Table 1. Optimization of Reaction Conditions[a]



		conditions			
entry	catalyst (mol %)	solvent	*T* °C	time (h)	yield (%)
1	$AgNO_3$ (5)	CH_2Cl_2	25	4	38
2	$AgNO_3$ (10)	CH_2Cl_2	25	4	60
3	$AgNO_3$ (10)	THF	50	1	62
4	$AgNO_3$ (10)	EDC	70	1	73
5	$AgNO_3$ (10)	DMF	110	1	70
6	$AgNO_3$ (10)	toluene	70	1	40
7	$AgNO_3$ (10)	EtOH	70	1	64
8	$AgNO_3$ (10)	H_2O	80	1	81
9	AgOAc (10)	H_2O	80	1	71
10	AgOTf (10)	H_2O	80	1	76
11	AgI (10)	H_2O	80	1	74
12		H_2O	80	1	
13	$PdCl_2$ (10)	H_2O	80	2	55
14	$Pd(OAc)_2$ (10)	H_2O	80	2	55
15	CuI (10)	H_2O	80	3	70
16	$AlCl_3$ (10)	H_2O	80	6	trace

[a] The reactions were performed using 0.5 mmol of *o*-alkynyl aldehyde **3a** and 1.1 equiv of amine **4a** in 2.0 mL of solvent.

Table 2, the reaction is tolerant toward a variety of *o*-alkynyl aldehyde **3** bearing different alkynyl substituents. We commenced our study by the reaction of substrate **3** and amines that had embedded nucleophiles **4a−d**. The results of this study are summarized in Table 2, showing not only that the use of amine **4a** gave a better yield of its respective product than the use of **4b−d** but also that the reaction was a bit faster in the case of the former amine. When electronically neutral, moderately donating groups such as Ph (**3a**) and 4-Et-C_6H_4 (**3b**) were used, the reaction proceeded well and afforded products **5a** and **5b** in 81 and 83% yields, respectively (Table 2, entries 1 and 2). When a strong donating group such as thienyl was used, the reaction proceeded well and afforded the product **5c** in 85% yield (entry 3). With aliphatic groups such as cyclohexyl and *n*-butyl, the reaction provided the desired products **5d** and **5e** in 77 and 75% yields, respectively (entries 4 and 5). Alkyne **3f**, bearing two methoxy groups at *meta* positions on the phenyl ring, afforded the cyclized product **5f** in a comparatively lower yield (entry 6), which may be the result of the reduced electrophilicity at the proximal end of alkyne, which thereby reduced the efficiency of the desired transformation. Encouraged by the above results, we further extended the same protocol with 3-aminopropan-1-ol **4b**. Reaction of substrates **3a−c** and **3g−i** with 3-aminopropan-1-ol proceeded well and afforded the desired products **5g−l** in 75−82% yields (Table 2, entries 7−12). Alkyne **3j**, bearing a cyclopropyl group, provided the desired product **5m** in 71% yields (entry 13). Reaction of amine **4b** with 2-((4-nitrophenyl)ethynyl)-quinoline-3-carbaldehyde (**3k**), bearing an electron-withdrawing nitro group at the *para* position of the phenyl ring, fails to afford the desired product **5o** (entry 15). Reaction of **3a** with ethane-1,2-diamine (**4c**) afforded the desired product **5p** in 68% yield (entry 16); however, an inseparable complex mixture was obtained when *N*-methylpropane-1,3-diamine (**4d**) was reacted with **3a** (entry 17).

Synthesis of Benzoxazine/Oxazine-Fused Naphthyridines. To gain further insight into the reaction, we continued our study by examining various nitrogen-containing substrates **3l−aa**, which furnished differently substituted benzoxazino/oxazino-naphthyridines **6a−v** (Table 3), and a similar observation can be inferred. Alkynes **3l−o** with electron-donating groups provided the respective desired products **6a−d** in 88−92% yields (entries 1−4), whereas alkyne **3p**, bearing

Table 2. Domino Synthesis of Benzoxazine/Oxazine-Fused Isoquinolines[a]

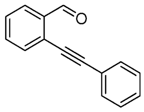
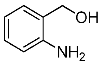
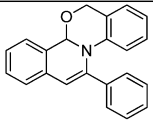
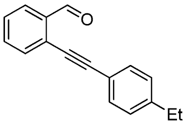
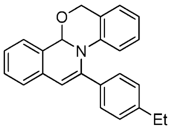
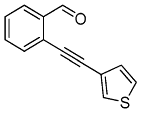
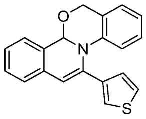
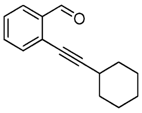
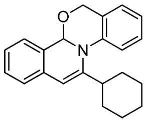
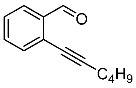
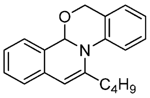
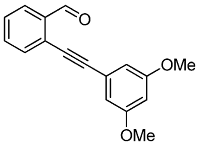
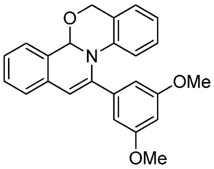
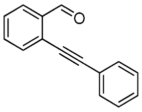
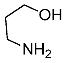
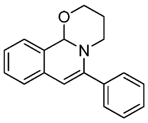
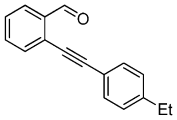
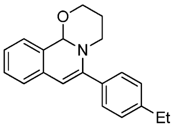
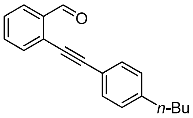
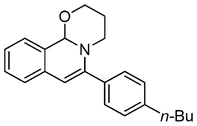
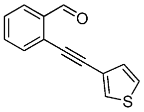
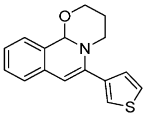
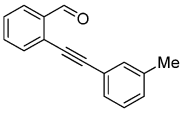
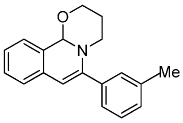
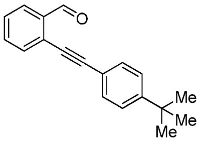
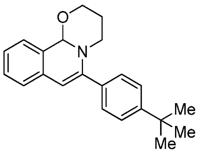
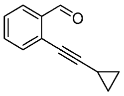
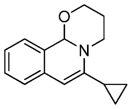
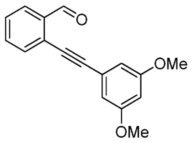
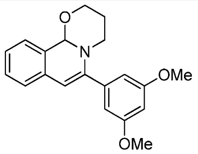
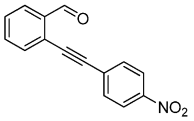
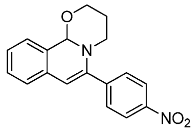
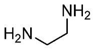
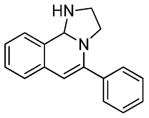
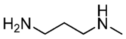
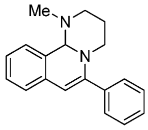
entry	substrate		amine	product		yield (%)
1		**3a**	 **4a**		**5a**	81
2		**3b**	**4a**		**5b**	83
3		**3c**	**4a**		**5c**	85
4		**3d**	**4a**		**5d**	77
5		**3e**	**4a**		**5e**	75
6		**3f**	**4a**		**5f**	70
7		**3a**	 **4b**		**5g**	75
8		**3b**	**4b**		**5h**	79
9		**3g**	**4b**		**5i**	78
10		**3c**	**4b**		**5j**	82
11		**3h**	**4b**		**5k**	77
12		**3i**	**4b**		**5l**	76
13		**3j**	**4b**		**5m**	71

Table 2. continued

entry	substrate		amine	product		yield (%)
14		**3f**	**4b**		**5n**	67
15		**3k**	**4b**		**5o**	–[b]
16		**3a**	 **4c**		**5p**	68
17		**3a**	 **4d**		**5q**	–[b]

[a] The reactions were performed using *o*-alkynyl aldehyde **3** (0.5 mmol), amines **4a–d** (1.1 equiv), and 10 mol % of $AgNO_3$ in 2.0 mL of H_2O at 80 °C for 1–1.5 h. [b] An inseparable mixture of products.

methoxy groups at *meta* positions on the phenyl ring, afforded the product **6e** in 75% yield (entry 5). Switching from aromatic amine (2-aminophenyl)methanol (**4a**) to aliphatic amine 3-aminopropan-1-ol (**4b**), the reaction proceeded with comparatively lower levels of reactivity (entries 6–16). We have also explored the reaction of 3-(substituted ethynyl)-isonicotinaldehydes **3q–v** with amine **4b** (entries 11–16). The desired products **6k–o** were obtained in good yields (entries 11–15). Presence of the electron-withdrawing $-CF_3$ group at the *para* position retarded the reaction, and the product was obtained in 62% yield (entries 16).

We further switched our strategy to a two-ring system in order to explore more diversity and complexity, so we reacted 2-(substituted)quinoline-3-carbaldehydes **3w–aa** with amines **4a** and **4b**. We observed that the reaction was slightly more sluggish than in the case of substituted pyridine alkynyl aldehydes **3l–v**. The substituted benzoxazino-fused naphthyridines **6q–u** were obtained in 72–87% yields (entries 17–21). Reaction of alkyne **3w** with 3-aminopropan-1-ol proceeded well and provided the oxazino-naphthyridine **6v** in 81% yield (entry 22). All the synthesized products were fully characterized by ^1H NMR, ^{13}C NMR, HRMS, and X-ray crystallographic analysis (Supporting Information). Products were obtained as racemic mixtures; no optical rotation was observed.

Competitive Study. In order to see the comparative studies of different nucleophiles such as (2-aminophenyl)-methanol (**4a**), 3-aminopropan-1-ol (**4b**), and methanol, we carried out different sets of reactions (Scheme 4). First, we studied the relative reactivity between aromatic and aliphatic nucleophiles by choosing 2-(phenylethynyl)benzaldehyde **3a** and amines **4a** and **4b** (1.1 equiv) in H_2O using 10 mol % of $AgNO_3$ as a catalyst (Scheme 4A). We observed that the product **5a** was obtained in 52% yield and product **5g** was obtained in 26% yield. The reason can be attributed that fact that the second intramolecular attack in the case of amine **4a** is more favorable due to the rigid and optimum conformation imparted by the aryl ring for faster trapping of the imine formed than in the case of amine **4b**. Formation of compound **5p** was not at all observed.

