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One-pot two-step synthesis of 1-position arylated 1,3-disubstituted isoquinoline *N*-oxides

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ABSTRACT

A one-pot two-step reaction of 2-alkynylbenzaldoximes with aryl halides has been developed, which offers the 1-position arylated 1,3-disubstituted isoquinoline *N*-oxides in moderate to good yields in most cases. The isoquinoline *N*-oxide intermediate was prepared in situ without isolation.

1. Introduction

Diversity-oriented synthesis[1] (DOS) is an emerging field involving the synthesis of combinatorial libraries of diverse small molecules. One important theme in DOS is the development of tandem reactions[2] for the efficient construction of complex structures in a single step from simple starting materials. Among the tandem reactions, much attention has been paid to the multicatalytic tandem processes,[3,4] the transformation where one or more catalysts are involved in at least two distinct catalytic bond forming steps in one-pot, without isolation of intermediate species. Multicomponent reactions (MCRs) in one-pot for DOS is another promising strategy.[5] Recently, one of us has reported multicatalytic tandem processes for the synthesis of tetrahydro-1,2-oxazine fused 1,2-dihydroisoquinolines[4g] and MCRs for the synthesis of 1,2-dihydroisoquinolines[5d] in one-pot.

The chemistry of 2-alkynylbenzaldoximes **1** mediated with transition metals, Lewis acids or electrophiles to generate isoquinoline *N*-oxides, which then undergoes various transformations to afford versatile useful isoquinoline derivatives has been well studied by several groups such as those of Wu[4g,6] and Shin.[7] For instance, Wu and co-workers disclosed the Lewis acid- or electrophiles-mediated tandem reactions of 2-alkylbenzaldoximes, leading to the library of isoquinoline derivatives.[4g,6]

As a privileged fragment, isoquinoline core shows remarkable biological activities.[8] Among these, isoquinoline *N*-oxide as one of isoquinoline derivatives possesses its own properties, such as to be used as a chiral scaffold in Lewis basic organocatalysis[9] or charge-transfer and metal (Li^+/Mg^{2+}) sensor and radical initiator for atom-transfer radical polymerization.[10] In addition, isoquinoline *N*-oxide can be readily reduced to the corresponding isoquinoline by Pd/C with ammonium formate at room temperature in good to excellent yield.

Recently, efficient methods for the synthesis of 1,3-disubstituted isoquinoline *N*-oxide have been demonstrated.[4g,6] However, only scattered examples of arylation in 1-position have been described and the isoquinoline *N*-oxides must be prepared and isolated in advance by oxidation of isoquinoline.[11] For example, Chang and co-workers disclosed Pd-catalyzed direct arylation of isoquinoline *N*-oxides using unactivated benzene.[11a] Fagnou reported the palladium-catalyzed direct arylation of isoquinoline *N*-oxides.[11d] Therefore, developing efficient and combinatorial synthetic methods for construction of functionalized isoquinoline *N*-oxides is still desirable. Herein, we report an efficient and general method for the preparation of 1-position arylated 1,3-disubstituted isoquinoline *N*-oxides via one-pot two-step process: Ag-catalyzed intramolecular addition–cyclization/Pd-catalyzed direct arylation of 2-alkynylbenzaldoximes **1**.

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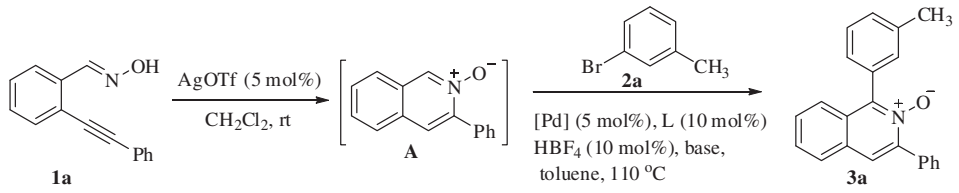
2. Results and discussions

As described above,[6e,7b] isoquinoline *N*-oxide **A** could be easily obtained via AgOTf-catalyzed cyclization of 2-alkynylbenzaldoxime **1a** at room temperature. Then the reaction of **1a** with **2a** was selected for optimization of reaction conditions. At the outset, various bases (K_2CO_3, Cs_2CO_3, $NaHCO_3$, DABCO, and DBU) were employed in the reaction. To our delight, we observed the formation of the desired cross-coupling product **3a** in 28% yield, when K_2CO_3 was employed in the reaction in the presence of AgOTf (5 mol %), $Pd(OAc)_2$ (5 mol %), and PCy_3 (10 mol %) in toluene at 110 °C (Table 1, entry 1). Product of arene homo-coupling was the main side product. Other bases such as Cs_2CO_3, $NaHCO_3$, DABCO, or DBU were unreactive (Table 1, entries 2–5). As described by Fagnou,[11b–d] palladium-catalyzed direct arylation of pyridine, diazine, and thiazole *N*-oxides occurred in high yield in the presence of K_2CO_3. Subsequent investigations showed that the result could be dramatically improved in the presence of HBF_4 (10 mol %) as additive (52% yield, Table 1, entry 6). At first, we think $AgBF_4$ was prepared in situ by HBF_4-mediated and then used as a catalyst in the reaction. Absence of HBF_4, using $AgBF_4$ instead of AgOTf as catalyst, desired product could not be found. Then the role of HBF_4 was deemed to form complex PR_3–HBF_4, which promoted the reaction.[11b–d] No product was generated when the reaction was employed in polar solvent such as DMF, DMA, DMSO, and 1,4-dioxane (Table 1, entries 7–10). We next studied the reactivity in the presence of a number of structurally varied ligands. We observed that on changing the ligand from tricyclohexylphosphine (L1) to tri-*p*-tolylphosphine (L2) to 2-(di-*tert*-butylphosphino)biphenyl (L3, JohnPhos), the yield remained almost the same (Table 1, entries 6, 11, and 12). An unsatisfactory reactivity was observed in the case of using the 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (L4, XantPhos) ligand (Table 1, entry 13). Different palladium(II) precatalysts were also employed in the reaction. $PdCl_2$ was proved to be the most efficient and the corresponding product **3a** was afforded in 67% yield (Table 1, entry 14). Inferior results were observed when other palladium(II) complexes [$PdCl_2(PhCN)_2$, $PdCl_2(CH_3CN)_2$, and $PdCl_2(PPh_3)_2$] were employed in the reaction (Table 1, entries 15–17).

