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Arkivoc **2017**, part v, 148-158

Synthesis of 3,4-dihydroisoquinoline *N*-oxides via palladium-catalyzed intramolecular cyclization of 2-alkylbenzaldoximes

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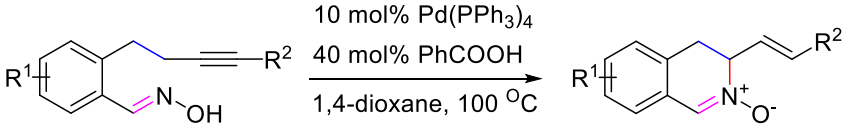
Received 05-20-2017 **Accepted** 08-02-2017 **Published on line** 08-29-2017

Abstract

A novel process for the synthesis of 3,4-dihydroisoquinoline *N*-oxides via $Pd(PPh_3)_4$/PhCOOH-catalyzed intramolecular cyclization of 2-alkylbenzaldoximes was reported. The reaction of 2-alkylbenzaldoximes proceeded smoothly in the presence of 10 mol% $Pd(PPh_3)_4$ and 40 mol% PhCOOH in 1,4-dioxane at 100 °C to give the corresponding 3,4-dihydroisoquinoline *N*-oxides in good to high yields. A possible pathway for the production of 3,4-dihydroisoquinoline *N*-oxides via a π-allylpalladium complex was proposed. The present study provides a useful and new method for the formation of C-N bond in organic synthesis.



> Novel construction of C-N bond
> Up to 99% yield
> Green synthesis

Keywords: Cross-coupling, cyclization, heterocycles, heterogeneous catalysis, palladium

Introduction

3,4-Dihydroisoquinoline *N*-oxides are an important class of organic compounds because of their wide utility. They are often seen as building blocks in natural products[1] and are used as free radical trap in chemical and biochemical system.[2] Moreover, 3,4-dihydroisoquinoline *N*-oxides have been shown to have potential ability to cure many diseases of aging, such as stroke, Parkinson disease, Alzheimer disease and cancer development.[3] They can also be used as antimicrobial agents,[4] pesticides (I),[5] and anti-HIV agents (II) (Figure 1).[6] The most widely use of 3,4-dihydroisoquinoline *N*-oxides are employed as synthetically versatile substrates for 1,3-dipolar cycloaddition and nucleophilic addition to afford corresponding isoxazolines[7-9] and hydroxylamines.[10-11] Due to the importance of 3,4-dihydroisoquinolines *N*-oxides, much attention has been attracted to their organic synthesis.

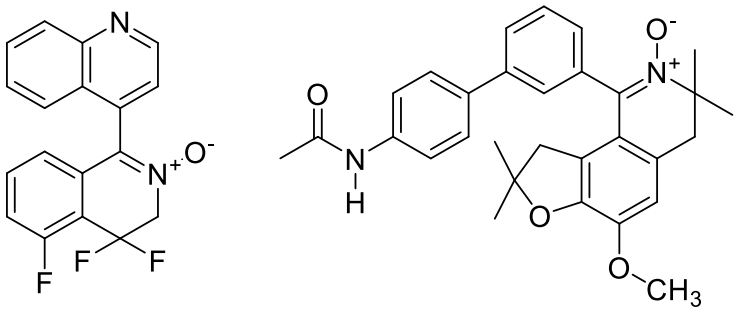
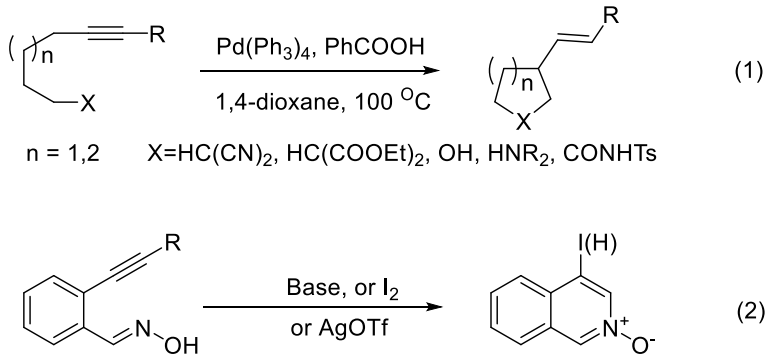


Figure 1. Compunds with isoquinoline N-oxides.

