JOC The Journal of Organic Chemistry

Article

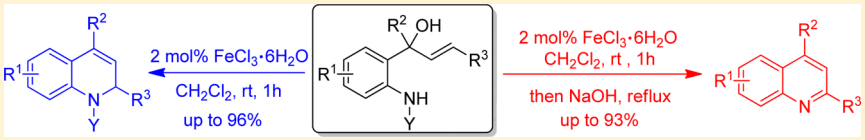
pubs.acs.org/joc

$FeCl_3·6H_2O$-Catalyzed Intramolecular Allylic Amination: Synthesis of Substituted Dihydroquinolines and Quinolines

Zhiming Wang,* Shen Li, Bin Yu, Haibo Wu, Yurong Wang, and Xiaoqiang Sun*

School of Petrochemical Engineering, Changzhou University, Changzhou, Jiangsu 213164, China

Supporting Information



ABSTRACT: A facile and efficient method to synthesize 2- or 4-substituted 1,2-dihydroquinolines and quinolines catalyzed by $FeCl_3·6H_2O$ (2 mol %) was described. The iron-catalyzed intramolecular allylic amination of 2-aminophenyl-1-en-3-ols proceeded smoothly to afford 13 1,2-dihydroquinoline and 8 quinoline derivatives under mild reaction conditions with good to excellent yields (up to 96%).

INTRODUCTION

Heterocyclic compounds, especially nitrogen-containing heterocycles, are ubiquitous in natural products and pharmaceuticals and represent the most important class of key structural units in a large number of bioactive molecules.[1] In particular, quinolines and their derivatives play an important role in the fields of natural products, medicinal chemistry, and materials chemistry.[2] In consequence, several significant methods for the quinoline framework constructions are well-known, such as the Skraup reaction,[3] Combes synthesis,[4] Gould–Jacobs reaction,[5] Friedländer synthesis,[6] and Doebner–von Miller reaction.[7] Because of their importance, the development of new synthetic methodologies of quinolines with high efficiency and mild reaction conditions is still an active research area.[8] Selected recent examples include reductive cyclizations of Baylis–Hillman adducts,[9] cascade reactions of alkynes,[8b] metal-catalyzed cyclizations with anilines,[10] and aza-Diels–Alder reactions with *N*-arylaldimines.[11]

In recent years, iron-catalyzed carbon–carbon and carbon–heteroatom bond formation processes have attracted considerable attention because iron is one of the most inexpensive and environmentally benign metals on earth.[12] Among the known methods in the literature,[13,14] the iron-catalyzed substitution reaction of alcohols with various nucleophiles has become one of the most efficient and environmentally friendly synthetic strategies for C- and N-alkylation.[15] Although the iron-catalyzed intermolecular allylic amination has been extensively studied, examples of iron-catalyzed intramolecular allylic amination between allylic alcohols and nitrogen nucleophiles are relatively limited.[15b] During the course of our ongoing study on the development of transition-metal-mediated heterocyclic compound formations,[16] we found that dihydroquinolines and quinolines could be efficiently prepared using iron catalyst under mild reaction conditions. Herein, we would like to report an efficient synthetic pathway to 2- or 4-substituted 1,2-dihydroquinolines and quinolines involving intramolecular allylic amination of *N*-protected 2-aminophenyl-1-en-3-ols catalyzed by $FeCl_3·6H_2O$ at room temperature. Unlike other methods that also utilize alcohol pro-electrophiles in 1,2-dihydroquinoline synthesis,[17] our reaction could be performed with the reaction vessel open to ambient air. Furthermore, with the same reaction setup and with the subsequent treatment of NaOH, substituted quinolines could be achieved instead.

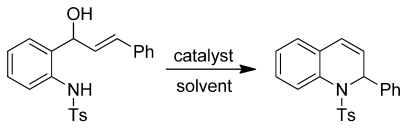
RESULTS AND DISCUSSION

Initially, we chose (*E*)-1-phenyl-3-(2-tosylaminophenyl)prop-1-en-3-ol (**1a**) to optimize the reaction conditions by varying the catalysts, solvents, and reaction temperature. The results are summarized in Table 1. Although 2-phenyl-1-tosyl-1,2-dihydroquinoline was barely detected in the absence of metal catalyst, a reaction yield of 96% was achieved in the presence of 2 mol % of $FeCl_3·6H_2O$ at room temperature (rt) in CH_2Cl_2 (entries 1 and 2). It indicated that the catalyst $FeCl_3·6H_2O$ was essential and efficient for the cyclization reaction. Increasing the catalyst loading to 5 mol % could not benefit the reaction time or the yield (entry 3). However, lowering the catalyst loading to 1 mol % led to a sluggish reaction and a moderate yield of 50% and longer reaction time (entry 4). Surprisingly, the reaction provided lower yield at elevated temperature, albeit shorter reaction time (entry 5). Among the solvents screened, the intramolecular allylic amination took place in toluene or benzene at rt (entries 6 and 8), but higher reaction temperature was needed to improve the reaction efficiency by using toluene, benzene, $CHCl_3$, CH_3NO_2, or $ClCH_2CH_2Cl$ as a reaction medium (entries 7 and 9–12). When $BF_3·Et_2O$, CF_3COOH, and TsOH were applied as the catalyst, 58–70% yields of **2a** were achieved (entries 13–15). It was noteworthy that other