With this promising result in hand, we started to investigate the scope of this reaction under optimized conditions [AgOTf (5 mol %), $PdCl_2$ (5 mol %), JohnPhos (10 mol %), HBF_4 (10 mol %), K_2CO_3 (2.0 equiv), toluene, 110 °C]. A variety of 1,3-disubstituted isoquinoline *N*-oxides were generated under the standard experimental conditions (Tables 2 and 3). As shown in Table 2, we found that the optimized conditions allowed us to perform a broad range of arylation reactions of isoquinoline *N*-oxide **A** with various aryl halides, including aryl bromides and aryl iodides with electron-withdrawing or electron-donating groups on the phenyl rings in one-pot. The expected 1,3-diarylated isoquinoline *N*-oxides were

Table 1
Optimization of reaction conditions[a]



Entry	[Pd]	Ligand	Additive	Base	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	L1	—	K_2CO_3	Toluene	28
2	$Pd(OAc)_2$	L1	—	Cs_2CO_3	Toluene	—
3	$Pd(OAc)_2$	L1	—	$NaHCO_3$	Toluene	—
4	$Pd(OAc)_2$	L1	—	DABCO	Toluene	—
5	$Pd(OAc)_2$	L1	—	DBU	Toluene	—
6	$Pd(OAc)_2$	L1	HBF_4	K_2CO_3	Toluene	52
7	$Pd(OAc)_2$	L1	HBF_4	K_2CO_3	DMF	—
8	$Pd(OAc)_2$	L1	HBF_4	K_2CO_3	DMA	—
9	$Pd(OAc)_2$	L1	HBF_4	K_2CO_3	DMSO	—
10	$Pd(OAc)_2$	L1	HBF_4	K_2CO_3	1,4-Dioxane	—
11	$Pd(OAc)_2$	L2	HBF_4	K_2CO_3	Toluene	51
12	$Pd(OAc)_2$	L3	HBF_4	K_2CO_3	Toluene	54
13	$Pd(OAc)_2$	L4	HBF_4	K_2CO_3	Toluene	22
14	$PdCl_2$	L3	HBF_4	K_2CO_3	Toluene	67
15	$PdCl_2(PhCN)_2$	L3	HBF_4	K_2CO_3	Toluene	18
16	$PdCl_2(CH_3CN)_2$	L3	HBF_4	K_2CO_3	Toluene	31
17	$PdCl_2(PPh_3)_2$	L3	HBF_4	K_2CO_3	Toluene	49

[a] Reaction conditions: 2-(phenylethynyl)benzaldehyde oxime **1a** (0.6 mmol, 2.0 equiv), AgOTf (5 mol %), 1-bromo-3-methylbenzene **2a** (0.3 mmol), [Pd] 5 mol %, ligand (10 mol %), additive (10 mol %), base (2.0 equiv).
[b] Isolated yield of **3a** based on **2a**.

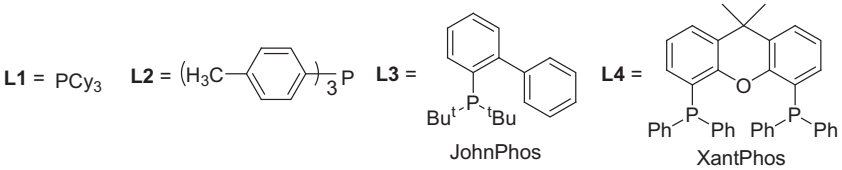
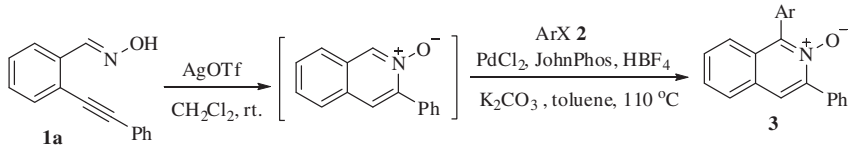
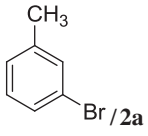
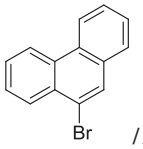
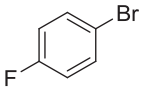
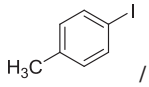
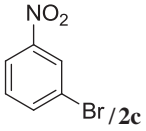
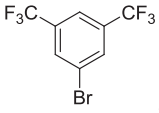
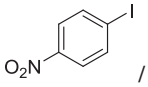