In general, the oxidative approach provides the most direct and general method for preparing 3,4-dihydroisoquinoline *N*-oxides, the raw materials are secondary amines or hydroxylamines.[12-15] Several extra oxidants used in these reactions included H_2O_2, mCPBA, O_2, cumene hydroperoxide and oxone, *etc*. However, the use of extra oxidants, complicated or noble metal catalysts, toxic additives, greater toxicity organic solvents and/or prolonged reaction times were usually needed in these processes. There were two other strategies to synthetize 3,4-dihydroisouinolines *N*-oxides: the isomerization of oxaziridines[16] and the cyclization reactions of nitrogen compounds.[17-19] Similarly, these two methods had obvious drawbacks. Strong corrosive acid, such as CH_3HSO_3 or H_2SO_4, was needed in the former method, and hypertoxic cyanide or thermal unstable NH_2OH was needed in the later method. These shortcomings limited their industrialized application. Therefore, the development of an efficient and environmentally benign protocol for the synthesis of 3,4-dihydroisoquinoilne *N*-oxides is still highly desired.

The transition metal-catalyzed intramolecular cyclization of carbon and heteroatom nucleophiles with activated C-C bonds such as alkenes, allenes and alkynes had proven to be a valuable route for the generation of carbocycle and heterocycle compounds.[20-24] Previously, Yamamoto *et al*. reported the synthesis of piperidines and pyrrolidines, lactams, furans and lactones by hydroamination,[25] hydroamidation,[26] hydroalkoxylation[23] and hydrocarboxylation[27] of alkynes using a $Pd(PPh_3)_4$/PhCOOH combined catalyst system (Eq. 1). Recently, several methods for the synthesis of isoquinoline *N*-oxides had been reported through cyclization reactions of 2-ethynylbenzaldehyde oximes (Eq. 2).[28-31] Based on the results of above researches, it occurred to us that the synthesis of 3,4-dihydroisoquinoline *N*-oxides from 2-alkylbenzaldoximes was possible with $Pd(PPh_3)_4$/PhCOOH combined catalyst system. With this in mind, intramolecular cyclization of 2-alkylbenzaldoximes with $Pd(PPh_3)_4$/PhCOOH was investigated, and the result indicated that the reaction

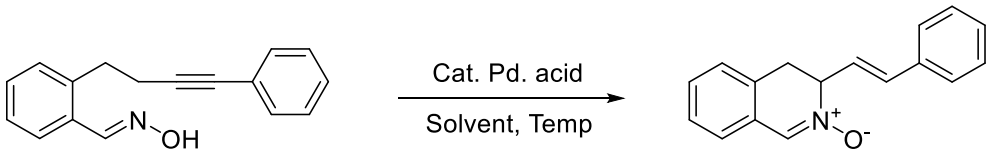
proceeded well to give the corresponding 3,4-dihydroisoquinoline *N*-oxides in good to high yields at mild reaction conditions (Eq. 3). The detailed results of the study are reported herein.



Results and Discussion

Initially, our research focused on the optimization of reaction conditions such as catalysts, solvents, temperature and acid, *etc*. and hoped to achieve a higher yield. The results were summarized in Table 1. 2-(4-Phenylbut-3-ynyl)benzaldehyde oxime (**1a**) was employed as a model substrate. The reactions of **1a** did not proceed in the absence of catalyst or acid (entries 1 and 2). When **1a** was treated with 10 mol% $Pd(PPh_3)_4$, 40 mol% benzoic acid in 1,4-dioxane at 100 °C under argon, the corresponding 3,4-dihydroisoquinoline *N*-oxides (**2a**) as sole product was obtained in 99% isolated yield (entry 3). The results clearly indicated that combined use of $Pd(PPh_3)_4$ and PhCOOH was essential for the transformation. Catalyst screening revealed that $Pd(PPh_3)_4$ gave a higher yield, while $PdCl_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$ were not effective and afforded only trace amount and 40% yield (entries 4 and 5). Other acid sources such as CH_3COOH, H_2O and MeOH instead of PhCOOH were examined. Acetic acid was effective and gave 72% yield (entry 6). The use of H_2O and MeOH did not afford the desired products (entries 7 and 8). Among the solvents such as AcOEt, benzene, CH_3CN, THF and CH_2Cl_2 tested, the desired products were also obtained in good to high yields, however the yields were low in comparison to the 99% yield in 1,4-dioxane (entries 9-13). We further investigated the effect of the amount of $Pd(PPh_3)_4$, the amount of benzoic acid and temperature on the yields of **2a**. The yields of **2a** were decreased as the amount of $Pd(PPh_3)_4$ or PhCOOH decreased (entries 14 and 15). Decreasing temperature to 80 °C led to a moderate yield (entry 16).