Received: July 27, 2012
Published: August 30, 2012

   dx.doi.org/10.1021/jo301560w | J. Org. Chem. 2012, 77, 8615–8620

Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	catalyst	solvent	temp (°C)	time (h)	yield (%)
1		CH_2Cl_2	rt	24	trace[b]
2	$FeCl_3·6H_2O$	CH_2Cl_2	rt	1	96
3	$FeCl_3·6H_2O$	CH_2Cl_2	rt	1	95[c]
4	$FeCl_3·6H_2O$	CH_2Cl_2	rt	12	50[d]
5	$FeCl_3·6H_2O$	CH_2Cl_2	40	0.5	72
6	$FeCl_3·6H_2O$	toluene	rt	24	40[e]
7	$FeCl_3·6H_2O$	toluene	110	6	85
8	$FeCl_3·6H_2O$	benzene	rt	24	45[e]
9	$FeCl_3·6H_2O$	benzene	80	6	90
10	$FeCl_3·6H_2O$	$CHCl_3$	70	6	86
11	$FeCl_3·6H_2O$	CH_3NO_2	100	8	83
12	$FeCl_3·6H_2O$	$ClCH_2CH_2Cl$	90	5	83
13	$BF_3·Et_2O$	CH_2Cl_2	rt	12	70
14	CF_3COOH	CH_2Cl_2	rt	12	65
15	TsOH	CH_2Cl_2	rt	1	58
16	CuCl	CH_2Cl_2	rt	24	trace[b]
17	$CuCl_2$	CH_2Cl_2	rt	24	trace[b]
18	$PdCl_2$	CH_2Cl_2	rt	24	trace[b]
19	HCl	CH_2Cl_2	rt	24	trace[b]
20	CH_3COOH	CH_2Cl_2	rt	24	trace[b]

[a]0.5 mmol of **1a**, 0.01 mmol of catalyst, and 2 mL of solvent. [b]Little desired product was detected, and up to 95% starting material was recovered. [c]5 mol % of catalyst was used. [d]1 mol % of catalyst was used. [e]Up to 50% starting material was recovered.

catalyst, such as CuCl, $CuCl_2$, $PdCl_2$, HCl, and CH_3COOH, gave little desired product (entries 16–20).

With the optimized reaction conditions in hand, the reaction scope was explored with a variety of *N*-protected 2-aminophenyl-1-en-3-ols. The results are summarized in Table 2. It was found that *N*-mesyl and *N*-benzoyl 2-aminophenyl-1-en-3-ols also worked for the cyclization reactions, albeit lower reaction yield (entries 1 vs entries 3 and 4). The regioisomer of **1a** (**1a**′) could lead to the same product **2a** despite longer reaction time and lower yield (entry 2). The iron-catalyzed synthesis of substituted dihydroquinolines could tolerate a methyl group, C–F bond, C–Cl bond, and C–Br at the terminal position of the allylic alcohol moiety, giving **2d–2h** with 86–96% yields (entries 5–9). Low reaction yield was obtained when furanyl-substituted allylic alcohol **1i** was used as a substrate (entry 10). The cyclization of alcohol with *trans*-diene gave an acceptable yield of the product **2j** (entry 11). Interestingly, 4-methyl and 4-phenyl substituted 1,2-dihydroquinoline products **2k–2m** were achieved by using the standard catalyzed conditions; however, the reaction yields greatly improved in benzene at 80 °C (entries 12–17).

To probe the reaction mechanism of the $FeCl_3·6H_2O$-catalyzed intramolecular allylic amination, (*S*,*E*)-1-phenyl-3-(2-tosylamino-phenyl)prop-1-en-3-ol and (*R*,*E*)-1-phenyl-3-(2-tosylamino-phenyl)prop-1-en-3-ol were subjected to the reaction.[18] In each case, dihydroquinoline **2a** was obtained in 93–95% yield as a racemic mixture,[19] and no chirality transfer was observed (Scheme 1).

According to the literature[15,17a] and the results of our experiments, a possible mechanism for the $FeCl_3·6H_2O$-catalyzed intramolecular allylic amination of (*E*)-1-phenyl-3-(2-tosylamino-phenyl)prop-1-en-3-ol is proposed in Scheme 2. The coordination of catalyst $FeCl_3$ to the hydroxyl group of **1a** leads to intermediate **I**, and the carbocation **II** is formed by dehydration of intermediate **I**. Cyclization of the newly formed carbocation **II** follows to generate dihydroquinoline **2a**.[15b] Although we have failed to isolate the intermediate **I** or **II**, it was found that the carbocation species **II** could be trapped by EtOH under the standard reaction conditions.[20]