Table 2
One-pot two-step addition–cyclization/arylation reactions of oxime **1a** and various aryl halides **2**[a]



Entry	ArX/**2**	Product **3**	Yield[b] %	Entry	ArX/**2**	Product **3**	Yield[b] %
1	 /**2a**	**3a**	67	5	 /**2e**	**3e**	80
2	 /**2b**	**3b**	45	6	 /**2f**	**3f**	78
3	 /**2c**	**3c**	77	7	 /**2g**	**3g**	36
4	 /**2d**	**3d**	60	8	 /**2h**	**3h**	52

[a] Reaction conditions: 2-(phenylethynyl)benzaldehyde oxime **1a** (0.6 mmol, 2.0 equiv), AgOTf (5 mol %), aryl halide **2** (0.3 mmol), $PdCl_2$ 5 mol %, JohnPhos (10 mol %), HBF_4 (10 mol %), K_2CO_3 (2.0 equiv).
[b] Isolated yield of **3** based on **2**.

obtained in moderate to good yields in most cases (Table 2). For instance, 2-alkynylbenzaldoxime **1a** reacted with 1-bromo-3-nitrobenzene **2c** leading to the desired product **3c** in 77% yield (Table 2, entry 3), while a 78% yield of product **3f** was obtained when 1-iodo-4-methylbenzene **2f** was employed in the reaction (Table 2, entry 6).

Then we investigated the substrates scope of the one-pot multicatalytic cascade reactions between aryl halides **2** and substituted 2-alkynylbenzaldoxime **1**. The results were shown in Table 3. To our delight, the one-pot Ag-catalyzed addition–cyclization/Pd-catalyzed arylation reaction occurred with a range of 2-alkynylbenzaldoxime **1** (R^1=aryl), including phenyl and phenyl rings substituted with electron-rich and electron-poor groups, leading to the corresponding product in moderate to good yields in most cases. For instance, **1c** reacted with **2a** to give the desired 1-aryl isoquinoline *N*-oxide **3j** in 71% yield. When R^1 was changed to alkyl group, the results are not very well. The reactions can occur smoothly to afford the corresponding products in moderate yields, when R^1=cyclopropyl (Table 3, entries 9 and 10). For example, the reaction of compound **1f** with **2b** furnished the desired product **3q** in 42% yield (Table 3, entry 9). To other substituents, such as $SiMe_3$, H, and ^{n}Bu (R^1), the reactions could not occur (Table 3, entries 11–13). Subsequently, we were pleased to find that 2-alkynylbenzaldoximes **1** with an electron-withdrawing group (R^2=F) were also suitable substrates under the optimized reaction conditions (Table 3, entries 14–18). For instance, reaction of 2-alkynylbenzaldoxime **1k** and **2f** gave rise to the 7-fluoro-3-phenyl-1-*p*-tolylisoquinoline 2-oxide **3w** in 92% yield (Table 3, entry 18).

Subsequently, under the standard experimental conditions, we investigated the reaction of isoquinoline *N*-oxide **A** with vinyl halide [(*E*)-(2-bromovinyl)benzene], but the desired product wasn't observed (Scheme 1).

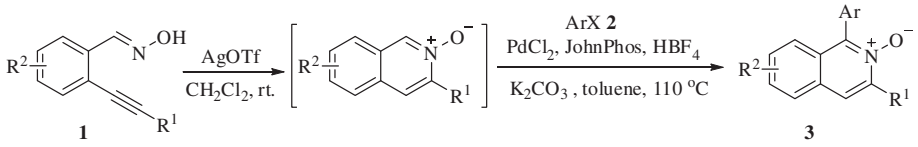
In summary, we have described an interesting method for the synthesis of 1-position arylated 1,3-disubstituted isoquinoline *N*-oxide using a one-pot two-step process: Ag-catalyzed intramolecular addition–cyclization/Pd-catalyzed direct arylation of 2-alkynylbenzaldoximes. The isoquinoline *N*-oxide intermediate was prepared in situ without isolation. These compounds should find wide applications in synthetic and medicinal chemistry both in academia and in industry.