We also studied the comparison of the reactivity between an intramolecular and an intermolecular reaction. We carried out the reaction of alkynyl aldehyde **3a**, amine **4a**, and MeOH (1.1 equiv) in EDC using 10 mol % of $AgNO_3$ (Scheme 4B). We found that fused benzoxazine **5a** was formed as a major product in 68% yield and 1-methoxy-1*H*-isochromene **7**[23g] was formed in trace amounts. Formation of 2-(2-(1*H*-pyrrol-1-yl)phenyl)-1-methoxy-3-phenyl-1,2-dihydroisoquinoline **8** was not at all observed. This clearly shows that an intramolecular reaction is favored over an intermolecular reaction, as amine **4a** with an attached nucleophile is in close proximity to attack an imine carbon as compared to a distal methanol molecule.

In light of the above preliminary results, a catalytic cycle for this domino transformation was proposed as shown in Scheme 5. Initially, the reaction of *o*-alkynyl aldehyde **3** with nucleophilic amine **4** produced condensation species **P**. After this, two possibilities exist for the formation of compounds **5** and **6** (i.e., either ring **A** forms first and then ring **B** or vice versa). Ring **A** could be formed first because **P**, upon activation with silver, would first undergo the intramolecular nucleophilic attack of the –OH group onto imine carbon to afford **Q**. Intramolecuar proton transfer would then produce **R**, which upon *π*-activation by $AgNO_3$, would undergo a second intramolecular nucleophilic attack of the –NH onto the triple bond to afford **S**, which gives the desired compounds **5** and **6**. Alternatively, ring **B** could be formed initially by the activation of the triple bond by silver to give **Q′**, followed by a second intramolecular nucleophilic attack to furnish **R′**, which after subsequent deprotonation would give compounds **5** and **6**.

■ CONCLUSIONS

In summary, we have developed an Ag(I)-catalyzed domino protocol in water using readily available starting materials that allowed facile access to an impressive variety of benzoxazines/oxazines-fused isoquinolines and naphthyridines in good yields with high regioselectivity under mild reaction conditions. The reaction proceeded with high 6-*endo-dig* regioselectivity, and the products were confirmed by X-ray crystallographic studies. The competitive experiments demonstrated the practicality of

Table 3. Domino Synthesis of Fused Benzoxazino/Oxazino-Naphthyridines[a]

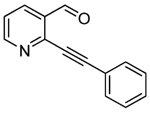
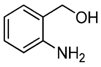
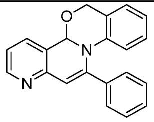
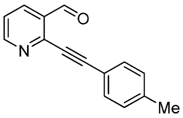
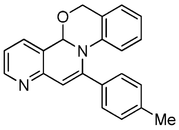
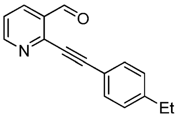
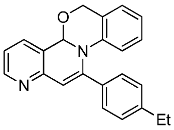
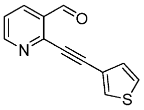
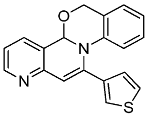
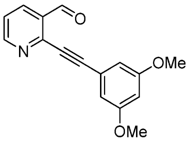
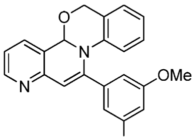
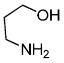
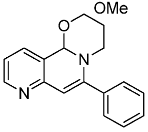
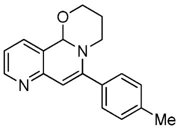
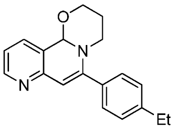
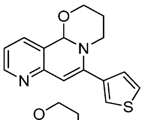
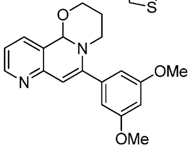
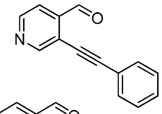
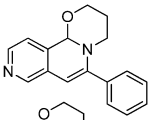
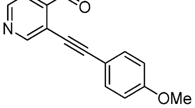
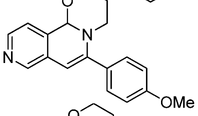
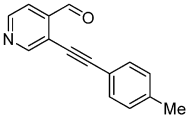
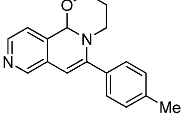
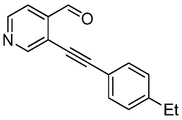
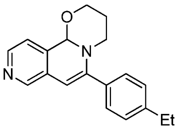
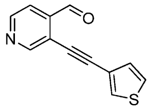
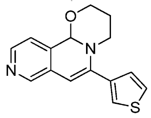
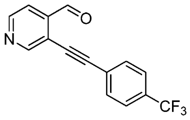
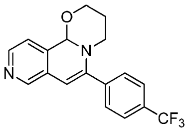
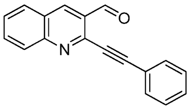
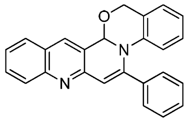
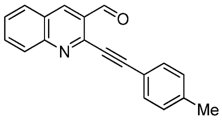
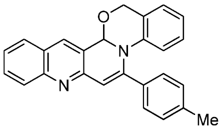
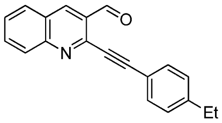
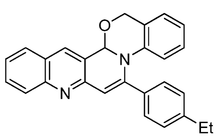
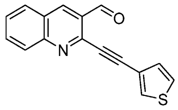
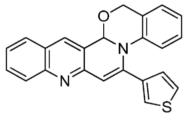
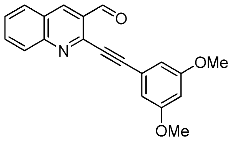
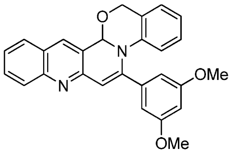
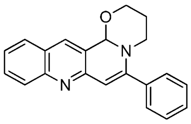
entry	substrate	amine	product	yield (%)
1	 **3l**	 **4a**	 **6a**	88
2	 **3m**	**4a**	 **6b**	90
3	 **3n**	**4a**	 **6c**	89
4	 **3o**	**4a**	 **6d**	92
5	 **3p**	**4a**	 **6e**	75
6	**3l**	 **4b**	 **6f**	82
7	**3m**	**4b**	 **6g**	86
8	**3n**	**4b**	 **6h**	84
9	**3o**	**4b**	 **6i**	88
10	**3p**	**4b**	 **6j**	69
11	 **3q**	**4b**	 **6k**	80
12	 **3r**	**4b**	 **6l**	86
13	 **3s**	**4b**	 **6m**	82
14	 **3t**	**4b**	 **6n**	81

Table 3. continued

entry	substrate		amine	product		yield (%)
15		**3u**	**4b**		**6o**	86
16		**3v**	**4b**		**6p**	62
17		**3w**	**4a**		**6q**	83
18		**3x**	**4a**		**6r**	87
19		**3y**	**4a**		**6s**	85
20		**3z**	**4a**		**6t**	87
21		**3aa**	**4a**		**6u**	72
22		**3w**	**4b**		**6v**	81

[a] The reactions were performed using *o*-alkynyl aldehyde **3** (0.5 mmol), amines **4a–b** (1.1 equiv), and 10 mol % of $AgNO_3$ in 2.0 mL of H_2O at 80 °C for 0.5–1 h.

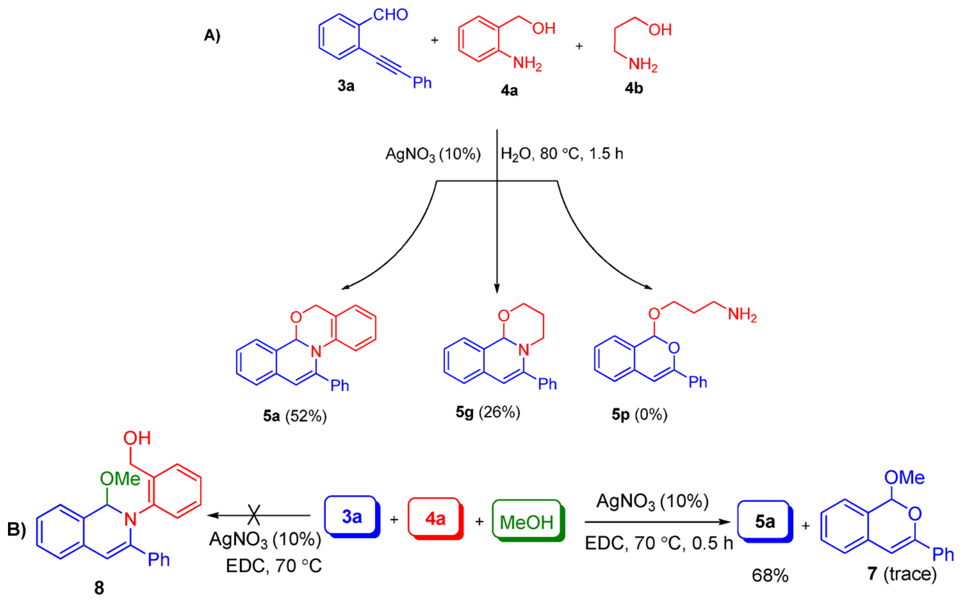
intramolecular nucleophilic attack over intermolecular attack. The product formation was also found to be higher in the case of aromatic amine over aliphatic amine. This method appeared to be very general and compatible with differently substituted starting materials that have different electronic properties, increasing its applicability to various functional groups. 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. It is likely that the efficiency of this environmentally friendly method combined with its operational simplicity will make it attractive for the construction of variety of heterocyclic compounds.