Table 1. Optimization of reaction conditions[a]



1a **2a**

Entry	Catalyst	Acid	Solvent	Time (h)	**1a** (%)[b]	**2a** (%)[b]
1	-	PhCOOH	1,4-dioxane	24	100	0
2	$Pd(PPh_3)_4$	-	1,4-dioxane	24	100	0
3	$Pd(PPh_3)_4$	PhCOOH	1,4-dioxane	2	0	100 (99)[c]
4	$Pd(dba)_3{\cdot}CHCl_3$	PhCOOH	1,4-dioxane	12	68	trace
5	$PdCl_2$	PhCOOH	1,4-dioxane	12	0	40
6	$Pd(PPh_3)_4$	CH_3COOH	1,4-dioxane	5	0	72
7	$Pd(PPh_3)_4$	H_2O	1,4-dioxane	12	72	trace
8	$Pd(PPh_3)_4$	MeOH	1,4-dioxane	12	70	0
9	$Pd(PPh_3)_4$	PhCOOH	AcOEt	5	0	84
10	$Pd(PPh_3)_4$	PhCOOH	Benzene	12	0	29
11	$Pd(PPh_3)_4$	PhCOOH	CH_3CN	5	0	74
12	$Pd(PPh_3)_4$	PhCOOH	THF	12	0	53
13	$Pd(PPh_3)_4$	PhCOOH	CH_2Cl_2	12	18	59
14[d]	$Pd(PPh_3)_4$	PhCOOH	1,4-dioxane	12	38	54
15[e]	$Pd(PPh_3)_4$	PhCOOH	1,4-dioxane	12	22	68
16[f]	$Pd(PPh_3)_4$	PhCOOH	1,4-dioxane	12	21	70

[a] Reaction conditions: The reaction of **1a** (0.05 mmol) in the presence of 10 mol% Pd catalysts and 40 mol% acid was carried out at 100 ^{O}C in 1,4-dioxane (1 mL) under Ar. [b] Yield were determined by ^{1}H NMR spectroscopy with *p*-xylene as internal standard. [c] Isolated yields. [d] 5 mol% $Pd(PPh_3)_4$ was used. [e] 20 mol% PhCOOH was used. [f] At 80 ^{O}C.

As shown in Figure 2a, the time profile of the reaction of **1a** monitoring by NMR indicated that the substrate **1a** was completely converted whereas the corresponding product **2a** was obtained in the highest yield of 99% within 2 h. Figure 2b showed the peak changes of **1a** and **2a** by ^{1}H NMR at different reaction time. It can be seen that the methylene (-CH_2-) peaks of **1a** at 3.0 ppm became smaller and smaller as the time increased from 0 to 40 min, until its peaks of **1a** disappeared at 2 h, whereas chemical shift was found to change at 40 min and the methylene (-CH_2-) peaks of **2a** at 3.1 ppm and 3.6 ppm occurred. Since then, the peaks changed from smaller to bigger, indicating clearly that the sole product **2a** was produced and gave the best result at 2 h.