Encouraged by the results above, we decided to apply this new methodology to the one-pot synthesis of substituted quinolines. As shown in Table 3, the corresponding substituted quinolines could be synthesized from the same *N*-protected 2-aminophenyl-1-en-3-ols in 66–93% yields using the iron-catalyzed intramolecular allylic amination followed by basic deprotection and aromatization. Both *N*-tosyl and *N*-mesyl protected 2-aminophenyl-1-en-3-ols gave the desired final quinoline derivatives with excellent reaction yields (entries 1 and 3). Surprisingly, when *N*-benzoyl protected 2-aminophenyl-1-en-3-ol was used as the starting material, only dihydroquinoline intermediate **2c** was detected (entry 4). Methyl group, C–F bond, C–Cl bond, C–Br bond, and C=C bond at the terminal position of the allylic alcohol moiety were suitable for this reaction (entries 5–11). It was also noteworthy that the presence of small amount of ethanol in the reaction system could improve the efficiency of the detosylation-aromatization reaction (entries 1 and 2).[21]

■ CONCLUSION

In conclusion, a new method to synthesize the substituted 1,2-dihydroquinolines via an iron-catalyzed intramolecular allylic amination of *N*-protected 2-aminophenyl-1-en-3-ols under mild conditions has been developed. The advantages of our approach are the use of inexpensive and environmentally friendly $FeCl_3·6H_2O$ as the catalyst, as well as the tolerance for the presence of water and air in the reaction system. In addition, the synthetic application of this new method to the one-pot synthesis of substituted quinolines has also been demonstrated. The methodology is highly facile and efficient and can be a useful tool for the synthesis of biologically and photochemically active molecules.

■ EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial suppliers and used without further purification. All ^1H NMR and ^{13}C MNR spectra were recorded in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. The starting materials protected 2-aminophenyl-1-en-3-ols were prepared according to the literature procedures.[17a]

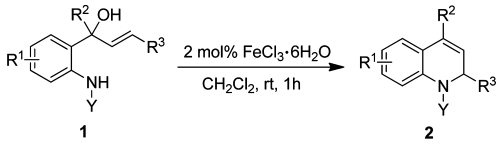
General Procedure for the Synthesis of Substituted 1,2-dihydroquinolines 2. To a solution of protected 2-aminophenyl-1-en-3-ol (0.5 mmol) in CH_2Cl_2 was added $FeCl_3·6H_2O$ (0.01 mmol). The reaction mixture was stirred at rt for 1 h (TLC monitored). The resulting mixture was purified by flash column chromatography on silical gel (petroleum ether/ethyl acetate) to give the desired pure product (**2a–m**).

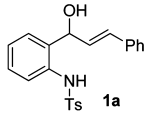
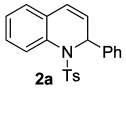
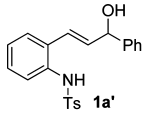
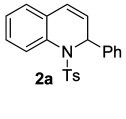
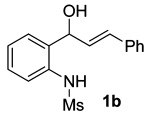
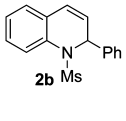
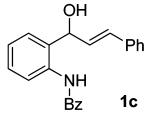
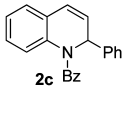
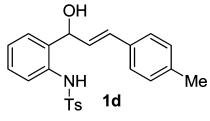
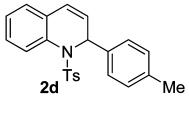
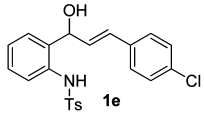
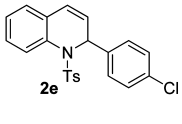
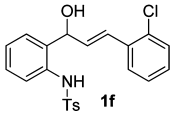
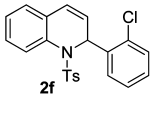
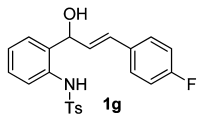
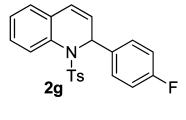
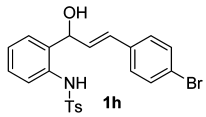
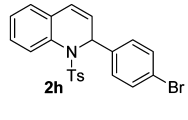
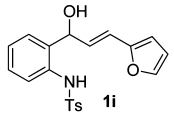
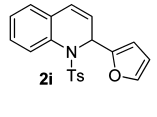
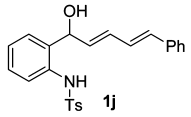
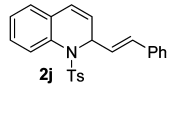
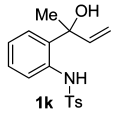
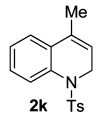
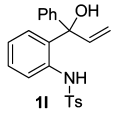
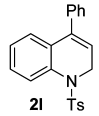
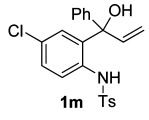
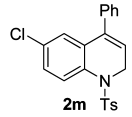
*2-Phenyl-1-tosyl-1,2-dihydroquinoline (**2a**).*[17a] 173 mg, 96% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.0 Hz, 1H), 7.34–7.33 (m, 4H), 7.24–7.18 (m, 4H), 7.14–7.08 (m, 3H), 6.96 (d, J = 7.2 Hz, 1H), 6.28 (d, J = 9.6 Hz, 1H), 6.02 (d, J = 6.0 Hz, 1H), 5.88 (dd, J = 9.6, 6.0 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 57.0, 125.5, 126.3, 126.4, 126.5, 127.2, 127.4, 127.6, 127.9, 128.2, 128.4, 128.6, 129.1, 132.9, 136.1, 138.4, 143.4; IR (neat) 3061, 2922, 1347, 1168, 687 cm^{-1}; MS (70 eV, EI) m/z = 361 [M^+].