3. Experimental section

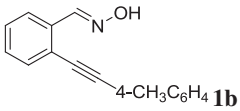
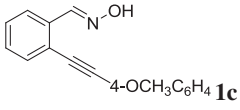
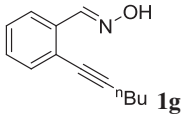
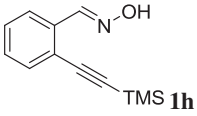
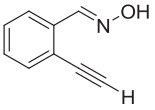
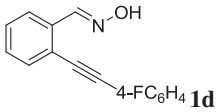
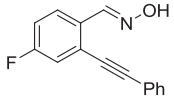
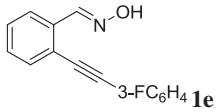
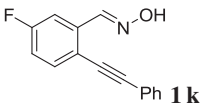
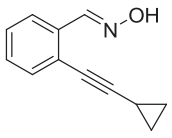
3.1. General procedure for one-pot two-step synthesis of 1-position arylated 1,3-disubstituted isoquinoline *N*-oxides from 2-alkynylbenzaldoximes 1 with aryl halides 2

A mixture of 2-alkynylbenzaldoxime **1** (0.6 mmol, 2.0 equiv) and AgOTf (5 mol %) in CH_2Cl_2 (2.0 mL) was stirred at room temperature under nitrogen atmosphere for 2 h, until 2-alkynylbenzaldoxime **1** was completed consumed. The solvent was removed under reduced pressure. A mixture of $PdCl_2$ 5 mol %, JohnPhos (10 mol %), and HBF_4 (10 mol %) in toluene (2.0 mL) was added to the residue. After 5 min, the mixture of aryl halide **2** (0.3 mmol) and K_2CO_3 (2.0 equiv) was added, and allowed to stir at 110 °C for overnight under nitrogen atmosphere. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature. The solvent was evaporated, residue was diluted with EtOAc (10 mL), washed with H_2O (10 mL) and brine (10 mL), dried by anhydrous $MgSO_4$. Evaporation of the solvent followed

Table 3
One-pot two-step addition–cyclization/arylation reactions of oximes **1** and various aryl halides **2**[a]



1 **3**

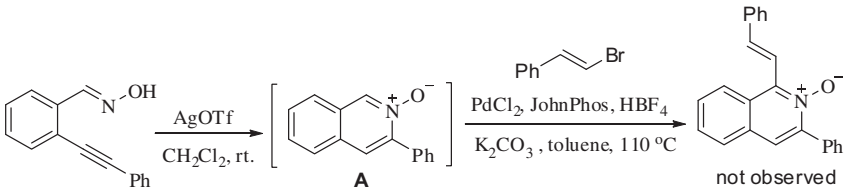
Entry	1	2	3	Yield[b] %	Entry	1	2	3	Yield[b] %
1	 4-$CH_3C_6H_4$ **1b**	**2a**	**3i**	67	10	**1f**	**2c**	**3r**	64
2	 4-$OCH_3C_6H_4$ **1c**	**2a**	**3j**	71	11	 ^nBu **1g**	**2a**	—	—
3	**1c**	**2c**	**3k**	45	12	 TMS **1h**	**2a**	—	—
4	**1c**	**2e**	**3l**	75	13	 H **1i**	**2a**	—	—
5	 4-FC_6H_4 **1d**	**2a**	**3m**	58	14	 Ph **1j**	**2a**	**3s**	67
6	**1d**	**2c**	**3n**	66	15	**1j**	**2b**	**3t**	43
7	**1d**	**2e**	**3o**	38	16	**1j**	**2c**	**3u**	53
8	 3-FC_6H_4 **1e**	**2e**	**3p**	43	17	 Ph **1 k**	**2a**	**3v**	81
9	 **1f**	**2b**	**3q**	42	18	**1k**	**2f**	**3w**	92

[a] Reaction conditions: 2-(phenylethynyl)benzaldehyde oxime **1** (0.6 mmol, 2.0 equiv), AgOTf (5 mol %), aryl halide **2** (0.3 mmol), $PdCl_2$ 5 mol %, JohnPhos (10 mol %), HBF_4 (10 mol %), K_2CO_3 (2.0 equiv).
[b] Isolated yield of **3** based on **2**.

purification by column chromatograph over silica gel provided the corresponding product **3**.

3.1.1. 3-Phenyl-1-m-tolylisoquinoline 2-oxide ***3a***. Yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 7.23–7.40 (m, 11H), 7.67–7.79 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 124.1, 125.6, 126.9, 127.3, 127.9, 128.3, 128.6, 128.7, 129.0, 129.2, 129.3, 130.0, 130.2, 130.8, 131.6, 133.5, 138.3, 147.0, 147.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{18}NO^+$: 312.1388; found: 312.1397.

3.1.2. 1-(4-Fluorophenyl)-3-phenylisoquinoline 2-oxide ***3b***. Yield: 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.29 (m, 2H), 7.42–7.51 (m, 5H), 7.54–7.60 (m, 3H), 7.80–7.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.7 (d, $^2J_{C-F}$=22 Hz), 123.2, 124.2, 125.9, 126.4, 127.0,



Scheme 1. Reaction of 2-(phenylethynyl)benzaldehyde oxime **1a** with (*E*)-(2-bromovinyl)benzene.

127.2, 127.7, 127.9, 128.2, 129.0, 131.5 (d, $^2J_{C-F}$=8 Hz), 132.2, 144.6, 146.2, 162.0 (d, $^1J_{C-F}$=248 Hz); HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{15}FNO^+$: 316.1138; found: 316.1132.