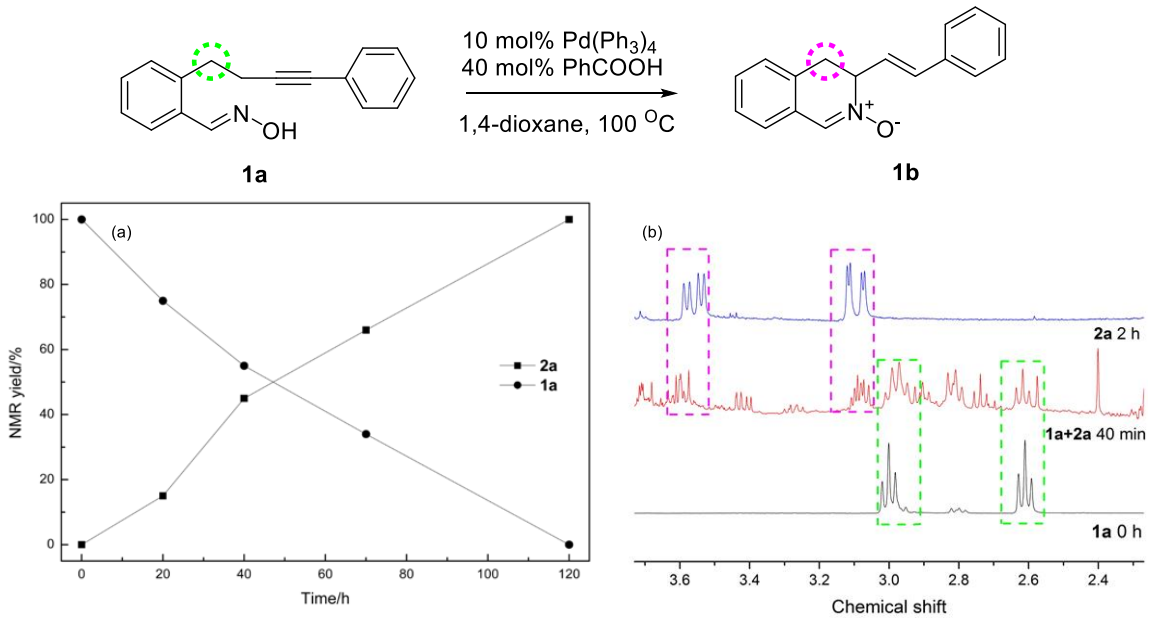
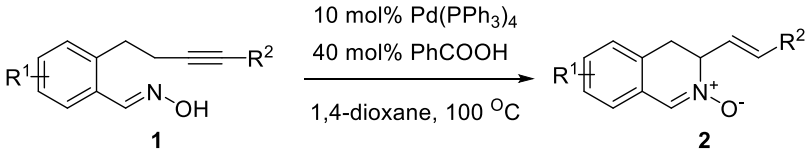


Figure 2. (a) Time profile of the cyclization of **1a**. (b) The peak changes of **1a** and **2a** by ^{1}H NMR at different time.

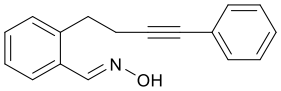
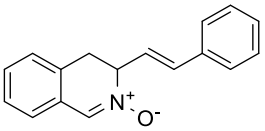
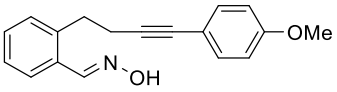
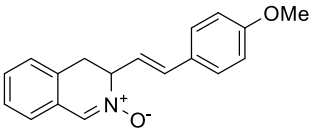
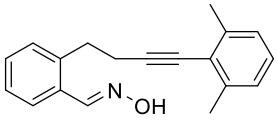
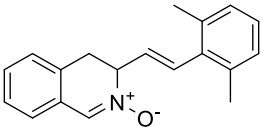
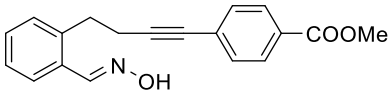
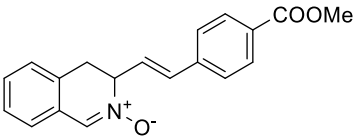
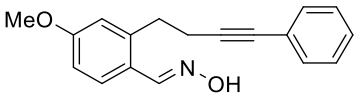
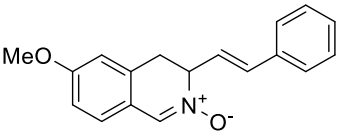
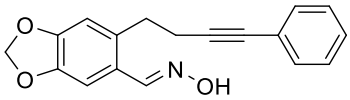
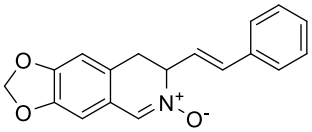
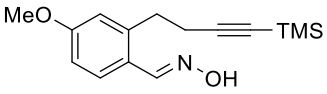
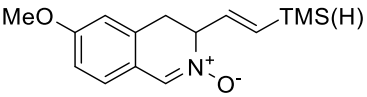
With optimized conditions in hand, intramolecular cyclization of various substituted 2-alkylbenzaldoximes to corresponding 3,4-dihydroisoquinoline *N*-oxides was then investigated, and the results were summarized in Table 2. The reactions of **1b** and **1c**, having 4-methoxy phenyl and 2,6-dimethyl phenyl groups at the alkyne terminus produced smoothly to give products **2b** and **2c** in 81% and 76% yields, respectively (entries 2 and 3). Treatment of **1d**, having an electron-withdrawing group, -COOMe, at the *para*-aromatic ring afforded good yield (entry 4). The yield of desired products were 81% (**2b**, entry 2), 76% (**2c**, entry 4), 80% (**2d**, entry 4) respectively. It was worth noting that, when substrates attached a bulk group (**1g**, entry 7), no desired products can be detected. We think that this may due to steric hindrance. In addition, methoxy and methylenedioxy were introduced to benzene ring (**1e**-**1f**, entries 5-6). The substrates **1e** and **1f**, in which the aromatic ring was substituted with RO groups, afforded products **2e** and **2f** in good to high yields (entries 5 and 6). But when R^1 group was methoxy group and R^2 group was trimethylsilyl group, the 3,4-dihydroisoquinoline *N*-oxide **2g** was not obtained at the present conditions. We tried various methods such as prolonging the reaction time or increasing the amount of palladium catalyst and benzoic acid, all of them failed to give the product **2g**, and a mixture was obtained (entry 7).