■ EXPERIMENTAL SECTION

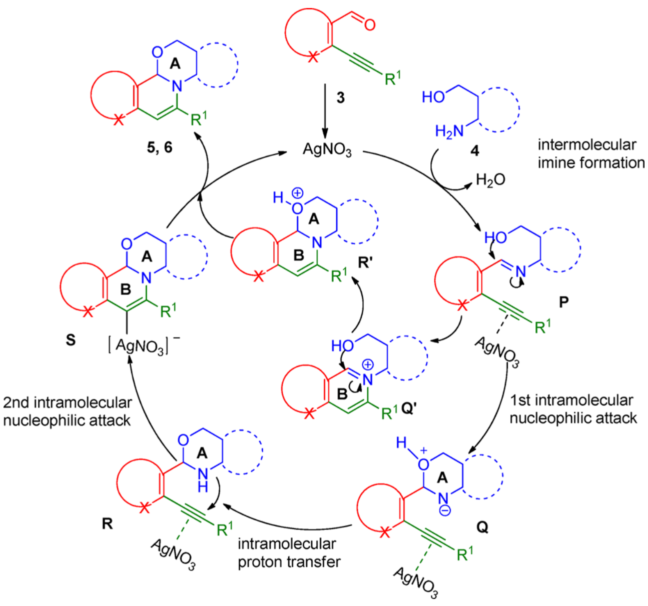
General Information. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts for protons are reported in parts per million from tetramethylsilane with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in parts per million 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), coupling constants, and integration. High-resolution mass spectra were recorded on a QqTOF mass analyzer. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates and visualized either by UV irradiation or by staining with I_2. Anhydrous forms of all reagents, such as diethyl ether, hexanes, ethyl acetate, EDC, Et_3N, 2-bromobenzaldehyde, 3-bromoisonicotinaldehyde, 2-bromonicotinaldehyde, 2-chloroquinoline-3-carbaldehyde, 3-bromobenzo[*b*]thiophene-2-carbaldehyde, silver nitrate, palladium salts, and copper salts, were used directly as obtained commercially unless otherwise noted.

Procedure for the Synthesis of Compounds 5 and 6. Amine **4** (1.1 equiv) was added to a solution of 0.5 mmol of *o*-alkynyl aldehyde **3** in 2.0 mL of H_2O, and this was followed by the addition of 10 mol % of $AgNO_3$. The reaction mixture was allowed to stir at 80 °C for 0.5–1.5 h. The disappearance of the starting material was determined by TLC. The reaction mixture was washed with brine solution and extracted with ethyl acetate (2 × 10 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated under a vacuum to yield the crude product. The crude product was purified by

Scheme 4. Competitive Study



Scheme 5. Probable Mechanism



column chromatography on neutral alumina using hexane/ethyl acetate as the eluent.

The structure and purity of the known starting materials **3a**, **3c**, **3o–q**,[23g] **3d**, **3l**, **3aa**,[29c] **3m**, **3r**, **3w–z**,[24b] **3f**, **3h**, **3k**,[30a] **3e**, **3j**,[30b] **3s**,[29e] **3i**,[23h] and **3g**[30c] were confirmed by a comparison of their experimental physical and spectral data (^{1}H NMR and ^{13}C NMR) with those reported in the literature.

*2-((4-Ethylphenyl)ethynyl)benzaldehyde (**3b**).* The product was obtained as an orange semisolid (90.2 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.67 (s, 1H), 7.96 (dd, J = 7.8, 0.92 Hz, 1H), 7.65–7.63 (m, 1H), 7.59 (td, J = 7.3, 1.8 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.44 (t, J = 7.3 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 2.69 (q, J = 7.8 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 191.7, 145.6, 135.7, 133.7, 133.1, 131.6, 128.3, 128.0, 127.9, 127.1, 119.4, 96.6, 84.2, 28.8, 15.2; HRMS (ESI) $[M]^+$ calcd for $[C_{17}H_{14}O]$ 234.1045, found 234.1046.

*3-((4-Ethylphenyl)ethynyl)isonicotinaldehyde (**3t**).* The product was obtained as pale yellow needle crystals (92.9 mg, 79%): mp 72–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.62 (s, 1H), 8.95 (s, 1H), 8.71 (d, J = 5.1 Hz, 1H), 7.71 (d, J = 5.1 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 2.61 (q, J = 7.3 Hz, 2H), 1.17 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 190.8, 154.5,149.0, 140.2, 140.0, 131.7, 129.3, 121.6, 119.1, 118.5, 99.4, 81.3, 32.8, 19.1; HRMS (ESI) $[M]^+$ calcd for $[C_{16}H_{13}NO]$ 235.0997, found 235.0998.

*3-(Thiophen-3-ylethynyl)isonicotinaldehyde (**3u**).* The product was obtained as orange needle crystals (89.6 mg, 84%): mp 66–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.86 (s, 1H), 8.63 (d, J = 5.2 Hz, 1H), 7.63 (d, J = 5.1 Hz, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.30–7.28 (m, 1H), 7.17 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 154.3, 149.0, 140.3, 130.5, 129.6, 126.0, 121.4, 120.6, 119.2, 94.3, 81.5; HRMS (ESI) $[M]^+$ calcd for $[C_{12}H_7NOS]$ 213.0248, found 213.0248.

*3-((4-(Trifluoromethyl)phenyl)ethynyl)isonicotinaldehyde (**3v**).* The product was obtained as yellow crystals (96.3 mg, 70%): mp 80–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.53 (s, 1H), 8.93 (s, 1H), 8.72 (d, J = 5.1 Hz, 1H), 7.70 (d, J = 5.1 Hz, 1H), 7.62 (q, J = 8.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 190.3, 154.6, 149.9, 140.6, 132.1, 125.6 (q, J = 3.8 Hz), 125.4, 125.0, 120.4, 119.6, 97.1, 84.1; HRMS (ESI) $[M]^+$ calcd for $[C_{15}H_8F_3NO]$ 275.0558, found 275.0558.

*12-Phenyl-4b,6-dihydrobenzo[4,5][1,3]oxazino[2,3-a]isoquinoline (**5a**).* The product was obtained as pale yellow crystals (126.1 mg, 81%): mp 176–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.42 (d, J = 7.3 Hz, 1H), 7.34–7.30 (m, 1H), 7.25–7.23 (m, 6H), 7.18 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 7.4 Hz, 1H), 6.91 (t, J = 8.0 Hz, 1H), 6.78 (t, J = 8.1 Hz, 1H), 6.22 (d, J = 8.1 Hz, 1H), 6.09 (s, 1H), 5.95 (s, 1H), 5.26 (d, J = 18.1 Hz, 1H), 5.09 (d, J = 14.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 140.8, 139.8, 136.9, 132.3, 129.0, 128.6, 128.4, 128.0, 127.8, 126.8, 126.0, 125.8, 124.7, 124.3, 123.8, 122.5, 105.7, 85.0, 68.0; HRMS (ESI) $[M]^+$ calcd for $[C_{22}H_{17}NO]$ 311.1310, found 311.1309.

Compound **5a** was crystallized in the triclinic crystal system with space group $P2_1$. The single-crystal X-ray data were collected using graphite monochromated Mo $K\alpha$ radiation (λ = 0.71 073 Å). The structures were solved using SIR-92 and refined by the full matrix least-squares technique on F2 using the SHELXL-97 program within the WinGX v1.80.05 software package. Crystal data for **5a**: $C_{22}H_{17}NO$, M = 311.37, monoclinic, space group $P2_1$, a = 11.3784(19) Å, b = 5.7382(8) Å, c = 13.148(3) Å, α = 90°, β = 114.27(2)°, γ = 90°, V = 782.6(2) Å^3, Z = 2, T = 296 K, D_{calcd} = 1.321 mg/m^3, R_{int} = 0.0203, $R1$ = 0.0503, $wR2$ = 0.1050 [$I > 2\sigma(I)$], $R1$ = 0.0664, $wR2$ = 0.1157 (all data), GOF = 1.058. Crystallographic data for **5a** have been deposited with the Cambridge Crystallographic Data Centre. CCDC 932014 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html. For further details on the crystal structure of compound **5a**, see the CIF file (Supporting Information).

12-(4-Ethylphenyl)-4b,6-dihydrobenzo[4,5][1,3]oxazino[2,3-a]-isoquinoline (***5b***). The product was obtained as a pale yellow semisolid (140.9 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.39 (d, *J* = 8.2 Hz, 1H), 7.31–7.27 (m, 1H), 7.21–7.18 (m, 1H), 7.16–7.10 (m, 3H), 7.05–7.02 (m, 3H), 6.91–6.87 (m, 1H), 6.77 (t, *J* = 7.8 Hz, 1H), 6.22 (d, *J* = 8.7 Hz, 1H), 6.06 (s, 1H), 5.93 (s, 1H), 5.23 (d, *J* = 14.2 Hz, 1H), 5.07 (d, *J* = 15.1 Hz, 1H), 2.60 (q, *J* = 7.4 Hz, 2H), 1.21–1.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 144.0, 140.8, 139.9, 134.2, 132.5, 128.9, 128.5, 128.3, 127.4, 126.6, 125.9, 125.8, 124.6, 124.2, 123.7, 122.3, 105.4, 85.0, 68.0, 26.9, 15.4; HRMS (ESI) $[M]^+$ calcd for $[C_{24}H_{21}NO]$ 339.1623, found 339.1623.

12-(Thiophen-3-yl)-4b,6-dihydrobenzo[4,5][1,3]oxazino[2,3-a]-isoquinoline (***5c***). The product was obtained as brown needle crystals (134.9 mg, 85%): mp 104–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.55 (d, *J* = 8.1 Hz, 1H), 7.18–7.17 (m, 1H), 7.06–7.04 (m, 1H), 7.02–6.97 (m, 3H), 6.92 (t, *J* = 7.3 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.63–6.61 (m, 1H), 6.29 (d, *J* = 8.8 Hz, 1H), 6.15 (s, 1H), 5.96 (s, 1H), 5.13 (d, *J* = 14.6 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 151.0, 150.2, 140.4, 139.1, 137.1, 134.4, 128.4, 127.6, 125.9, 125.1, 124.8, 124.71, 124.68, 123.6, 123.4, 121.9, 120.4, 105.6, 84.5, 67.9; HRMS (ESI) $[M]^+$ calcd for $[C_{20}H_{15}NOS]$ 317.0874, found 317.0875.