*1-(Mesyl)-2-phenyl-1,2-dihydroquinoline (**2b**).*[21] 128 mg, 90% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6

dx.doi.org/10.1021/jo301560w | J. Org. Chem. 2012, 77, 8615–8620

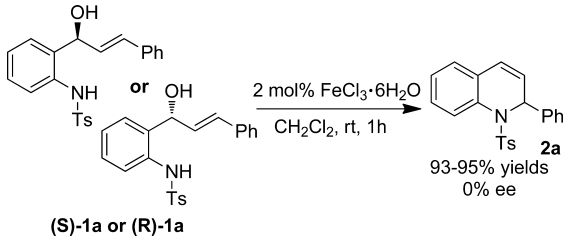
Table 2. $FeCl_3·6H_2O$-Catalyzed Intramolecular Allylic Amination for the Synthesis of Substituted Dihydroquinolines[a]



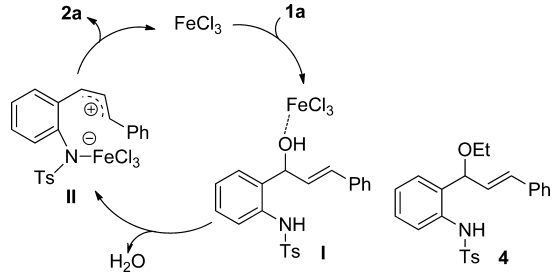
Entry	Alcohol	Product	Yield (%)
1	 **1a**	 **2a**	96
2	 **1a'**	 **2a**	84[b]
3	 **1b**	 **2b**	90
4	 **1c**	 **2c**	87
5	 **1d**	 **2d**	86
6	 **1e**	 **2e**	87
7	 **1f**	 **2f**	94
8	 **1g**	 **2g**	96
9	 **1h**	 **2h**	88
10	 **1i**	 **2i**	18
11	 **1j**	 **2j**	68
12			47
13	**1k**	**2k**	69[c]
14			52
15	**1l**	**2l**	78[c]
16			50
17	**1m**	**2m**	77[c]

[a]0.5 mmol of **1**, 0.01 mmol of $FeCl_3·6H_2O$, and 2 mL of CH_2Cl_2 at rt. [b]Reaction time of 8 h. [c]Benzene was used as a solvent instead of CH_2Cl_2 and at 80 °C.

Scheme 1. Intramolecular Allylic Amination of (*S*)-1a and (*R*)-1a



Scheme 2. Possible Mechanism for Iron-Catalyzed Intramolecular Allylic Amination of (*E*)-1-Phenyl-3-(2-tosylamino-phenyl)prop-1-en-3-ol



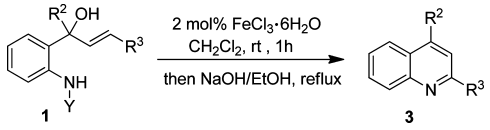
Hz, 1H), 7.34–7.32 (m, 2H), 7.25–7.17 (m, 6H), 6.81 (d, J = 9.6 Hz, 1H), 6.30 (dd, J = 9.6, 6.0 Hz, 1H), 6.00 (d, J = 6.0 Hz, 1H), 2.76 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.8, 56.9, 126.4, 126.6, 126.7, 127.0, 127.2, 127.3, 128.0, 128.4, 128.7, 132.9, 138.1; IR (neat) 3029, 2929, 1343, 1153, 760 cm^{-1}; MS (70 eV, EI) m/z = 285 [M$^+$].

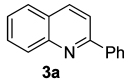
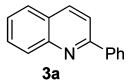
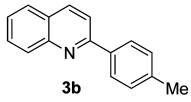
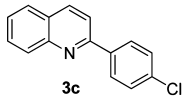
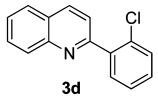
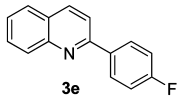
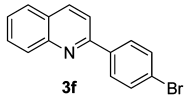
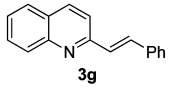
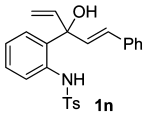
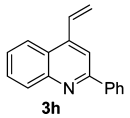
*1-(Benzoyl)-2-phenyl-1,2-dihydroquinoline (**2c**).*[22] 135 mg, 87% yield; white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (t, J = 7.2 Hz, 1H), 7.33–7.21 (m, 10H), 7.01 (t, J = 7.2 Hz, 1H), 6.89–6.82 (m, 2H), 6.58 (dd, J = 9.2, 6.0 Hz, 1H), 6.52 (d, J = 7.6 Hz, 1H), 6.23 (d, J = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 54.3, 124.9, 125.0, 125.6, 126.4, 126.7, 127.0, 127.2, 127.5, 128.2, 128.4, 128.6, 129.9, 130.4, 135.4, 135.5, 139.2, 169.4; IR (neat) 3060, 2928, 1647, 1337, 698 cm^{-1}; MS (70 eV, EI) m/z = 311 [M$^+$].