3.1.3. 1-(3-Nitrophenyl)-3-phenylisoquinoline 2-oxide ***3c***. Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J*=8.4 Hz, 1H), 7.47–7.52 (m, 3H), 7.55 (t, *J*=7.6 Hz, 1H), 7.63 (t, *J*=7.6 Hz, 1H), 7.80 (t, *J*=8.0 Hz, 1H), 7.82–7.85 (m, 2H), 7.89 (d, *J*=8.0 Hz, 1H), 7.94 (s, 1H), 7.99 (d, *J*=7.6 Hz, 1H), 8.41 (d, *J*=8.0 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.2, 124.5, 124.9, 125.9, 127.3, 128.1, 128.5, 128.8, 129.4, 129.5, 129.7, 130.0, 132.7, 133.1, 137.0, 143.9, 144.1, 147.2, 148.4; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{15}N_2O_3^+$: 343.1083; found: 343.1073.

3.1.4. 1-(3,5-Bis(trifluoromethyl)phenyl)-3-phenylisoquinoline 2-oxide ***3d***. Yield: 66%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (d, *J*=8.0 Hz, 1H), 7.47–7.53 (m, 3H), 7.58–7.69 (m, 2H), 7.79–7.86 (m, 2H), 8.07 (d, *J*=8.0 Hz, 1H), 8.29 (d, *J*=8.8 Hz, 2H), 8.36 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 121.4, 121.8 (q, $^1J_{C-F}$=273 Hz), 122.4, 124.1, 126.2, 126.6, 127.4, 127.8, 128.0, 128.5, 129.9, 130.0, 130.3, 131.5, 132.7, 141.3, 145.2; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{14}F_6NO^+$: 434.0980; found: 434.0982.

3.1.5. 1-(Phenanthren-9-yl)-3-phenylisoquinoline 2-oxide ***3e***. Yield: 80%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (t, *J*=8.4 Hz, 2H), 7.40–7.49 (m, 5H), 7.57 (t, *J*=7.2 Hz, 1H), 7.64–7.70 (m, 2H), 7.76 (t, *J*=7.6 Hz, 1H), 7.84–7.89 (m, 3H), 7.94 (d, *J*=8.0 Hz, 1H), 7.97 (d, *J*=8.0 Hz, 1H), 8.09 (s, 1H), 8.81 (t, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 121.5, 121.9, 123.5, 123.6, 124.6, 125.7, 125.8, 125.9, 126.0, 126.5, 127.1, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.5, 128.7, 129.2, 129.4, 129.9, 132.0, 144.1, 144.5; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{29}H_{20}NO^+$: 398.1545; found: 398.1539.

3.1.6. 3-Phenyl-1-p-tolylisoquinoline 2-oxide ***3f***. Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.37 (d, *J*=8.0 Hz, 2H), 7.43–7.49 (m, 6H), 7.50–7.57 (m, 3H), 7.80–7.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 123.9, 125.7, 125.9, 126.8, 127.9, 128.1, 128.4, 128.5, 129.1, 129.3, 129.5, 130.1, 130.2, 133.4, 139.1, 146.8, 147.2; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{18}NO^+$: 312.1388; found: 312.1386.

3.1.7. 1,3-Diphenylisoquinoline 2-oxide ***3g***. Yield: 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.49 (m, 6H), 7.50–7.60 (m, 5H), 7.81–7.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.1, 125.5, 126.9, 128.0, 128.2, 128.5, 128.6, 129.0, 129.1, 129.2, 130.1, 130.3, 131.6, 133.4, 146.6, 147.2; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{16}NO^+$: 298.1232; found: 298.1228.

3.1.8. 1-(4-Nitrophenyl)-3-phenylisoquinoline 2-oxide ***3h***. Yield: 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*=8.8 Hz, 1H), 7.44–7.50 (m, 3H), 7.53 (t, *J*=7.2 Hz, 1H), 7.61 (t, *J*=8.0 Hz, 1H), 7.78–7.84 (m, 4H), 7.87 (d, *J*=8.0 Hz, 1H), 7.92 (s, 1H), 8.44 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.9, 124.4, 124.9, 127.3, 128.1, 128.4, 128.6, 129.2, 129.3, 129.5, 130.0, 131.9, 132.7, 138.3, 144.2, 147.3, 148.2; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{15}N_2O_3^+$: 343.1083; found: 343.1077.

3.1.9. 1-m-Tolyl-3-p-tolylisoquinoline 2-oxide ***3i***. Yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.43 (s, 3H), 7.25–7.29 (m, 3H), 7.29–7.36 (m, 2H), 7.38 (s, 1H), 7.42–7.48 (m, 3H), 7.50–7.55 (m, 1H), 7.75–7.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.5, 123.7, 125.6, 126.8, 127.3, 128.1, 128.4, 128.5, 128.6, 128.9, 129.2, 129.9, 130.0, 130.4, 130.7, 131.6, 138.3, 139.2, 146.8, 147.3; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{20}NO^+$: 326.1545; found: 326.1551.

3.1.10. 3-(4-Methoxyphenyl)-1-m-tolylisoquinoline 2-oxide ***3j***. Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.84 (s, 3H), 6.97 (d, *J*=7.6 Hz, 2H), 7.32 (d, *J*=6.8 Hz, 2H), 7.37 (s, 1H), 7.40–7.53 (m, 4H), 7.78 (d, *J*=8.4 Hz, 1H), 7.80 (s, 1H), 7.84 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 55.4, 113.3, 123.4, 125.6, 125.7, 126.7, 127.2, 128.1, 128.3, 128.6, 128.8, 129.2, 129.9, 130.7, 131.6, 138.3, 146.9, 160.3; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{20}NO_2^+$: 342.1494; found: 342.1489.