12-Cyclohexyl-4b,6-dihydrobenzo[4,5][1,3]oxazino[2,3-a]-isoquinoline (***5d***). The product was obtained as a pale yellow semisolid (122.2 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.23–7.17 (m, 2H), 7.16–7.09 (m, 2H), 7.07–7.00 (m, 4H), 5.71–5.69 (m, 2H), 5.09 (d, *J* = 15.1 Hz, 1H), 4.88 (d, *J* = 15.1 Hz, 1H), 2.58–2.51 (m, 1H), 1.98–1.95 (m, 1H), 1.78–1.75 (m, 1H), 1.57–1.47 (m, 4H), 1.45–1.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 147.5, 140.7, 132.4, 131.0, 129.1, 127.4, 125.8, 125.4, 124.93, 124.89, 124.7, 124.6, 123.8, 98.1, 84.8, 67.7, 38.4, 26.7, 26.5, 26.1; HRMS (ESI) $[M]^+$ calcd for $[C_{22}H_{23}NO]$ 317.1780, found 317.1781.

12-Butyl-4b,6-dihydrobenzo[4,5][1,3]oxazino[2,3-a]isoquinoline (***5e***). The product was obtained as a brown oil (109.3 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.33–7.29 (m, 2H), 7.24–7.18 (m, 3H), 7.17–7.12 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 5.81 (s, 1H), 5.74 (s, 1H), 5.20 (d, *J* = 15.1 Hz, 1H), 4.98 (d, *J* = 15.1 Hz, 1H), 1.47–1.43 (m, 2H), 0.93–0.87 (m, 4H), 0.80 (t, *J* = 9.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 142.4, 140.8, 132.4, 130.8, 129.1, 127.6, 125.8, 125.2, 125.0, 124.9, 124.8, 124.7, 123.5, 100.3, 84.8, 67.6, 32.5, 29.6, 22.1, 13.7; HRMS (ESI) $[M]^+$ calcd for $[C_{20}H_{21}NO]$ 291.1623, found 291.1623.

12-(3,5-Dimethoxyphenyl)-4b,6-dihydrobenzo[4,5][1,3]oxazino-[2,3-a]isoquinoline (***5f***). The product was obtained as a yellow semisolid (130.0 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.39 (d, *J* = 6.9 Hz, 1H), 7.33–7.29 (m, 1H), 7.24–7.16 (m, 3H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.92 (t, *J* = 8.2 Hz, 1H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.34–6.31 (m, 3H), 6.07 (s, 1H), 5.95 (s, 1H), 5.24 (d, *J* = 14.6 Hz, 1H), 5.07 (d, *J* = 14.7 Hz,1H), 3.62 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 160.2, 140.7, 139.9, 138.8, 132.1, 129.0, 126.9, 126.0, 125.9, 124.6, 124.4, 123.7, 122.7, 106.8, 105.2, 100.2, 96.4, 84.9, 68.0, 55.3; HRMS (ESI) $[M]^+$ calcd for $[C_{24}H_{21}NO_3]$ 371.1521, found 371.1520.

6-Phenyl-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a]isoquinoline (***5g***). The product was obtained as a brown semisolid (98.8 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.33–7.30 (m, 5H), 7.23–7.18 (m, 2H), 7.08 (t, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 5.97 (s, 1H), 5.51 (s, 1H), 4.07–4.01 (m, 2H), 3.74–3.70 (m, 1H), 3.30–3.22 (m, 1H), 2.03–1.93 (m, 1H), 1.88–1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 145.1, 137.6, 132.7, 129.1, 128.3, 128.2, 127.9, 127.4, 125.0, 124.8, 123.7, 101.8, 88.7, 68.1, 47.7, 26.8; HRMS (ESI) $[M]^+$ calcd for $[C_{18}H_{17}NO]$ 263.1310, found 263.1310.

6-(4-Ethylphenyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a]-isoquinoline (***5h***). The product was obtained as a brown semisolid (115.1 mg, 79%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.30 (t, *J* = 8.0 Hz, 3H), 7.24 (t, *J* = 10.2 Hz, 3H), 7.14 (t, *J* = 9.1 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.04 (s, 1H), 5.58 (s, 1H), 4.15–4.05 (m, 2H), 3.84–3.81 (m, 1H), 3.36–3.29 (m, 1H), 2.70–2.68 (m, 2H), 2.05–1.88 (m, 2H), 1.37–1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 145.2, 143.9, 139.2, 134.9, 132.1, 129.4, 128.2, 127.6, 124.9, 123.5, 114.0, 101.6, 87.7, 68.0, 47.6, 26.8, 22.6, 14.1; HRMS (ESI) $[M]^+$ calcd for $[C_{20}H_{21}NO]$ 291.1623, found 291.1624.

6-(4-Butylphenyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a]-isoquinoline (***5i***). The product was obtained as a red oil (124.6 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.31–7.23 (m, 4H), 7.23–7.19 (m, 2H), 7.14 (t, *J* = 6.8, 1H), 7.05 (d, *J* = 10.1 Hz, 1H), 6.04 (s, 1H), 5.57 (s, 1H), 4.15–4.05 (m, 2H), 2.60–2.57 (m, 4H), 1.73–1.59 (m, 4H), 1.42–1.34 (m, 2H), 0.95 (t, *J* = 8.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 145.1, 142.5, 134.7, 132.7, 128.9, 128.1, 127.3, 124.8, 124.7, 101.6, 88.7, 68.0, 47.6, 35.3, 33.4, 26.8, 22.3, 13.9; HRMS (ESI) $[M]^+$ calcd for $[C_{22}H_{25}NO]$ 319.1936, found 319.1937.

6-(Thiophen-3-yl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a]-isoquinoline (***5j***). The product was obtained as a red semisolid (113.1 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.34–7.33 (m, 2H), 7.28–7.23 (m, 2H), 7.15–7.12 (m, 1H), 7.09–7.08 (m, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.00 (s, 1H), 5.66 (s, 1H), 4.16–4.05 (m, 2H), 3.85–3.80 (m, 1H), 3.33 (t, *J* = 13.0 Hz, 1H), 2.07–1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 140.1, 137.8, 132.4, 129.1, 127.9, 127.4, 125.4, 125.1, 124.9, 123.6, 123.5, 102.0, 88.6, 68.1, 47.7, 26.8; HRMS (ESI) $[M]^+$ calcd for $[C_{16}H_{15}NOS]$ 269.0874, found 269.0874.

2,3,4,11b-Tetrahydro-6-m-tolyl-[1,3]oxazino[2,3-a]isoquinoline (***5k***). The product was obtained as a dark yellow semisolid (112.6 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.22–7.16 (m, 3H), 7.13–7.04 (m, 4H), 6.97 (d, *J* = 7.3 Hz, 1H), 5.96 (s, 1H), 5.49 (s, 1H), 4.08–3.97 (m, 2H), 3.76–3.71 (m, 1H), 3.28–3.20 (m, 1H), 2.31 (s, 3H), 1.98–1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 145.2, 137.9,137.5, 132.7, 129.1, 129.0, 128.6, 128.0, 127.4, 125.4, 124.9, 124.8, 123.6, 101.6, 88.7, 68.0, 47.7, 26.9, 21.4; HRMS (ESI) $[M]^+$ calcd for $[C_{19}H_{19}NO]$ 277.1467, found 277.1467.

6-(4-(tert-Butyl)phenyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a]-isoquinoline (***5l***). The product was obtained as orange crystals (121.4 mg, 76%): mp 96–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.32–7.30 (m, 2H), 7.24–7.21 (m, 2H), 7.19–7.14 (m, 2H), 7.04 (t, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 1H), 5.48 (s, 1H), 4.07–3.96 (m, 2H), 3.85–3.72 (m, 2H), 1.97–1.92 (m, 1H), 1.87–1.74 (m, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 150.8, 145.2, 134.6, 132.7, 129.0, 127.9, 127.4, 125.1, 124.8, 124.7, 123.5, 101.6, 88.7, 68.0, 47.6, 34.6, 31.3, 26.9; HRMS (ESI) $[M]^+$ calcd for $[C_{22}H_{25}NO]$ 319.1936, found 319.1935.

6-Cyclopropyl-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a]-isoquinoline (***5m***). The product was obtained as a reddish yellow semisolid (80.7 mg, 71%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.19–7.16 (m, 2H), 7.06–7.02 (m, 1H), 6.96–6.94 (m, 1H), 5.91 (s, 1H), 5.45 (s, 1H), 4.15–4.03 (m, 2H), 3.40–3.35 (m, 2H), 1.59–1.45 (m, 2H), 0.92–0.77 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 144.6, 133.0, 128.8, 127.4, 124.4, 123.1, 114.0, 97.3, 88.9, 68.7, 46.4, 27.1, 13.1, 5.6, 5.5; HRMS (ESI) $[M]^+$ calcd for $[C_{15}H_{17}NO]$ 227.1310, found 227.1310.

6-(3,5-Dimethoxyphenyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a]isoquinoline (***5n***). The product was obtained as a pale yellow semisolid (108.3 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.29–7.24 (m, 2H), 7.15–7.11 (m, 1H), 7.06–7.02 (m, 1H), 6.54 (s, 2H), 6.45–6.44 (m, 1H), 6.01 (s, 1H), 5.61 (s, 1H), 4.12–4.02 (m, 2H), 3.79 (s, 6H), 3.35–3.28 (m, 2H), 2.07–1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 160.6, 145.1, 139.5, 132.5, 129.1, 127.4, 125.1, 124.8, 123.7, 106.5, 101.5, 100.1, 88.7, 68.1, 55.4, 47.7, 27.1; HRMS (ESI) $[M]^+$ calcd for $[C_{20}H_{21}NO_3]$ 323.1521, found 323.1520.