According to present results and previous works,[32-34] a plausible mechanism for the synthesis of 3,4-dihydroisoquinoline *N*-oxide is illustrated in Scheme 1. Initially, Pd(0) catalyst reacted with benzoic acid to form hydridopalladium species **A**, hydropalladation of 2-alkylbenzaldoximes **1a** with formed **A** gave the substituted phenylallene **B**.[35] Subsequent hydropalladation of the phenyl allene **B** with formed **A** occurred again and generated π-allyl palladium species **C**. Then, intramolecular nucleophilic substitution in the π-allyl palladium complex **C** gave the intermediate **D**. Finally, loss of hydrogen atom afforded the desired 3,4-dihydroisoquinoline *N*-oxide **2a** along with regeneration of the species **A**.

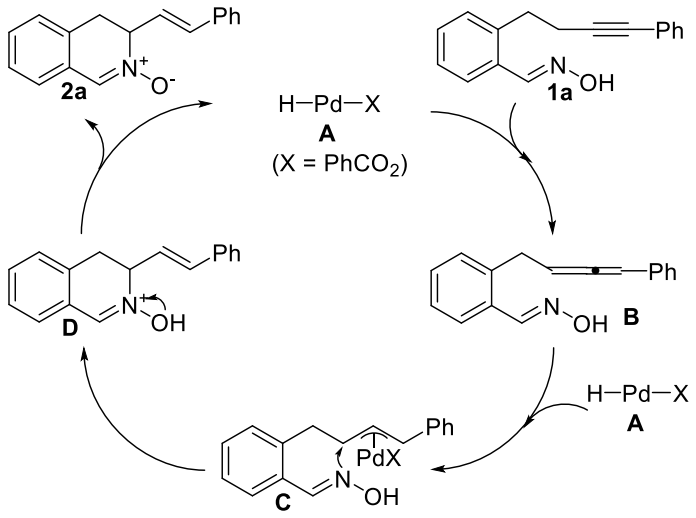
Table 2. Synthesis of 3,4-dihydroisoquinoline *N*-oxides with various substrates[a]



1 **2**

Entry	Substrate (**1**)	Time (h)	Product (**2**)	Yield (%)[b]
1	 **1a**	2	 **2a**	99
2	 **1b**	2	 **2b**	81
3	 **1c**	2	 **2c**	76
4	 **1d**	2	 **2d**	80
5	 **1e**	3	 **2e**	57
6	 **1f**	2	 **2f**	82
7	 **1g**	12	 **2g**	n. d.[c]

[a] Reaction conditions: **1** (0.05 mmol), $Pd(PPh_3)_4$ (10 mol%), benzoic acid (40 mol%), 1,4-dioxane (1 mL), under Ar, 100 °C, 2 h. [b] Isolated yield. [c] Not determined.



Scheme 1. Proposed mechanism for the formation of **2a**.

Conclusions

We developed a novel and efficient method for the synthesis of 3,4-dihydroisoquinoline *N*-oxides via palladium-catalyzed intramolecular cyclization of 2-alkylbenzaldoximes. The combined use of $Pd(PPh_3)_4$/benzoic acid as catalyst showed the high catalytic acitivity and gave desired products in good to high yields. Our present study provides a new and useful method for the generation of C-N bond and has also meaningful results for the synthesis of nitrogen heterocycles.

Experimental Section

General. ^1H and ^{13}C NMR spectra were operated at 400 and 100 MHz respectively. The reactions were monitored by thin-layer chromatography (TLC). Column chromatography was performed on neutral silica gel (60N, 45-75 μm) and hexane/AcOEt was used as an eluent. The catalyst $Pd(PPh_3)_4$ was prepared according to the literature procedure.[36] All starting materials used in our study were prepared in the laboratory. TLC was performed on aluminum-precoated plates of silica gel 60 with an HSGF254 indicator and visualized under UV light or developed by immersion in the solution of 0.6 % $KMnO_4$ and 6 % K_2CO_3 in water.