*2-(p-Tolyl)-1-tosyl-1,2-dihydroquinoline (**2d**).*[17a] 161 mg, 86% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.23–7.18 (m, 3H), 7.14–7.08 (m, 3H), 7.04 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 7.6 Hz, 1H), 6.26 (d, J = 9.6 Hz, 1H), 5.98 (d, J = 6.0 Hz, 1H), 5.87 (dd, J = 9.6, 6.0 Hz, 1H), 2.35 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.6, 56.8,

dx.doi.org/10.1021/jo301560w | J. Org. Chem. 2012, 77, 8615–8620

Table 3. $FeCl_3·6H_2O$-Catalyzed Intramolecular Allylic Amination for the Synthesis of Substituted Quinolines[a]



Entry	Alcohol	Product	Yield (%)
1	**1a**	 **3a**	93
2			48[b]
3	**1b**	 **3a**	90
4	**1c**	--[c]	--[c]
5	**1d**	 **3b**	86
6	**1e**	 **3c**	87
7	**1f**	 **3d**	92
8	**1g**	 **3e**	93
9	**1h**	 **3f**	89
10	**1j**	 **3g**	67
11	 **1n**	 **3h**	72[d]

[a]0.5 mmol of **1**, 0.01 mmol of $FeCl_3·6H_2O$, and 2 mL of CH_2Cl_2 at rt for 1 h; then 2.5 mmol of NaOH and 0.1 mL EtOH were added to the reaction mixture, and the reaction was continued for 12 h under reflux. [b]Without EtOH and 50% dihydroquinoline intermediate **2a** was recovered. [c]Only 86% of dihydroquinoline intermediate **2c** was isolated. [d]Benzene was used as a solvent instead of CH_2Cl_2 and at 80 °C.

125.4, 126.2, 126.4, 126.7, 127.3, 127.4, 127.7, 128.2, 128.7, 129.1, 129.2, 132.9, 135.3, 136.2, 137.7, 143.3; IR (neat) 3028, 2923, 1598, 1347, 1346, 1167, 687 cm^{-1}; MS (70 eV, EI) m/z = 375 [M^+].

*2-(4-Chlorophenyl)-1-tosyl-1,2-dihydroquinoline (**2e**).*[17a] 172 mg, 87% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 2H), 7.24–7.19 (m, 3H), 7.16–7.08 (m, 3H), 6.97 (d, J = 7.6 Hz, 1H), 6.28 (d, J = 9.6 Hz, 1H), 5.98 (d, J = 6.0, 1H), 5.85 (dd, J = 9.6, 6.0 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 56.2, 125.9, 126.0, 126.4, 126.6, 127.2, 127.6, 128.5, 128.6, 128.9, 129.2, 132.7, 133.8, 136.0, 136.9, 143.6; IR (neat) 3063, 2923, 1597, 1347, 1168, 687 cm^{-1}; MS (70 eV, EI) m/z = 395 [M^+].

*2-(2-Chlorophenyl)-1-tosyl-1,2-dihydroquinoline (**2f**).* 186 mg, 94% yield; white solid; mp 85–86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 1H), 7.39–7.34 (m, 3H), 7.30 (t, J = 7.6 Hz, 1H), 7.18–7.09 (m, 5H), 7.01 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.45 (d, J = 5.6 Hz, 1H), 6.15 (d, J = 9.6 Hz, 1H), 6.01 (dd, J = 9.6, 5.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 55.2, 124.6, 126.0, 126.5, 126.6, 127.1, 127.5, 128.1,128.3, 128.6, 129.0, 129.1, 129.9, 131.3, 134.0, 135.8, 137.3, 143.6; IR (neat) 3065, 2924, 1598, 1353, 1168, 685 cm^{-1}; HRMS (TOF, EI) $[M]^+$ calculated for $C_{22}H_{18}ClNO_2S$ 395.0747, found 395.0748.

*2-(4-Fluorophenyl)-1-tosyl-1,2-dihydroquinoline (**2g**).*[17a] 182 mg, 96% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 1H), 7.33–7.29 (m, 4H), 7.21 (t, J = 7.6 Hz, 1H), 7.16–7.08 (m, 3H), 6.98 (d, J = 7.6 Hz, 1H), 6.91 (t, J = 8.6 Hz, 2H), 6.29 (d, J = 9.6 Hz, 1H), 5.99 (d, J = 5.6 Hz, 1H), 5.85 (dd, J = 9.6, 5.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 56.3, 115.3 (d, $^2J_{FC}$ = 22.1 Hz), 125.8, 126.2, 126.3, 126.6, 127.2, 127.6, 128.4, 128.5, 129.1, 129.2 (d, $^3J_{FC}$ = 8.2 Hz), 132.7, 134.0 (d, $^4J_{FC}$ = 2.9 Hz), 136.0, 143.5, 162.4 (d, $^1J_{FC}$ = 244.5 Hz); IR (neat) 3066, 2925, 1601, 1346, 1167, 687 cm^{-1}; MS (70 eV, EI) m/z = 379 [M^+].