5-Phenyl-1,2,3,10b-tetrahydroimidazo[2,1-a]isoquinoline (***5p***). The product was obtained as a brown semisolid (84.4 mg, 68%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.55 (t, *J* = 8.1 Hz, 1H), 7.47–7.41 (m, 4H), 7.40–7.38 (m, 1H), 7.28–7.27 (m, 1H), 7.03–7.00 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.19 (s, 1H), 5.00 (s, 1H), 4.08–4.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 158.1, 141.6, 136.5, 132.6, 129.3, 128.7, 128.2, 127.3, 127.0, 126.1, 123.3, 119.9, 114.0, 113.1, 106.3, 49.8, 49.7; HRMS (ESI) $[M]^+$ calcd for $[C_{17}H_{16}N_2]$ 248.1313, found 248.1313.

12-Phenyl-4b,6-dihydrobenzo[4,5][1,3]oxazino[2,3-f][1,6]-naphthyridine (***6a***). The product was obtained as yellow needle crystals (137.4 mg, 88%): mp 154–158 °C; ^{1}H NMR (400 MHz,

$CDCl_3$, δ) 8.43−8.41 (m, 1H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.19−7.15 (m, 5H), 7.02−6.98 (m, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.69 (t, *J* = 8.1 Hz, 1H), 6.12 (d, *J* = 8.1 Hz, 1H), 6.08 (s, 1H), 5.98 (s, 1H), 5.13 (d, *J* = 16.8 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 151.1, 150.1, 145.0, 139.1, 136.2, 134.4, 128.5, 128.3, 128.1, 125.9, 124.7, 123.7, 123.0, 122.0, 120.4, 106.2, 84.7, 68.0; HRMS (ESI) $[M]^+$ calcd for $[C_{21}H_{16}N_2O]$ 312.1263, found 312.1263.

*12-(p-Tolyl)-4b,6-dihydrobenzo[4,5][1,3]oxazino[2,3-f][1,6]-naphthyridine (**6b**).* The product was obtained as yellow crystals (146.9 mg, 90%): mp 166−170 °C; ^1H NMR (400 MHz, $CDCl_3$, δ) 8.44−8.43 (m, 1H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.08−7.06 (m, 2H), 7.03−6.97 (m, 4H), 6.87 (t, *J* = 14.6 Hz, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.18 (d, *J* = 13.3 Hz, 1H), 6.09 (s, 1H), 6.00 (s, 1H), 5.15 (d, *J* = 14.6 Hz, 1H), 5.01 (d, *J* = 14.6 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 151.3, 150.2, 145.2, 139.2, 138.4, 134.3, 133.3, 128.8, 128.4, 128.3, 126.0, 124.7, 123.8, 122.9, 122.2, 120.4, 106.2, 84.8, 68.0, 21.3; HRMS (ESI) $[M]^+$ calcd for $[C_{22}H_{18}N_2O]$ 326.1419, found 326.1420.

*12-(4-Ethylphenyl)-4b,6-dihydrobenzo[4,5][1,3]oxazino[2,3-f]-[1,6]naphthyridine (**6c**).* The product was obtained as yellow crystals (151.5 mg, 89%): mp 162−166 °C; ^1H NMR (400 MHz, $CDCl_3$, δ) 8.45−8.44 (m, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.11−7.09 (m, 2H), 7.06−6.98 (m, 3H), 6.96−6.93 (m, 2H), 6.78−6.73 (m, 2H), 6.18 (d, *J* = 8.0 Hz, 1H), 6.11 (s, 1H), 6.02 (s, 1H), 5.17 (d, *J* = 13.9 Hz, 1H), 5.02 (d, *J* = 13.9 Hz, 1H), 2.56 (q, *J* = 7.3 Hz, 2H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 151.3, 150.0, 145.3, 139.2, 138.5, 134.3, 133.4, 128.7, 128.5, 126.0, 124.7, 123.8, 122.9, 122.0, 120.4, 106.1, 84.8, 68.0, 28.6, 15.3; HRMS (ESI) $[M]^+$ calcd for $[C_{23}H_{20}N_2O]$ 340.1576, found 340.1576.

*12-(Thiophen-3-yl)-4b,6-dihydrobenzo[4,5][1,3]oxazino[2,3-f]-[1,6]naphthyridine (**6d**).* The product was obtained as brown needle crystals (146.5 mg, 92%): mp 100−104 °C; ^1H NMR (400 MHz, $CDCl_3$, δ) 8.43−8.42 (m, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.18−7.17 (m, 1H), 7.06−7.04 (m, 1H), 7.02−6.97 (m, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.63−6.61 (m, 1H), 6.29 (d, *J* = 8.8 Hz, 1H), 6.15 (s, 1H), 5.96 (s, 1H), 5.13 (d, *J* = 14.6 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 151.0, 150.2, 140.4, 139.1, 137.1, 134.4, 128.4, 127.6, 125.9, 125.1, 124.8, 124.7, 123.6, 123.4, 121.9, 120.4, 105.6, 84.5, 67.9; HRMS (ESI) $[M]^+$ calcd for $[C_{19}H_{14}N_2OS]$ 318.0827, found 318.0828.

*12-(3,5-Dimethoxyphenyl)-4b,6-dihydrobenzo[4,5][1,3]oxazino-[2,3-f][1,6]naphthyridine (**6e**).* The product was obtained as pale yellow needle crystals (139.6 mg, 75%): mp 80−86 °C; ^1H NMR (400 MHz, $CDCl_3$, δ) 8.47−8.45 (m, 1H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.06 (m, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.92−6.88 (m, 1H), 6.80 (t, *J* = 8.1 Hz, 1H), 6.32 (s, 2H), 6.28 (d, *J* = 8.0 Hz, 1H), 6.22−6.20 (m, 1H), 6.14 (s, 1H), 6.03 (s, 1H), 5.18 (d, *J* = 13.9 Hz, 1H), 5.02 (d, *J* = 13.9 Hz, 1H), 3.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 160.4, 151.0, 150.1,145.1, 139.2, 138.0, 134.6, 128.1, 126.1, 124.7, 123.7, 123.2, 122.2, 120.6, 107.1, 106.7, 105.9, 101.0, 84.7, 68.1, 55.3; HRMS (ESI) $[M]^+$ calcd for $[C_{23}H_{20}N_2O_3]$ 372.1474, found 372.1474.

*6-Phenyl-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-f][1,6]-naphthyridine (**6f**).* The product was obtained as a brown oil (108.4 mg, 82%): ^1H NMR (400 MHz, $CDCl_3$, δ) 8.36−8.35 (m, 1H), 7.47−7.45 (m, 1H), 7.32−7.27 (m, 5H), 6.94−6.91 (m, 1H), 6.01 (s, 1H), 5.66 (s, 1H), 4.09−3.95 (m, 2H), 3.72−3.67 (m, 1H), 3.37−3.19 (m, 2H), 1.88−1.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 151.7, 150.7, 150.2, 137.1, 135.5, 129.2, 128.7, 128.4, 120.4, 119.9, 102.1, 88.9, 68.5, 47.9, 27.6; HRMS (ESI) $[M]^+$ calcd for $[C_{17}H_{16}N_2O]$ 264.1263, found 264.1263.

*6-(p-Tolyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-f][1,6]-naphthyridine (**6g**).* The product was obtained as brown crystals (119.7 mg, 86%): mp 110−114 °C; ^1H NMR (400 MHz, $CDCl_3$, δ) 8.39−8.38 (m, 1H), 7.47 (d, *J* = 6.6 Hz, 1H), 7.22−7.14 (m, 4H), 6.96−6.93 (m, 1H), 6.03 (s, 1H), 5.66 (s, 1H), 4.08−4.01 (m, 2H), 3.77−3.73 (m, 1H), 3.27−3.20 (m, 1H), 2.32 (s, 3H), 2.09−1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 151.4, 150.3, 149.9, 138.2, 135.2, 133.9, 129.0, 128.0, 120.0, 119.5, 101.7, 88.6, 68.2, 47.6, 27.2, 21.3; HRMS (ESI) $[M]^+$ calcd for $[C_{18}H_{18}N_2O]$ 278.1419, found 278.1419.

*6-(4-Ethylphenyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-f][1,6]-naphthyridine (**6h**).* The product was obtained as a brown oil (122.8 mg, 84%): ^1H NMR (400 MHz, $CDCl_3$, δ) 8.39−8.38 (m, 1H), 7.48−7.46 (m, 1H), 7.23 (d, *J* = 9.5 Hz, 2H), 7.19−7.16 (m, 2H), 6.95−6.92 (m, 1H), 6.03 (s, 1H), 5.66 (s, 1H), 4.11−4.04 (m, 1H), 4.01−3.98 (m,1H), 3.37−3.73 (m, 1H), 3.27−3.20 (m, 1H), 2.61 (q, *J* = 8.0 Hz, 2H), 1.91−1.83 (m, 2H), 1.21 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 151.6, 150.5, 149.8, 144.4, 135.0, 134.1, 128.1, 127.8, 120.0, 119.4, 101.9, 88.7, 68.2, 47.6, 28.6, 27.2, 15.3; HRMS (ESI) $[M]^+$ calcd for $[C_{19}H_{20}N_2O]$ 292.1576, found 292.1576.

*6-(Thiophen-3-yl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-f][1,6]-naphthyridine (**6i**).* The product was obtained as a brown oil (118.9 mg, 88%): ^1H NMR (400 MHz, $CDCl_3$, δ) 8.36 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.45 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.31−7.27 (m, 2H), 7.02−7.00 (m, 1H), 6.95−6.92 (m, 1H), 5.99 (s, 1H), 5.74 (s, 1H), 4.11−4.04 (m, 1H), 4.01−3.98 (m, 1H), 3.81−3.76 (m, 1H), 3.28−3.21 (m, 1H), 1.95−1.85 (m, 1H), 1.30−1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 153.1, 152.0, 151.1, 145.5, 137.8, 135.8, 128.3, 126.5, 124.9, 120.8, 120.4, 102.9, 89.2, 69.0, 48.3, 27.9; HRMS (ESI) $[M]^+$ calcd for $[C_{15}H_{14}N_2OS]$ 270.0827, found 270.0827.