Synthesis of substrates 1a, 1e, 1f. Taking **1a** as example, to 1-phenyl-1-propyne (12 mmol, 1.5 mL), *n*-butyllithium (12 mmol, 1.15 mL) and $HgCl_2$ (0.15 mmol, 40 mg) was added in 20 mL THF under argon in a 50 mL three-necked flask. After stirring for 1 h at -78 °C, 2-bromobenzyl bromide (10 mmol, 2.5 g) was added in to the reaction mixture and then reacted for 5-10 h at room temperature (monitored by TLC). The reaction mixture was washed with saturated NH_4Cl solutions, dried with anhydrous $MgSO_4$ and extracted with Et_2O.[37] The concentrated yellow oil was added with *n*-butyllithium (20 mmol, 1.88 mL) at -78 °C. After 1 h, DMF (12 mmol, 0.93 mL) was added dropwise into this mixture. Then, the reaction was brought to room temperature for 5-10 h (monitored by TLC), and quenched by saturated NH_4Cl, and the resulting residue was purified through a short silica gel column using hexane/EtOAc as eluent.[38] After removing the solvent, hydroxyl-ammonium chloride (4.5 mmol, 312 mg) was added and sodium acetate (4.5 mmol, 123 mg) into a mixed solution of ethanol and water (6 mL) with the volume ration of 1:1. After a certain period of time, this reaction

was quenched with saturated $NaHCO_3$ and purified by silica gel column (hexane/EtOAc) to afford desired substrates **1a**, **1e**, **1f**.[39]

Synthesis of substrates 1b, 1c, 1d, 1g. The procedures for preparing substrates **1b**, **1c**, **1d**, **1g** were similar. During the reaction, trimethylsilyl was removed by potassium fluoride using methanol and tetrahydrofuran as solvent to afford terminal alkynes.[40] R^2 group was connected to the terminal alkynes by Sonogashira reaction.[41]

(*E*)-2-(4-Phenylbut-3-ynyl)benzaldehyde oxime (1a). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69-2.56 (t, *J* 7.5 Hz, 2H), 3.08-2.97 (t, *J* 7.5 Hz, 2H), 7.38-7.14 (m, 8H), 7.70-7.60 (d, *J* 7.6, 1H), 8.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 139.4, 131.5, 130.4, 129.9, 129.8, 128.1, 127.6, 127.1, 126.9, 123.6, 88.7, 81.8, 32.1, 21.4. FT-IR (KBr): 3060, 2916, 1958, 1489, 951, 755, 691 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{17}H_{16}NO$ $[M + H]^+$ 250.1232, Found 250.1229.

(*E*)-2-(4-(4-Methoxyphenyl)but-3-ynyl)benzaldehyde oxime (1b). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72-2.60 (t, *J* 7.5 Hz, 2H), 3.12-3.00 (t, *J* 7.5 Hz, 2H), 3.79 (s, 3H), 6.86-6.76 (m, 2H), 7.38-7.20 (m, 5H), 7.70-7.60 (d, *J* 7.6, 1H), 8.50 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 148.9, 139.5, 132.8, 130.4, 130.1, 129.8, 127.0, 126.9, 115.7, 113.8, 87.2, 81.5, 55.2, 32.2, 21.5. FT-IR (KBr): 2915, 1605, 1508, 1245, 1032, 952, 831, 757 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1338, Found 280.1338.

(*E*)-2-(4-(2,6-Dimethylphenyl)but-3-ynyl)benzaldehyde oxime (1c). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 6H), 2.73-2.60 (t, *J* 7.5 Hz, 2H), 3.15-2.99 (t, *J* 7.5 Hz, 2H), 6.91 (s, 1H), 7.01 (s, 2H), 7.41-7.20 (m, 3H), 7.73-7.65 (t, *J* 7.7 Hz, 1H), 8.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 139.4, 137.6, 130.3, 129.9, 129.8, 129.5, 129.2, 126.9, 126.8, 123.1, 87.9, 82.0, 32.1, 21.4, 20.9. FT-IR (KBr): 2958, 2201, 1585, 1264, 1200, 930, 672 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{19}H_{20}NO$ $[M + H]^+$ 278.1545, Found 278.1565.