*2-(4-Bromophenyl)-1-tosyl-1,2-dihydroquinoline (**2h**).*[17a] 193 mg, 88% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.24–7.20 (m, 3H), 7.16–7.08 (m, 3H), 6.97 (d, J = 7.2 Hz, 1H), 6.29 (d, J = 9.6 Hz, 1H), 5.96 (d, J = 5.6 Hz, 1H), 5.85 (dd, J = 9.6, 5.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 56.3, 122.0, 125.8, 126.0, 126.4, 126.7, 127.2,127.6, 128.4, 128.5, 129.1, 129.2, 131.5, 132.6, 135.9, 137.4, 143.6; IR (neat) 3047, 2923, 1598, 1348, 1167, 687 cm^{-1}; MS (70 eV, EI) m/z = 439 [M^+].

*(E)-2-Styryl-1-tosyl-1,2-dihydroquinoline (**2j**).*[17a] 132 mg, 68% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.28–7.26 (m, 1H), 7.26–7.13 (m, 6H), 7.08 (d, J = 8.0 Hz, 2H), 6.96 (dd, J = 7.6, 1.2 Hz, 1H), 6.52 (dd, J = 15.6, 1.2 Hz, 1H), 6.16 (d, J = 9.2 Hz, 1H), 6.04 (dd, J = 16.0, 6.0 Hz, 1H), 5.72 (dd, J = 9.2, 6.0 Hz, 1H), 5.57 (t, J = 5.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 56.0, 125.3, 125.4, 126.0, 126.5, 126.6, 127.2, 127.5, 127.8, 128.2, 128.4, 129.1, 132.1, 133.0, 136.1, 136.3, 143.4; IR (neat) 3027, 2924, 1598, 1349, 1168, 687 cm^{-1}; MS (70 eV, EI) m/z = 387 [M^+].

*4-Methyl-1-tosyl-1,2-dihydroquinoline (**2k**).*[17a] 103 mg, 69% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 1H), 7.32–7.28 (m, 1H), 7.26–7.16 (m, 3H), 7.11 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 8.0 Hz, 2H), 5.32 (br, 1H), 4.34–4.33 (m, 2H), 2.33 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 21.4, 45.3, 120.3, 123.3, 126.7, 127.2, 127.4, 127.8, 128.8, 131.4, 131.6, 135.2, 136.1, 143.2; IR (neat) 3064, 2924, 1350, 1164, 682 cm^{-1}; MS (70 eV, EI) m/z = 299 [M^+].

*4-Phenyl-1-tosyl-1,2-dihydroquinoline (**2l**).*[17a] 141 mg, 78% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 1H), 7.35–7.32 (m, 3H), 7.25–7.22 (m, 3H), 7.14 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 7.6 Hz, 1H), 6.71 (d, J = 7.0 Hz, 2H), 5.58 (t, J = 4.4 Hz, 1H), 4.54 (d, J = 4.4 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 45.5, 121.6, 126.0, 126.6, 127.57, 127.61, 127.64, 127.9, 128.3, 128.5, 129.1, 131.0, 135.5, 136.1, 138.1, 138.7, 143.4; IR (neat) 3030, 2924, 1351, 1165, 681 cm^{-1}; MS (70 eV, EI) m/z = 361 [M^+].

*6-Chloro-4-phenyl-1-tosyl-1,2-dihydroquinoline (**2m**).*[17a] 152 mg, 77% yield; white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.31–7.23 (m, 4H), 7.06 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 2.4 Hz, 1H), 6.71–6.68 (m, 2H), 5.61 (t, J = 4.5 Hz, 1H), 4.53 (d, J = 4.5 Hz, 2H), 2.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 45.4, 122.9, 125.8, 127.5, 127.9, 128.1, 128.2, 128.4, 129.0, 129.2, 132.3, 132.4, 134.0, 135.8, 137.3, 137.9, 143.7; IR (neat) 3028, 2920, 1354, 1163, 676 cm^{-1}; MS (70 eV, EI) m/z = 395 [M^+].

General Procedure for the Synthesis of Substituted Quinolines 3. To a solution of protected 2-aminophenyl-1-en-3-ol (0.5 mmol) in CH_2Cl_2 was added $FeCl_3·6H_2O$ (0.01 mmol). After the reaction mixture was stirred at rt for 1 h (TLC monitored), NaOH (2.5 mmol) and EtOH (0.1 mL) were added, and the reaction was continued for 12 h under reflux (TLC monitored). The resulting mixture was purified by flash column chromatography on silical gel (petroleum ether/ethyl acetate) to give the desired pure product (**3a–h**).

dx.doi.org/10.1021/jo301560w | J. Org. Chem. 2012, 77, 8615–8620

*2-Phenylquinoline (**3a**).*[23] 95 mg, 93% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22−8.16 (m, 4H), 7.87 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 8.4 Hz, 1H), 7.55−7.51 (m, 3H), 7.46 (t, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.0, 126.3, 127.2, 127.5, 127.6, 128.9, 129.3, 129.6, 129.7, 136.8, 139.7, 148.3, 157.4; IR (neat) 3058, 2926, 1597, 1491, 772 cm^{-1}; MS (70 eV, EI) m/z = 205 [M$^+$].