*6-(3,5-Dimethoxyphenyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-f][1,6]naphthyridine (**6j**).* The product was obtained as a pale yellow semisolid (111.9 mg, 69%): ^1H NMR (400 MHz, $CDCl_3$, δ) 8.45−8.44 (m, 1H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.02−6.99 (m, 1H), 6.52 (s, 2H), 6.47−6.46 (m, 1H), 6.07 (s, 1H), 5.76 (s, 1H), 4.14−4.13 (m, 1H), 4.06 (td, *J* = 12.8, 3.2 Hz, 1H), 3.88−3.81 (m, 2H), 3.79 (s, 6H), 3.29 (td, *J* = 13.8, 2.8 Hz, 1H), 2.03−1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 160.7, 151.4, 150.5, 149.7, 139.3, 138.6, 135.1, 119.6, 106.3, 101.6, 100.5, 88.7, 68.3, 55.5, 47.6, 27.4; HRMS (ESI) $[M]^+$ calcd for $[C_{19}H_{20}N_2O_3]$ 324.1474, found 324.1475.

*6-Phenyl-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a][2,6]-naphthyridine (**6k**).* The product was obtained as a brown oil (105.7 mg, 80%): ^1H NMR (400 MHz, $CDCl_3$, δ) 8.39 (s, 2H), 7.43−7.41 (m, 5H), 7.23 (d, *J* = 5.1 Hz, 1H), 6.10 (s, 1H), 5.57 (s, 1H), 4.22−4.08 (m, 2H), 3.83−3.79 (m, 1H), 3.36−3.29 (m, 1H), 2.01−1.91 (m, 1H), 1.46−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 145.8, 145.4, 142.0, 137.2, 130.9, 128.3, 127.7, 125.9, 124.0, 121.5, 97.7, 87.2, 68.5, 47.6, 27.0; HRMS (ESI) $[M]^+$ calcd for $[C_{17}H_{16}N_2O]$ 264.1263, found 264.1263.

*6-(4-Methoxyphenyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a]-[2,6]naphthyridine (**6l**).* The product was obtained as a brown semisolid (126.6 mg, 86%): ^1H NMR (400 MHz, $CDCl_3$, δ) 8.33 (s, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 5.1 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.03 (s, 1H), 5.50 (s, 1H), 4.16−4.03 (m, 2H), 3.82−3.80 (m, 3H), 3.77−3.76 (m, 1H), 3.30−3.23 (m, 1H), 1.30−1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 159.5, 146.8, 145.5, 145.3, 130.7, 129.4, 129.2, 128.6, 121.5, 113.7, 97.2, 87.3, 68.4, 55.3, 47.4, 27.0; HRMS (ESI) $[M]^+$ calcd for $[C_{18}H_{18}N_2O_2]$ 294.1368, found 294.1367.

*6-(p-Tolyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a][2,6]-naphthyridine (**6m**).* The product was obtained as brown crystals (114.1 mg, 82%): mp 95−98 °C; ^1H NMR (400 MHz, $CDCl_3$, δ) 8.36 (s, 2H), 7.27−7.17 (m, 5H), 6.06 (s, 1H), 5.53 (s, 1H), 4.19−4.15 (m, 1H), 4.08 (td, *J* = 11.7, 2.2 Hz, 1H), 3.83−3.79 (m, 1H), 3.33−3.25 (m, 1H), 2.40 (s, 3H), 1.98−1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 147.1, 145.5, 145.3, 138.2, 134.0, 130.8, 129.0, 128.1, 121.5, 97.2, 87.3, 68.4, 47.5, 27.0, 21.3; HRMS (ESI) $[M]^+$ calcd for $[C_{18}H_{18}N_2O]$ 278.1419, found 278.1420.

*6-(4-Ethylphenyl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a][2,6]-naphthyridine (**6n**).* The product was obtained as a brown semisolid (118.4 mg, 81%): ^1H NMR (400 MHz, $CDCl_3$, δ) 8.28 (s, 2H), 7.24−7.16 (m, 4H), 7.10 (d, *J* = 5.1 Hz, 1H), 5.99 (s, 1H), 5.46 (s, 1H), 4.12−4.08 (m, 1H), 4.04−3.98 (m, 1H), 3.77−3.73 (m, 1H), 3.22 (td, *J* = 14.6, 2.2 Hz, 1H), 2.62 (q, *J* = 8.0 Hz, 2H), 2.54 (d, *J* = 1.4 Hz, 1H), 1.88−1.82 (m, 1H), 1.23−1.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 147.2, 145.5, 145.3, 144.4, 134.1, 130.7, 128.6, 128.1, 127.8, 121.5, 97.1, 87.2, 68.4, 47.4, 28.6, 27.0, 15.4; HRMS (ESI) $[M]^+$ calcd for $[C_{19}H_{20}N_2O]$ 292.1576, found 292.1575.

*6-(Thiophen-3-yl)-2,3,4,11b-tetrahydro-[1,3]oxazino[2,3-a][2,6]naphthyridine (**6o**).* The product was obtained as yellow brown needle crystals (116.2 mg, 86%): mp 100−104 °C; ^{1}H NMR (400 MHz, CDCl$_3$, δ) 8.30−8.29 (m, 2H), 7.30 (d, J = 2.7 Hz, 2H), 7.09 (d, J = 5.0 Hz, 1H), 7.02−7.00 (m, 1H), 5.97 (s, 1H), 5.56 (s, 1H), 4.13−4.08 (m, 1H), 4.01 (td, J = 11.9, 2.3 Hz, 1H), 3.79−3.75 (m, 1H), 3.28−3.21 (m, 1H), 1.96−1.86 (m, 1H), 1.30−1.18 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 145.8, 145.4, 142.0, 137.2, 130.9, 128.3, 127.6, 125.9, 124.0, 121.5, 97.7, 87.2, 68.5, 47.6, 27.0; HRMS (ESI) [M]$^+$ calcd for [$C_{15}H_{14}N_2OS$] 270.0827, found 270.0827.

*6-(4-(Trifluoromethyl)phenyl)-2,3,4,11b-tetrahydro-[1,3]oxazino-[2,3-a][2,6]naphthyridine (**6p**).* The product was obtained as off white crystals (103.0 mg, 62%): mp 150−154 °C; ^{1}H NMR (400 MHz, CDCl$_3$, δ) 8.38−8.35 (m, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.17 (d, J = 4.6 Hz, 1H), 6.03 (s, 1H), 5.54 (s, 1H), 4.18−4.04 (m, 2H), 3.71−3.66 (m, 1H), 3.36−3.29 (m, 1H), 1.94−1.84 (m, 1H), 1.33 (d, J = 13.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 146.2, 145.5, 140.6, 131.1, 128.6, 128.0, 125.4 (q, J = 3.8 Hz), 121.5, 98.4, 87.1, 68.3, 47.6, 27.0; HRMS (ESI) [M]$^+$ calcd for [$C_{18}H_{15}F_3N_2O$] 332.1136, found 332.1137.

*6-Phenyl-13b,15-dihydrobenzo[b]benzo[4,5][1,3]oxazino[2,3-f]-[1,6]naphthyridine (**6q**).* The product was obtained as yellow needle crystals (150.4 mg, 83%): mp 138−142 °C; ^{1}H NMR (400 MHz, CDCl$_3$, δ) 8.06 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.58 (t, J = 7.3 Hz, 1H), 7.35−7.29 (m, 3H), 7.23−7.21 (m, 3H), 7.09−7.07 (m, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.80 (m, 1H), 6.73 (t, J = 8.1 Hz, 1H), 6.44 (s, 1H), 6.15 (s, 1H), 5.14 (d, J = 13.9 Hz, 1H), 5.04 (d, J = 13.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 151.5, 148.4, 146.8, 138.4, 136.0, 133.2, 130.0, 129.5, 128.8, 128.7, 128.3, 128.0, 127.9, 127.5, 127.1, 126.7, 125.2, 124.8, 124.1, 122.6, 108.8, 85.0, 67.9; HRMS (ESI) [M]$^+$ calcd for [$C_{25}H_{18}N_2O$] 362.1419, found 362.1420.

*6-(p-Tolyl)-13b,15-dihydrobenzo[b]benzo[4,5][1,3]oxazino[2,3-f][1,6]naphthyridine (**6r**).* The product was obtained as pale yellow needle crystals (163.7 mg, 87%): mp 146−150 °C; ^{1}H NMR (400 MHz, CDCl$_3$, δ) 8.06 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.61−7.56 (m, 1H), 7.34 (t, J = 8.1 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.07−7.02 (m, 3H), 6.82 (t, J = 7.3 Hz, 1H), 6.76 (t, J = 8.1 Hz, 1H), 6.47 (s, 1H), 6.17−6.16 (m, 2H), 5.13 (d, J = 13.1 Hz, 1H), 5.04 (d, J = 13.9 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 151.9, 148.5, 146.7, 145.2, 138.5, 133.3, 132.7, 129.9, 128.4, 128.2, 127.9, 127.8, 127.4, 127.1, 126.8, 125.1, 124.7, 124.3, 122.4, 121.9, 109.0, 85.1, 67.8, 21.3; HRMS (ESI) [M]$^+$ calcd for [$C_{26}H_{20}N_2O$] 376.1576, found 376.1577.

*6-(4-Ethylphenyl)-13b,15-dihydrobenzo[b]benzo[4,5][1,3]-oxazino[2,3-f][1,6]naphthyridine (**6s**).* The product was obtained as pale yellow crystals (165.9 mg, 85%): mp 158−162 °C; ^{1}H NMR (400 MHz, CDCl$_3$, δ) 8.06 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.58 (td, J = 8.8, 1.5 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.07−7.02 (m, 3H), 6.82 (t, J = 7.3 Hz, 1H), 6.76 (t, J = 8.1 Hz, 1H), 6.47 (s, 1H), 6.17−6.16 (m, 2H), 5.13 (d, J = 13.2 Hz, 1H), 5.04 (d, J = 13.9 Hz, 1H), 2.58 (q, J = 7.3 Hz, 2H), 1.18−1.15 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 151.9, 148.5, 146.7, 145.2, 138.5, 133.3, 132.7, 129.9, 128.7, 128.4, 128.2, 127.9, 127.8, 127.5, 127.4, 127.1, 126.8, 125.1, 124.7, 124.3, 122.4, 121.9, 109.0, 67.8, 28.6, 15.2; HRMS (ESI) [M]$^+$ calcd for [$C_{27}H_{22}N_2O$] 390.1732, found 390.1733.