(*E*)-Methyl 4-(4-(2-((hydroxyimino)methyl)phenyl)but-1-ynyl)benzoate (1d). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76-2.65 (t, *J* 7.5 Hz, 2H), 3.15-3.04 (t, *J* 7.5 Hz, 2H), 3.91 (s, 3H), 7.44-7.26 (m, 5H), 7.73-7.65 (d, *J* 7.8 Hz, 1H), 7.97-7.90 (d, *J* 8.4 Hz, 2H), 8.48 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 149.1, 139.1, 131.4, 130.5, 130.1, 129.8, 129.4, 128.9, 128.5, 127.5, 126.9, 92.3, 81.2, 52.1, 32.1, 21.5. FT-IR (KBr): 2951, 2210, 1721, 1615, 1435, 1276, 1109, 960, 769 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{19}H_{18}NO_3$ $[M+H]^+$ 308.1287, Found 308.1283.

(*E*)-4-Methoxy-2-(4-phenylbut-3-ynyl)benzaldehyde oxime (1e). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72-2.67 (t, *J* 7.5 Hz, 2H), 3.09-2.96 (t, *J* 7.5 Hz, 2H), 3.80 (s, 3H), 6.90-6.75 (m, 2H), 7.43-7.30 (m, 5H), 7.69-7.57 (d, *J* 7.6, 1H), 8.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 148.8, 141.2, 131.7, 131.5, 129.0, 128.3, 128.2, 127.7, 123.7, 122.7, 88.9, 81.8, 55.3, 32.5, 21.3. FT-IR (KBr): 2916, 1603, 1505, 1254, 1040, 756, 691 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1338, Found 280.1334.

(*E*)-6-(4-Phenylbut-3-ynyl)benzo[*d*][1,3]dioxole-5-carbaldehyde oxime (1f). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70-2.63 (t, *J* 7.5 Hz, 2H), 3.03-2.92 (t, *J* 7.5 Hz, 2H), 5.99 (s, 2H), 6.77 (s, 1H), 7.33-7.26 (m, 4H), 7.46-7.34 (m, 2H), 8.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 148.2, 146.7, 134.5, 131.5, 128.2, 128.0, 127.7, 123.5, 109.9, 105.8, 101.3, 88.5, 82.0, 31.7, 21.9. FT-IR (KBr): 2918, 2097, 1650, 1202, 1033, 933, 688 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{18}H_{16}NO_3$ $[M + H]^+$ 294.1140, Found 294.1133.

(*E*)-4-Methoxy-2-(4-(trimethylsilyl)but-3-ynyl)benzaldehyde oxime (1g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.14 (s, 9H), 2.58-2.43 (t, *J* 7.5 Hz, 2H), 3.02-2.91 (t, *J* 7.5 Hz, 2H), 3.82 (s, 3H), 6.85-6.72 (m, 2H), 7.69-7.57 (d, *J* 7.6, 1H), 8.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 148.8, 141.1, 128.8, 122.6, 115.6, 112.6, 105.9, 85.8, 55.2, 32.3, 21.8, 0.1. FT-IR: 2957, 2915, 2173, 1604, 1504, 1249, 1042, 842 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{15}H_{22}NOSi$ $[M + H]^+$ 276.1420, Found 276.1418.

(*E*)-3-Styryl-3,4-dihydroisoquinoline 2-oxide (2a). To a 3-mL screw-capped vial equipped with a magnetic stirring bar was added **1a** (0.05 mmol, 13 mg), $Pd(PPh_3)_4$ (0.005 mmol, 5.8 mg), PhCOOH (0.02 mmol, 2.6 mg), 1,4-dioxane (1 mL) under argon atmosphere. The mixture was stirred for 2 h at 100 °C. The reaction process

was monitored by TLC (hexane/ethyl acetate, 10/1). After consumption of the starting material **1a**, the reaction mixture was cooled to room temperature and filtered through a short column with the use of ethyl acetate as eluent. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 30/1~10/1) to provide the desired product **2a** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.19-3.04 (m, 1H), 3.67-3.51 (m, 1H), 4.80-4.68 (m, 1H), 6.31-6.16 (dd, *J* 7.3, 15.8 Hz, 1H), 6.78-6.70 (d, *J* 15.8 Hz, 1H), 7.35-7.26 (m, 5H), 7.42-7.38 (m, 2H), 7.54-7.50 (m, 2H), 7.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 134.6, 132.9, 132.1, 131.9, 128.5, 128.4, 127.7, 127.4, 126.7, 125.4, 124.7, 123.1, 70.5, 33.5. FT-IR (KBr): 2917, 2849, 1436, 1179, 1118, 721, 694, 541 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{17}H_{16}NO$ $[M + H]^+$ 250.1232, Found 250.1242.