*2-(p-Tolyl)quinoline (**3b**).*[23] 94 mg, 86% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.71 (td, J = 8.0, 1.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 118.8, 126.6, 127.06, 127.08, 127.4, 129.5, 129.6, 136.6, 136.8, 139.4, 148.3, 157.3; IR (neat) 3039, 2925, 1596, 1432, 814 cm^{-1}; MS (70 eV, EI) m/z = 219 [M$^+$].

*2-(4-Chlorophenyl)quinoline (**3c**).*[23] 104 mg, 87% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.15−8.10 (m, 2H), 7.84−7.82 (m, 2H), 7.75−7.71 (m, 1H), 7.55−7.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.6, 126.5, 127.2, 127.5, 128.8, 129.0, 129.7, 129.9, 135.6, 137.0, 138.0, 148.2, 156.0; IR (neat) 3055, 2924, 1594, 1486, 817 cm^{-1}; MS (70 eV, EI) m/z = 239 [M$^+$].

*2-(2-Chlorophenyl)quinoline (**3d**).*[23] 110 mg, 92% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.76−7.72 (m, 2H), 7.70 (dd, J = 7.2, 2.0 Hz, 1H), 7.59−7.55 (m, 1H), 7.51 (dd, J = 7.6, 1.6 Hz, 1H), 7.43−7.35 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.8, 126.8, 127.1, 127.2, 127.6, 129.6, 129.7, 129.9, 130.1, 131.7, 132.4, 135.7, 139.7, 148.1, 157.4; IR (neat) 3058, 2922, 1598, 1504, 1037, 760 cm^{-1}; MS (70 eV, EI) m/z = 239 [M$^+$].

*2-(4-Fluorophenyl)quinoline (**3e**).*[23] 104 mg, 93% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.4 Hz, 1H), 8.18−8.15 (m, 3H), 7.83 (d, J = 8.8 Hz, 2H), 7.75−7.71 (m, 1H), 7.55−7.51 (m, 1H), 7.23−7.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.8 (d, $^3J_{FC}$ = 7.8 Hz), 118.6, 126.4, 127.1, 127.5, 129.4 (d, $^2J_{FC}$ = 22.1 Hz), 129.6, 129.8, 135.8 (d, $^4J_{FC}$ = 2.0 Hz), 137.0, 148.2, 156.2, 163.8 (d, $^1J_{FC}$ = 246.9 Hz); IR (neat) 3066, 2926, 1593, 1498, 1432, 821 cm^{-1}; MS (70 eV, EI) m/z = 223 [M$^+$].

*2-(4-Bromophenyl)quinoline (**3f**).*[23] 126 mg, 89% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.76−7.71 (m, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.5, 123.9, 126.5, 127.2, 127.5, 129.1, 129.7, 129.9, 132.0, 137.0, 138.5, 148.2, 156.0; IR (neat) 3060, 2924, 1594, 1550, 1429 cm^{-1}; MS (70 eV, EI) m/z = 283 [M$^+$].

*(E)-2-Styrylquinoline (**3g**).*[24] 77 mg, 67% yield; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.72−7.64 (m, 5H), 7.50 (t, J = 7.8 Hz, 1H), 7.44−7.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.3, 126.2, 127.3, 127.5, 128.7, 128.8, 129.0, 129.2, 129.8, 134.4, 136.4, 136.5, 148.3, 156.0; MS (70 eV, EI) m/z = 231 [M$^+$].

*2-Phenyl-4-vinylquinoline (**3h**).* 83 mg, 72% yield; white solid; mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.17 (m, 2H), 8.10 (d, J = 8.4 Hz, 1H), 7.95 (s, 1H), 7.80−7.69 (m, 1H), 7.57−7.45 (m, 4H), 7.34−7.28 (m, 1H), 7.25−7.19 (m, 1H), 6.05 (d, J = 17.2 Hz, 1H), 5.71 (d, J = 11.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.5, 120.6, 123.4, 125.2, 126.3, 127.5, 128.8, 129.3, 129.5, 130.3, 132.6, 139.8, 144.2, 148.6, 157.3; IR (neat) 3062, 2925, 1592, 1348, 764 cm^{-1}; HRMS (TOF, EI) [M]$^+$ calculated for $C_{17}H_{13}N$ 231.1048, found 231.1045.

***(E)*-*N*-(2-(1-Ethoxy-3-phenylallyl)phenyl)-4-methylbenzenesulfonamide (4).** 187 mg, 92% yield; semisolid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.68−7.62 (m, 3H), 7.36−7.27 (m, 3H), 7.25−7.23 (m, 3H), 7.11−7.00 (m, 4H), 6.41 (dd, J = 15.9, 1.2 Hz, 1H), 6.08 (dd, J = 15.9, 6.0 Hz, 1H), 4.89 (dd, J = 6.0, 1.2 Hz, 1H), 3.62−3.48 (m, 2H), 2.28 (s, 3 H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 21.5, 64.7, 83.1, 119.7, 123.8, 126.8, 127.2, 127.7, 128.0, 128.3, 128.5, 129.0, 129.1, 129.5, 131.9, 136.1, 136.2, 136.7, 143.5; HRMS (TOF, EI) [M]$^+$ calculated for $C_{24}H_{25}NO_3S$ 407.1555, found 407.1556.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of compounds **2a**−**m** and **3a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wzmmol@hotmail.com; xqsun@cczu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Natural Science Foundation of China (no. 21102009), the Priority Academic Program Development of Jiangsu Higher Education Institutions, and Natural Science Foundation of Jiangsu Province (no. BK2011230).