3.1.11. 3-(4-Methoxyphenyl)-1-(3-nitrophenyl)isoquinoline 2-oxide ***3k***. Yield: 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 7.00 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 1H), 7.50 (t, *J*=8.0 Hz, 1H), 7.57–7.62 (m, 1H), 7.76 (t, *J*=7.6 Hz, 1H), 7.81 (d, *J*=8.0 Hz, 2H), 7.86 (d, *J*=8.0 Hz, 1H), 7.90 (s, 1H), 7.95 (d, *J*=7.6 Hz, 1H), 8.39 (d, *J*=8.0 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 122.1, 122.3, 124.1, 124.3, 124.4, 125.1, 125.9, 127.1, 128.3, 128.5, 129.1, 129.3, 129.7, 131.5, 133.3, 137.0, 147.0, 148.5, 160.6; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{17}N_2O_4^+$: 373.1188; found: 373.1183.

3.1.12. 3-(4-Methoxyphenyl)-1-(phenanthren-9-yl)isoquinoline 2-oxide ***3l***. Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.97 (d, *J*=8.8 Hz, 2H), 7.31–7.38 (m, 3H), 7.46 (t, *J*=7.6 Hz, 1H), 7.51–7.55 (m, 1H), 7.60–7.67 (m, 2H), 7.73 (t, *J*=7.6 Hz, 1H), 7.82–7.93 (m, 5H), 7.96 (s, 1H), 8.78 (t, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 113.4, 122.8, 123.2, 123.8, 125.4, 126.0, 126.7, 126.8, 127.0, 127.4, 127.6, 128.3, 128.6, 129.0, 129.2, 129.5, 129.6, 129.9, 130.7, 131.0, 131.4, 131.6, 146.0, 147.1, 160.4; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{30}H_{22}NO_2^+$: 428.1651; found: 428.1645.

3.1.13. 3-(4-Fluorophenyl)-1-m-tolylisoquinoline 2-oxide ***3m***. Yield: 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 7.05 (t, *J*=8.4 Hz, 2H), 7.24 (d, *J*=7.2 Hz, 2H), 7.28 (s, 1H), 7.36–7.40 (m, 3H), 7.43–7.49 (m, 1H), 7.72 (d, *J*=8.4 Hz, 1H), 7.73 (s, 1H), 7.77 (d, *J*=8.4 Hz, 1H), 7.78 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 114.9 (d, $^2J_{C-F}$=22 Hz), 123.8, 125.7, 126.8, 127.2, 128.3, 128.6, 128.7, 129.1 (d, $^3J_{C-F}$=8 Hz), 129.3, 130.0, 130.6, 131.4, 132.2 (d, $^3J_{C-F}$=9 Hz), 138.4, 146.1, 147.0, 163.2 (d, $^1J_{C-F}$=248 Hz); HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{17}FNO^+$: 330.1294; found: 330.1299.

3.1.14. 3-(4-Fluorophenyl)-1-(3-nitrophenyl)isoquinoline 2-oxide ***3n***. Yield: 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90–7.20 (m, 2H), 7.40 (s, 1H), 7.54–7.61 (m, 2H), 7.77–7.98 (m, 6H), 8.39 (d, *J*=6.0 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.2 (d, $^2J_{C-F}$=22 Hz), 124.2, 124.5, 124.8, 125.9, 127.3, 128.5, 128.8, 129.2, 129.5, 129.8, 132.0, 132.1 (d, $^3J_{C-F}$=8 Hz), 133.2, 136.9, 143.9, 146.2, 148.5, 163.3 (d, $^1J_{C-F}$=249 Hz); HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{14}FN_2O_3^+$: 361.0988; found: 361.0989.

3.1.15. 3-(4-Fluorophenyl)-1-(phenanthren-9-yl)isoquinoline 2-oxide ***3o***. Yield: 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J*=8.8 Hz, 2H), 7.35–7.40 (m, 3H), 7.47 (t, *J*=7.6 Hz, 1H), 7.55–7.59 (m, 1H), 7.61–7.69 (m, 2H), 7.74 (t, *J*=7.2 Hz, 1H), 7.85 (s, 1H), 7.88–7.95 (m, 4H), 7.98 (s, 1H), 8.79 (t, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.0 (d, $^2J_{C-F}$=21 Hz), 122.8, 123.3, 124.3, 125.5, 125.8, 126.8, 126.9, 127.1, 127.4, 127.6, 128.5, 128.7, 128.9, 129.0, 129.1, 129.2, 129.6, 129.8, 130.7, 131.1, 131.4, 132.2 (d, $^3J_{C-F}$=8 Hz), 146.2, 146.3, 163.4 (d, $^1J_{C-F}$=247 Hz); HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{29}H_{19}FNO^+$: 416.1451; found: 416.1456.