(*E*)-3-(4-Methoxystyryl)-3,4-dihydroisoquinoline 2-oxide (2b). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15-3.07 (m, 1H), 3.52-3.44 (m, 1H), 3.71 (s, 3H), 4.81-4.72 (m, 1H), 6.16-6.03 (m, 1H), 6.74-6.69 (m, 1H), 7.30-7.20 (m, 5H), 7.56-7.53 (m, 3H), 7.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 134.5, 132.2, 132.1, 130.0, 128.6, 128.5, 128.3, 128.0, 127.9, 127.7, 120.4, 113.9, 70.2, 55.2, 33.5. FT-IR (KBr): 3058, 2913, 1704, 1509, 1247, 1119, 720, 540 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1338, Found 280.1340.

(*E*)-3-(2,6-Dimethylstyryl)-3,4-dihydroisoquinoline 2-oxide (2c). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 6H), 3.16-3.07 (m, 1H), 3.67-3.51 (m, 1H), 4.81-4.68 (m, 1H), 6.25-6.16 (dd, *J* 7.3, 15.8 Hz, 1H), 6.72-6.62 (d, *J* 15.8 Hz, 1H), 6.86 (s, 1H), 6.93 (s, 2H), 7.19-7.13 (m, 1H), 7.32-7.22 (m, 3H), 7.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 135.6, 134.8, 133.7, 129.9, 129.6, 128.9, 128.2, 127.8, 127.7, 125.5, 124.6, 122.6, 70.4, 33.5, 21.1. FT-IR (KBr): 2916, 1599, 1552, 1247, 1178, 962, 681 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{19}H_{20}NO$ $[M + H]^+$ 278.1545, Found 278.1541.

(*E*)-3-(4-(Methoxycarbonyl)styryl)-3,4-dihydroisoquinoline 2-oxide (2d). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.19-3.05 (m, 1H), 3.53-3.42 (m, 1H), 3.88 (s, 3H), 4.90-4.82 (m, 1H), 6.43-6.28 (m, 1H), 6.82-6.73 (m, 1H), 7.27-7.21 (m, 3H), 7.46-7.42 (m, 3H), 7.56-7.53 (m, 2H), 7.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 140.0, 133.8, 133.2, 132.2, 132.1, 130.0, 129.8, 128.6, 128.4, 128.3, 127.9, 126.7, 125.5, 70.1, 52.1, 33.3. FT-IR (KBr): 3057, 2916, 1716, 1603, 1436, 1282, 721, 541 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{19}H_{18}NO_3$ $[M + H]^+$ 308.1287, Found 308.1284.

(*E*)-6-Methoxy-3-styryl-3,4-dihydroisoquinoline 2-oxide (2e). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10-3.02 (m, 1H), 3.60-3.51 (m, 1H), 3.83 (s, 3H), 4.81-4.68 (m, 1H), 6.31-6.16 (m, 1H), 6.85-6.69 (m, 3H), 7.12-7.08 (m, 1H), 7.35-7.18 (m, 5H), 7.77 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 135.7, 134.5, 133.7, 130.9, 128.5, 128.2, 127.2, 126.7, 123.2, 120.8, 114.3, 112.6, 69.7, 55.4, 33.8. FT-IR (KBr): 3057, 2918, 1705, 1602, 1437, 1258, 1119, 721, 694, 541 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1338, Found 280.1339.

(*E*)-7-Styryl-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline 6-oxide (2f). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06-2.98 (m, 1H), 3.56-3.47 (m, 1H), 4.74-4.65 (m, 1H), 6.00 (s, 2H), 6.27-6.23 (m, 1H), 6.64 (s, 1H), 6.77-6.69 (m, 2H), 7.37-7.20 (m, 5H), 7.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 134.8, 134.6, 129.9, 128.6, 128.5, 128.4, 126.7, 124.2, 122.8, 121.2, 108.8, 106.1, 101.7, 69.4, 33.4. FT-IR (KBr): 2916, 1621, 1502, 1483, 1244, 1034, 930, 692 cm^{-1}. HRMS-ESI (*m/z*) $[M]^+$ calcd for $C_{18}H_{16}NO_3$ $[M + H]^+$ 294.1140, Found 294.1123.

Acknowledgements

Supported by the State Key Program of National Natural Science Foundation of China (Grant No. 21436007). Key Basic Research Projects of Science and Technology Commission of Shanghai (14JC1403100). The Program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning (ZXDF160002). Supported by State Key Laboratory of Fine Chemicals (KF1411).

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