■ REFERENCES

(1) (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (b) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (c) Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2125.

(2) (a) Solomon, V. R.; Lee, H. *Curr. Med. Chem.* **2011**, *18*, 1488. (b) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245. (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223. (d) Chiang, C.-L.; Shu, C.-F. *Chem. Mater.* **2002**, *14*, 682.

(3) Skraup, Z. H. *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 2086.

(4) Combes, A. *Bull. Soc. Chim. Fr.* **1883**, *49*, 89.

(5) Gould, R. G.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890.

(6) Friedländer, F. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2572.

(7) Doebner, O.; von Miller, W. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2812.

(8) (a) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157. (b) Barluenga, J.; Rodriguez, F.; Fananas, F. J. *Chem. Asian J.* **2009**, *4*, 1036. (c) Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116. (d) Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141.

(9) (a) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447. (b) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 2412. (c) Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1.

(10) (a) Cai, S.; Zeng, J.; Bai, Y.; Liu, X.-W. *J. Org. Chem.* **2012**, *77*, 801. (b) Suresh, R.; Muthusubramanian, S.; Senthilkumaran, R.; Manickam, G. *J. Org. Chem.* **2012**, *77*, 1468. (c) Sakai, N.; Tamura, K.; Shimamura, K.; Ikeda, R.; Konakahara, T. *Org. Lett.* **2012**, *14*, 836. (d) Zhang, Y.; Li, P.; Wang, L. *J. Heterocycl. Chem.* **2011**, *48*, 153.

(11) Zhang, X.; Liu, B.; Shu, X.; Gao, Y.; Lv, H.; Zhu, J. *J. Org. Chem.* **2012**, *77*, 501.

(12) (a) Sun, C.-L.; Li, B.-J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (b) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (c) Bolm, C.; Legros, J.; Paih, J. L.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(13) For reviews, see: (a) Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077. (b) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (d) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

(14) For recent selected examples, see: (a) Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036. (b) Souto, J. A.; Zian, D.; Muñiz, K. *J. Am. Chem. Soc.* **2012**, *134*, 7242. (c) Wang, Z.; Mo, H.; Cheng, D.; Bao, W. *Org. Biomol. Chem.* **2012**, *10*, 4249. (d) Yamamoto, H.; Ho, E.; Namba, K.; Imagawa, H.; Nishizawa, M. *Chem.—Eur. J.* **2010**, *16*, 11271. (e) Hande, S. M.; Kawai, N.; Uenishi, J. *J. Org. Chem.*

2009, *74*, 244. (f) Yang, H.; Fang, L.; Zhang, M.; Zhu, C. *Eur. J. Org. Chem.* **2009**, 666. (g) Wu, W.; Rao, W.; Er, Y. Q.; Loh, J. K.; Poh, C. Y.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2620. (h) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409. (i) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett.* **2006**, *8*, 4617.

(15) (a) Zhao, Y.; Foo, S. W.; Saito, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3006. (b) Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808. (c) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2008**, *49*, 858. (d) Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4065. (e) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2007**, *48*, 7160.

(16) (a) Wang, Z.; Yu, B.; Cui, Y.; Sun, X.; Bao, W. *Chin. J. Chem.* **2011**, *29*, 2769. (b) Wang, Z.; Yu, B.; Zhang, X.; Sun, X.; Bao, W. *Chin. J. Chem.* **2011**, *29*, 2775.

(17) (a) Kothandaraman, P.; Foo, S. J.; Chan, P. W. H. *J. Org. Chem.* **2009**, *74*, 5947. (b) Migneault, D.; Bernstein, M. A.; Lau, C. K. *Can. J. Chem.* **1995**, *73*, 1506. (c) Kobayashi, K.; Nagato, S.; Kawakita, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1995**, 575.

(18) Optically pure (*S*)-**1a** and (*R*)-**1a** were obtained from racemic **1a** by using chiral prep HPLC; separation conditions: OD-H column and elution with hexane/isopropanol (70:30); flow rate 1.0 mL min^{-1}.

(19) Separation conditions: OD-H column and elution with hexane/isopropanol (80:20); flow rate 1.0 mL min^{-1}.

(20) Reaction conditions: 0.5 mmol of **1a** or **1a**′, 0.025 mmol of $FeCl_3{\cdot}6H_2O$, 2.5 mmol of EtOH and 2 mL of CH_2Cl_2 at rt; 45% yield of product **4** from **1a** and 92% yield of product **4** from **1a**′ were obtained, respectively.

(21) Petasis, N. A.; Butkevich, A. N. *J. Organomet. Chem.* **2009**, *694*, 1747.

(22) Crawforth, C. E.; Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1972**, 865.

(23) Han, R.; Chen, S.; Lee, S. J.; Qi, F.; Wu, X.; Kim, B. H. *Heterocycles* **2006**, *68*, 1675.

(24) Yan, Y.; Xu, K.; Fang, Y.; Wang, Z. *J. Org. Chem.* **2011**, *76*, 6849.