3.1.16. 3-(3-Fluorophenyl)-1-(phenanthren-9-yl)isoquinoline 2-oxide ***3p***. Yield: 43%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J*=8.8 Hz, 1H), 7.32–7.50 (m, 5H), 7.53–7.70 (m, 4H), 7.72–7.76 (m, 2H), 7.85 (s, 1H), 7.89–7.92 (m, 2H), 8.01 (s, 1H), 8.79 (t, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.3 (d, $^2J_{C-F}$=21 Hz), 117.3 (d, $^2J_{C-F}$=23 Hz), 122.8, 123.3, 124.7, 125.6, 125.8, 125.9, 126.9, 127.0, 127.1, 127.4, 127.7, 128.5, 128.6, 129.0, 129.2, 129.5, 129.6, 129.7, 129.8, 129.9, 130.7,

131.1, 131.3, 146.9, 146.0, 164.3(d, $^1J_{C-F}$=243 Hz); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{29}H_{19}FNO^+$: 416.1451; found: 416.1447.

3.1.17. 3-Cyclopropyl-1-(4-fluorophenyl)isoquinoline 2-oxide ***3q***. Yield: 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80–0.96 (m, 2H), 1.15–1.27 (m, 2H), 2.77 (m, 1H), 7.25–7.29 (m, 2H), 7.30–7.45 (m, 3H), 7.48–7.53 (m, 3H), 7.72 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.03, 11.2, 115.8 (d, $^2J_{C-F}$=21 Hz), 118.3, 125.2, 126.3, 127.6, 127.8, 128.0, 128.2, 129.1, 132.3 (d, $^3J_{C-F}$=8 Hz), 145.4, 150.9, 163.0 (d, $^1J_{C-F}$=248 Hz); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{18}H_{15}FNO^+$: 280.1138; found: 280.1143.

3.1.18. 3-Cyclopropyl-1-(3-nitrophenyl)isoquinoline 2-oxide ***3r***. Yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.96 (m, 2H), 1.26–1.30 (m, 2H), 2.73–2.76 (m, 1H), 7.27–7.33 (m, 1H), 7.40–7.48 (m, 2H), 7.55 (s, 1H), 7.75–7.82 (m, 2H), 7.93 (s, 1H), 8.35–8.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0, 11.1, 119.1, 124.1, 124.3, 125.8, 126.6, 127.3, 128.4, 128.5, 129.1, 129.8, 133.4, 136.9, 143.5, 148.5, 151.0; HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{18}H_{15}N_2O_3^+$: 307.1083; found: 307.1084.

3.1.19. 6-Fluoro-3-phenyl-1-m-tolylisoquinoline 2-oxide ***3s***. Yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.21–7.26 (m, 1H), 7.30–7.39 (m, 3H), 7.40–7.53 (m, 6H), 7.78 (s, 1H), 7.82–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 110.5 (d, $^2J_{C-F}$=21 Hz), 118.8 (d, $^2J_{C-F}$=25 Hz), 123.2, 126.2, 127.2, 128.0, 128.7, 129.4, 130.1, 130.2, 130.3, 130.7, 131.2, 133.0, 138.5, 147.0, 148.2, 161.9 (d, $^1J_{C-F}$=250 Hz); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{22}H_{17}FNO^+$: 330.1294; found: 330.1289.

3.1.20. 6-Fluoro-1-(4-fluorophenyl)-3-phenylisoquinoline 2-oxide ***3t***. Yield: 43%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.46 (m, 7H), 7.55–7.60 (m, 2H), 7.78–7.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.7 (d, $^2J_{C-F}$=22 Hz), 115.9 (d, $^2J_{C-F}$=21 Hz), 119.1 (d, $^2J_{C-F}$=26 Hz), 123.4, 126.2, 127.2, 128.1, 128.3 (d, $^3J_{C-F}$=9 Hz), 129.5, 130.0, 130.2 (d, $^3J_{C-F}$=10 Hz), 132.5 (d, $^3J_{C-F}$=8 Hz), 132.9, 145.8, 148.2, 161.9 (d, $^1J_{C-F}$=250 Hz), 163.2 (d, $^1J_{C-F}$=247 Hz); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{21}H_{14}F_2NO^+$: 334.1043; found: 334.1048.

3.1.21. 6-Fluoro-1-(3-nitrophenyl)-3-phenylisoquinoline 2-oxide ***3u***. Yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dt, *J*=2.4, 8.8 Hz, 1H), 7.41 (dd, *J*=5.2, 9.2 Hz, 1H), 7.47–7.52 (m, 4H), 7.76 (d, *J*=8.0 Hz, 1H), 7.79–7.83 (m, 2H), 7.87 (s, 1H), 7.95 (d, *J*=7.6 Hz, 1H), 8.40 (d, *J*=8.0 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.1 (d, $^2J_{C-F}$=21 Hz), 119.7 (d, $^2J_{C-F}$=25 Hz), 124.0, 124.3, 125.7, 125.9, 127.4 (d, $^3J_{C-F}$=9 Hz), 128.2, 129.7, 129.8, 129.9, 130.2, 130.3, 132.5, 133.0, 136.8, 144.0, 148.4 (d, $^2J_{C-F}$=23 Hz), 162.0 (d, $^1J_{C-F}$=251 Hz); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{21}H_{14}FN_2O_3^+$: 361.0988; found: 361.0983.