*6-(Thiophen-3-yl)-13b,15-dihydrobenzo[b]benzo[4,5][1,3]-oxazino[2,3-f][1,6]naphthyridine (**6t**).* The product was obtained as a dark red semisolid (160.3 mg, 87%): ^{1}H NMR (400 MHz, CDCl$_3$, δ) 8.04 (s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.59 (td, J = 9.6, 2.8 Hz, 1H), 7.33 (td, J = 7.8, 2.8 Hz, 1H), 7.30−7.29 (m, 1H), 7.14−7.12 (m, 1H), 7.04 (d, J = 7.3 Hz, 1H), 6.90−6.80 (m, 3H), 6.94 (s, 1H), 6.29 (d, J = 8.2 Hz, 1H), 6.13 (s, 1H), 5.13 (d, J = 13.2 Hz, 1H), 5.03 (d, J = 14.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 151.6, 148.6, 141.9, 138.6, 137.3, 133.1, 130.0, 128.4, 127.9, 127.7, 127.4, 127.1, 126.8, 125.5, 125.2, 125.1, 124.8, 124.0, 122.47, 122.44, 108.2, 67.8; HRMS (ESI) [M]$^+$ calcd for [$C_{23}H_{16}N_2OS$] 368.0983, found 368.0983.

*6-(3,5-Dimethoxyphenyl)-13b,15-dihydrobenzo[b]benzo[4,5]-[1,3]oxazino[2,3-f][1,6]naphthyridine (**6u**).* The product was obtained as yellow needle crystals (152.1 mg, 72%): mp 86−90 °C; ^{1}H NMR (400 MHz, CDCl$_3$, δ) 8.10 (s, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.64 (td, J = 5.8, 1.4 Hz, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.07 (d, J = 6.6 Hz, 1H), 6.91−6.83 (m, 2H), 6.54−6.52 (m, 3H), 6.42−6.41 (m, 1H), 6.31 (d, J = 7.3 Hz, 1H), 6.20 (s, 1H), 5.18 (d, J = 13.9 Hz, 1H), 5.08 (d, J = 13.9 Hz, 1H), 3.66 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 160.5, 151.5, 148.5, 146.5, 138.5, 137.9, 133.1, 129.9, 128.4, 127.9, 127.2, 127.1, 126.8, 125.2, 124.6, 124.1, 122.3, 122.2, 108.9, 106.3, 101.4, 85.0, 67.8, 55.3; HRMS (ESI) [M]$^+$ calcd for [$C_{27}H_{22}N_2O_3$] 422.1630, found 422.1631.

*6-Phenyl-2,3,4,13b-tetrahydrobenzo[b][1,3]oxazino[2,3-f][1,6]-naphthyridine (**6v**).* The product was obtained as a brown oil (127.3 mg, 81%): ^{1}H NMR (400 MHz, CDCl$_3$, δ) 7.95 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.43−7.42 (m, 1H), 7.39−7.32 (m, 4H), 7.28 (t, J = 7.3 Hz, 1H), 6.09 (s, 1H), 5.82 (s, 1H), 4.15−4.01 (m, 2H), 3.78−3.73 (m, 1H), 3.41−3.39 (m, 1H), 3.28−3.25 (t, J = 10.3 Hz, 1H), 1.96−1.83 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 152.0, 151.3, 148.9, 138.9, 132.6, 130.0, 129.4, 128.8, 128.6, 128.4, 127.9, 127.8, 126.5, 124.4, 121.7, 102.2, 84.4, 68.4, 47.7, 26.9; HRMS (ESI) [M]$^+$ calcd for [$C_{21}H_{18}N_2O$] 314.1419, found 314.1420.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra, HRMS, and a CIF file for compound **5a** (CCDC 932014). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: averma@acbr.du.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Department of Science and Technology (SR/S1/OC-66/2010), New Delhi, India and the University of Delhi for financial support. The University Science Instrumentation Centre, University of Delhi, is also gratefully acknowledged for NMR and XRD facilities. D.C., R.K.S., V.R., and M.P. are thankful to the CSIR, UGC, and DST for a fellowship.

■ REFERENCES

(1) (a) Walsh, D. P.; Chang, Y.-T. *Chem. Rev.* **2006**, *106*, 2476. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Arya, P.; Chou, D. T. H.; Baek, M.-G. *Angew. Chem., Int. Ed.* **2001**, *40*, 339.

(2) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2878. (c) Dandapani, S.; Marcaurelle, L. A. *Curr. Opin. Chem. Biol.* **2010**, *14*, 362. (d) Hsu, Y.-C.; Ting, C.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2009**, *131*, 2090. (e) Teng, T.-M.; Das, A.; Huple, D. B.; Liu, R.-S. *J. Am. Chem. Soc.* **2010**, *132*, 12565. (f) Teng, T.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2010**, *132*, 9298.

(3) (a) Weibel, J. M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149. (b) Corral, M. A.; Dorado, M. M.; Garcia, I. R. *Chem. Rev.* **2008**, *108*, 3174. (c) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132.

(4) (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Amsterdam, 1998; Vol. *1*. (b) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.; Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G. D.; Dinsmore, C. J. *J. Med. Chem.* **2006**, *49*, 6954. (c) Ramesh, P.; Reddy, S.; Venkateswarlu, Y. *J. Nat. Prod.* **1999**, *62*, 780. (d) Oi, S.; Ikedou, K.; Takeuchi, K.; Gino, M.; Banno, Y.; Tawada, H. Yamane, T. WO 2002062764, 2002. (e) Kaneda, T.; Takeuchi, Y.; Matsui, H.; Shimizu,

K.; Urakawa, N.; Nakajyo, S. *J. Pharmacol. Sci.* **2005**, *98*, 275. (f) Mikami, Y.; Yokoyama, K.; Tabeta, H.; Nakagaki, K.; Arai, T. *J. Pharm. Dyn.* **1981**, *4*, 282. (g) Marchand, C.; Antony, S.; Kohn, K. W.; Cushman, M.; Ioanoviciu, A.; Staker, B. L.; Burgin, A. B.; Stewart, L.; Pommier, Y. *Mol. Cancer Ther.* **2006**, *5*, 287. (h) Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995.

(5) (a) Chylinska, J. B.; Janowiec, M.; Urbarnsky, T. *Br. J. Pharmacol.* **1971**, *43*, 649. (b) Moloney, G. P.; Craik, D. J.; Iskander, M. N. *J. Pharm. Sci.* **1992**, *81*, 692. (c) Shakil, N. A.; Dhawan, A.; Sharma, N. K.; Kumar, V.; Kumar, S.; Bose, M.; Raj, H. G.; Olsen, C. E.; Cholli, A. L.; Samuelson, L. A.; Kumar, J.; Watterson, A. C.; Parmar, V. S.; Prasad, A. K. *Indian J. Chem. Sect. B* **2003**, *42B* (8), 1958. (d) Gurupadayya, B. M.; Manohara, Y. N.; Gopal, M. *Indian J. Heterocycl. Chem.* **2005**, *15*, 113.

(6) Gemma, S.; Camodeca, C.; Brindisi, M.; Brogi, S.; Kukreja, G.; Kunjir, S.; Gabellieri, E.; Lucantoni, L.; Habluetzel, A.; Taramelli, D.; Basilico, N.; Gualdani, R.; Tadini-Buoninsegni, F.; Bartolommei, G.; Moncelli, M. R.; Martin, R. E; Summers, R. L; Lamponi, S.; Savini, L.; Fiorini, I.; Valoti, M.; Novellino, E.; Campiani, G.; Butini, S. *J. Med. Chem.* **2012**, *55*, 10387.

(7) Gogliotti, R. D.; Muccioli, K. L.; Para, K. S.; Visnick, M. WO 2004056820, 2004.

(8) Largeron, M.; Lackhart, B.; Pfeiffer, B.; Fleury, M. B. *J. Med. Chem.* **1999**, *42*, 5043.

(9) Bromidge, S. M.; Arban, R.; Bertani, B.; Bison, S.; Borriello, M.; Cavanni, P.; Forno, G. D.; Di-Fabio, R.; Donati, D.; Fontana, S.; Gianotti, M.; Gordon, L. J.; Granci, E.; Leslie, C. P.; Moccia, L.; Pasquarello, A.; Sartori, I.; Sava, A.; Watson, J. M.; Worby, A.; Zonzini, L.; Zucchelli, V. *J. Med. Chem.* **2010**, *53*, 5827.

(10) Koini, E. N.; Papazafiri, P.; Vassilopoulos, A.; Koufaki, M.; Horváth, Z.; Koncz, I.; Virág, L.; Papp, G. J.; Varró, A.; Calogeropoulou, T. *J. Med. Chem.* **2009**, *52*, 2328.

(11) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022.

(12) Böhme, T. M.; Augelli-Szafran, C. E.; Hallak, H.; Pugsley, T.; Serpa, K.; Schwarz, R. D. *J. Med. Chem.* **2002**, *45*, 3094.

(13) Ilaš, J.; Jakopin, Ž.; Borštnar, T.; Stegnar, M.; Kikelj, D. *J. Med. Chem.* **2008**, *51*, 5617.

(14) Zhang, P.; Terefenko, E. A.; Fensome, A.; Wrobel, J.; Winneker, R.; Lundeen, S.; Marschke, K. B.; Zhang, Z. *J. Med. Chem.* **2002**, *45*, 4379.

(15) Zhou, Y.-G.; Yang, P.-Y.; Han, X.-W. *J. Org. Chem.* **2005**, *70*, 1679.