3.1.22. 7-Fluoro-3-phenyl-1-m-tolylisoquinoline 2-oxide ***3v***. Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.10 (dd, *J*=2.4, 10.0 Hz, 1H), 7.26–7.37 (m, 4H), 7.42–7.50 (m, 4H), 7.79–7.86 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 109.5 (d, $^2J_{C-F}$=24 Hz), 118.4 (d, $^2J_{C-F}$=24 Hz), 123.7, 126.1, 127.1, 128.0, 128.8, 129.3, 129.5 (d, $^3J_{C-F}$=9 Hz), 130.1, 130.2, 130.4, 130.5, 131.1, 133.1, 138.6, 146.4, 146.8, 162.0 (d, $^1J_{C-F}$=251 Hz); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{22}H_{17}FNO^+$: 330.1294; found: 330.1299.

3.1.23. 7-Fluoro-3-phenyl-1-p-tolylisoquinoline 2-oxide ***3w***. Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.13 (dd, *J*=2.0, 10.0 Hz, 1H), 7.28 (dd, *J*=2.0, 8.8 Hz, 1H), 7.35–7.50 (m, 7H), 7.78–7.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 109.4 (d, $^2J_{C-F}$=23 Hz), 118.3 (d, $^2J_{C-F}$=25 Hz), 123.6, 126.1, 128.0, 128.1, 129.3, 129.5, 129.6, 130.1, 130.3, 130.4, 133.2, 139.4, 146.3, 146.7, 162.0 (d, $^1J_{C-F}$=248 Hz); HRMS (ESI): *m*/*z* [M+H]$^+$ calcd for $C_{22}H_{17}FNO^+$: 330.1294; found: 330.1289.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.08.039.

References and notes

1. (a) Walsh, D. P.; Chang, Y.-T. *Chem. Rev.* **2006**, *106*, 2476; (b) Arya, P.; Chou, D. T. H.; Baek, M.-G. *Angew. Chem., Int. Ed.* **2001**, *40*, 339; (c) Schreiber, S. L. *Science* **2000**, *287*, 1964; (d) Spaller, M. R.; Burger, M. T.; Fardis, M.; Bartlett, P. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 47.
2. For reviews, see: (a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890; (b) Negishi, E.; Coprret, C.; Ma, S.; Liou, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (d) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65; (e) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217; For recent examples, see: (f) Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528; (g) Subburaj, K.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 11210; (h) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354.
3. For selected recent reviews on multicatalysis, see: (a) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754; (b) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302; (c) Wasilke, J. C.; Brey, O. S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001; (d) Enders, D.; Grondal, C.; Huttl, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570; (e) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1; (f) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477; (g) Wang, C.; Xi, Z. *Chem. Soc. Rev.* **2007**, *36*, 1395.
4. For recent selected examples, see: (a) Cernak, T. A.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 3124; (b) Kelly, B. D.; Allen, J. M.; Tundel, R. E.; Lambert, T. H. *Org. Lett.* **2009**, *11*, 1381; (c) Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; Ming, Z.-H.; Xiao, W.-J. *J. Am. Chem. Soc.* **2008**, *130*, 6946; (d) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329; (e) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320; (f) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 11152; (g) Ding, Q.; Wang, Z.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 198; (h) Gao, K.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8611.
5. (a) Weber, L.; Almstetter, M. *Synlett* **1999**, 366; (b) *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim: Germany, 2005; (c) Doemling, A. *Chem. Rev.* **2006**, *106*, 17; (d) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959.
6. For recent selected examples, see: (a) Ding, Q.; Wang, Z.; Wu, J. *J. Org. Chem.* **2009**, *74*, 921; (b) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850; (c) Ye, S.; Wang, H.; Wu, J. *Eur. J. Org. Chem.* **2010**, 6436; (d) Ye, S.; Wang, H.; Wu, J. *ACS Comb. Sci.* **2011**, *13*, 120; (e) Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702; (f) Ye, S.; Gao, K.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 1746.
7. (a) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040; (b) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, 924.
8. (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Australia, 1998; Vol. 1; (b) Phillipson, J. D.; Roberts, M. F.; Zenk, M. H. *The Chemistry and Biology of Isoquinoline Alkaloids*; Springer: New York, NY, 1985; (c) Ramesh, P.; Reddy, N. S.; Venkateswarlu, Y. *J. Nat. Prod.* **1999**, *62*, 780; (d) Kaneda, T.; Takeuchi, Y.; Matsui, H.; Shimizu, K.; Urakawa, N.; Nakajyo, S. *J. Pharmacol. Sci.* **2005**, *98*, 275.
9. (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6419; (b) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799; (c) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047; (d) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674; (e) Hrdina, R.; Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. *Adv. Synth. Catal.* **2007**, *349*, 822.
10. (a) Collado, D.; Perez-Inestrosa, E.; Suau, R. *J. Org. Chem.* **2003**, *68*, 3574; (b) Collado, D.; Perez-Inestrosa, E.; Suau, R.; Desvergne, J.-P.; Bouas-Laurent, H. *Org. Lett.* **2002**, *4*, 855; (c) Collado, D.; Perez-Inestrosa, E.; Suau, R.; Navarrete, J. T. L. *Tetrahedron* **2006**, *62*, 2927; (d) Durmaz, Y. Y.; Yilmaz, G.; Yagci, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 423.
11. (a) Cho, S.; Hwang, S.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254; (b) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020; (c) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266; (d) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.