(16) (a) Kobzina, J. W. U.S. Patent 4,030,906, 1977; *Chem. Abstr.* **1977**, *87*, 79678e. (b) Imperial Chernkal Industries Ltd. Japanese Patent 8047665, 1980; *Chem. Abstr.* **1980**, *93*, 204681. (c) Boyle, F. T.; Taylor, M. A. Spanish Patent 484 472, 1980; *Chem. Abstr.* **1981**, *94*, 156956t.

(17) (a) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 4108. (b) Terano, H.; Takase, S.; Hosoda, J.; Kohsaka, M. *J. Antibiot.* **1989**, *42*, 145. (c) Yu, Q.-S.; Zhu, X.; Holloway, H. W.; Whittaker, N. F.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2002**, *45*, 3684. (d) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10229. (e) Judd, T. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4683. (f) Suzuki, M.; Kambe, J.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4686.

(18) (a) Pulz, R.; Al-Harrasi, A.; Reibg, H.-U. *Org. Lett.* **2002**, *4*, 2353. (b) Tishkov, A. A.; Reibg, H.-U.; Ioffe, S.L. *Synlett* **2002**, 863. (c) Buchholz, M.; Reibg, H.-U. *Eur. J. Org. Chem.* **2003**, 3524. (d) Al-Harrasi, A.; Reibg, H.-U. *Angew. Chem., Int. Ed.* **2005**, *44*, 6227. (e) Carson, C. A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6560. (f) Gilchrist, T. L.; Wood, J. E. In *Comprehensive Heterocyclic Chemistry II*; Elsevier: Oxford, U.K., 1996; Vol. 6, pp 279−299, 1177. (g) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 1149. (h) Yoon, S. C.; Kim, K.; Park, Y. J. *J. Org. Chem.* **2001**, *66*, 7334. (i) Pulz, R.; Cicchi, S.; Brandi, A.; Reibg, H.-U. *Eur. J. Org. Chem.* **2003**, 1153. (j) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (k) Kumarn, S.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Lett.* **2005**, *7*, 4189. (l) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fišera, L.; Hlobilová, I.; Zahn, G.; Reißig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003. (m) Kumarn, S.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2006**, 3211.

(19) (a) Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953. (b) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011. (c) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (d) Yue, D.; Ca, N. D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581. (e) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677. (f) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (g) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432. (h) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *71*, 62. (i) Yue, D.; Cá, N. D.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3381. (j) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1347. (k) Manarin, F. V.; Roehrs, J. A.; Gay, R. M.; Brandãao, R.; Menezes, P. H.; Nogueiraand, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 2153. (l) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.

(20) (a) Asao, N.; Yudha, S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (b) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462 ; see also references therein. (c) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822. (d) Asao, N.; Iso, K.; Salprima, Y. S. *Org. Lett.* **2006**, *8*, 4149. (e) Asao, N.; Chan, C. S.; Takahashi, K.; Yamamoto, Y. *Tetrahedron* **2005**, *61*, 11322. (f) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339. (g) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem., Int. Ed.* **2003**, *42*, 4257. (h) Yavari, I.; Ghazanfarpour-Darjani, M.; Sabbaghan, M.; Hossaini, Z. *Tetrahedron Lett.* **2007**, *48*, 3749. (i) Shaabani, A.; Soleimani, E.; Khavasi, H. R. *Tetrahedron Lett.* **2007**, *48*, 4743. (j) Wang, G.-W.; Li, J.-X. *Org. Biomol. Chem.* **2006**, *4*, 4063. (k) Diaz, J. L.; Miguel, M.; Lavilla, R. *J. Org. Chem.* **2004**, *69*, 3550.

(21) (a) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920. (c) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042. (d) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. (e) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86. (f) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042. (g) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.

(22) (a) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959. (b) Gao, K.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8611. (c) Ding, Q.; Ye, Y.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 5439. (d) Sun, W.; Ding, Q.; Sun, X.; Fan, R.; Wu, J. *J. Comb. Chem.* **2007**, *9*, 690. (e) Chen, Z.; Yang, X.; Wu, J. *Chem. Commun.* **2009**, 3469. (f) Yu, X.; Wu, J. *J. Comb. Chem.* **2010**, *12*, 238. (g) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462. (h) Yanada, R.; Hashimoto, K.; Tokizane, R.; Miwa, Y.; Minami, H.; Yanada, K.; Ishikura, M.; Takemoto, Y. *J. Org. Chem.* **2008**, *73*, 5135. (i) Ding, Q.; Wang, B.; Wu, J. *Tetrahedron* **2007**, *63*, 12166. (j) Yu, M.; Wang, Y.; Li, C.-J.; Yao, X. *Tetrahedron Lett.* **2009**, *50*, 6791. (k) Zhou, H.; Jin, H.; Ye, S.; He, X.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 4616. (l) Das, A.; Sohel, S. M. A.; Liu, R.-S. *Org. Biomol. Chem.* **2010**, *8*, 960.

(23) (a) Asao, N.; Salprima, Y. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (b) Gao, H.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 85. (c) Ohta, Y.; Kubota, Y.; Watabe, T.; Chiba, H.; Oishi, S.; Fujii, S.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 6299. (d) Ouyang, H.-C.; Tang, R.-Y.; Zhong, P.; Zhang, X.-G.; Li, J.-H. *J. Org. Chem.* **2011**, *76*, 223. (e) Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G. V. V; Raju, P. V. K.; Sridhar, B. *Eur. J. Org. Chem.* **2010**, 1999. (f) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138. (g) Rustagi, V.; Tiwari, R.; Verma, A. K. *Eur. J. Org. Chem.* **2012**, 4590. (h) Rustagi, V.; Aggarwal, T.; Verma, A. K. *Green Chem.* **2011**, *13*, 1640.

(24) (a) Aggarwal, T.; Jha, R. R.; Tiwari, R. K.; Kumar, S.; Kotla, S. K. R.; Kumar, S.; Verma, A. K. *Org. Lett.* **2012**, *14*, 5184. (b) Verma, A. K.; Kotla, S. K. R.; Choudhary, D.; Patel, M.; Tiwari, R. K. *J. Org. Chem.* **2013**, *78*, 4386.

(25) (a) Zhou, Y.; Zhai, Y.; Li, J.; Ye, D.; Jiang, H.; Liu, H. *Green Chem.* **2010**, *12*, 1397. (c) Dyker, G.; Stirner, W.; Henkel, G. *Eur. J. Org. Chem.* **2000**, 1433.

(26) (a) Campi, E. N.; Jackson, W. R.; McCubbin, Q. J.; Trnacek, A. E. *Aust. J. Chem.* **1996**, *49*, 219. (b) Campi, E. N.; Jackson, W. R.; McCubbin, Q. J.; Trnacek, A. E. *J. Chem. Soc., Chem. Commun.* **1994**, 2763. (c) Feng, E.; Zhou, Y.; Zhang, D.; Zhang, L.; Sun, H.; Jiang, H.; Liu, H. *J. Org. Chem.* **2010**, *75*, 3274. (d) Li, Y.; Li, Z.; Xiong, T.; Zhang, Q.; Zhang, X. *Org. Lett.* **2012**, *14*, 3523. (e) Jin, Z.; Wang, X.; Huang, H.; Liang, X.; Ye, J. *Org. Lett.* **2011**, *13*, 564. (f) Butler, J. D.; Solano, D. M.; Robins, L. I.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2008**, *73*, 234. (g) Agag, T.; Takeichi, T. *Macromolecules* **2003**, *36*, 6010. (h) Cheng, Y.; Yang, J.; Jin, Y.; Deng, D.; Xiao, F. *Macromolecules* **2012**, *45*, 4085. (i) Hashmi, A. S. K.; Schuster, A. M.; Zimmer, M.; Rominger, F. *Chem.—Eur. J.* **2011**, *17*, 5511. (j) Ozturkcan, S. A.; Turhan, K.; Turgut, Z. *J. Chem. Soc. Pak.* **2011**, *33*, 939.

(27) (a) Li, C. J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68. (b) Naryan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275. (c) Shapiro, N.; Vigalok, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2849. (d) Saggiorrio, V.; Luning, U. *Tetrahedron Lett.* **2009**, *50*, 4663. (e) Norcott, P.; Spielman, C.; McErlean, C. S. P. *Green Chem* **2012**, *14*, 605.

(28) (a) Lindstrom, U. M.; Andersson, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 548. (b) HerrerTas, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (c) Liu, X. Y.; Che, C. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3805. (d) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (e) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (f) Meijer, A.; Otto, S.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8989. (g) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365. (h) Klijn, J. E.; Engberts, J. B. F. N. *Nature* **2005**, *435*, 746. (i) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302. (j) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.

(29) (a) Verma, A. K.; Aggarwal, T.; Rustagi, V.; Larock, R. C. *Chem. Commun.* **2010**, *46*, 4064. (b) Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691. (c) Verma, A. K.; Jha, R. R.; Sankar, V. K.; Aggarwal, T.; Singh, R. P.; Chandra, R. *Eur. J. Org. Chem.* **2011**, 6998. (d) Shukla, S. P.; Tiwari, R. K.; Verma, A. K. *Tetrahedron* **2012**, *68*, 9035. (e) Shukla, S. P.; Tiwari, R. K.; Verma, A. K. *J. Org. Chem.* **2012**, *77*, 10382. (f) Aggarwal, T.; Kumar, S.; Dhaked, D. K.; Tiwari, R. K.; Bharatam, P. V.; Verma, A. K. *J. Org. Chem.* **2012**, *77*, 8562. (g) Tiwari, R. K.; Singh, J.; Singh, D.; Verma, A. K.; Chandra, R. *Tetrahedron* **2005**, *61*, 9513.

(30) (a) Markina, N. A.; Mancuso, R.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *ACS Comb. Sci.* **2011**, *13*, 265. (b) Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* **2011**, *13*, 2228. (c) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Nçsel, P.; Jongbloed, L.; Rudolph, M.; Romingera, F. *Adv. Synth. Catal.* **2012**, *354*, 555.