Synthesis X. Chen et al. Paper

Synthesis of 4-(Dimethylamino)quinazoline via Direct Amination of Quinazolin-4(3*H*)-one Using *N*,*N*-Dimethylformamide as a Nitrogen Source at Room Temperature

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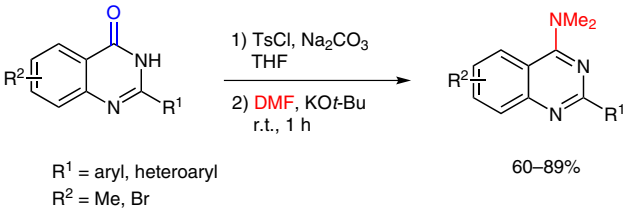
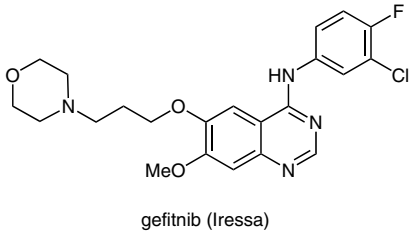


Received: 17.01.2015
Accepted after revision: 18.03.2015
Published online: 22.04.2015
DOI: 10.1055/s-0034-1380550; Art ID: ss-2015-h0036-op

Abstract An efficient direct amination of quinazolin-4(3*H*)-ones using *N*,*N*-dimethylformamide as a nitrogen source is described that affords the corresponding 4-(dimethylamino)quinazolines in high yields. This transformation proceeds through efficient 4-toluenesulfonyl chloride mediated C–OH bond activation at room temperature.

Key words amination, quinazolin-4(3*H*)-one, 4-aminoquinazoline



gefitnib (Iressa)

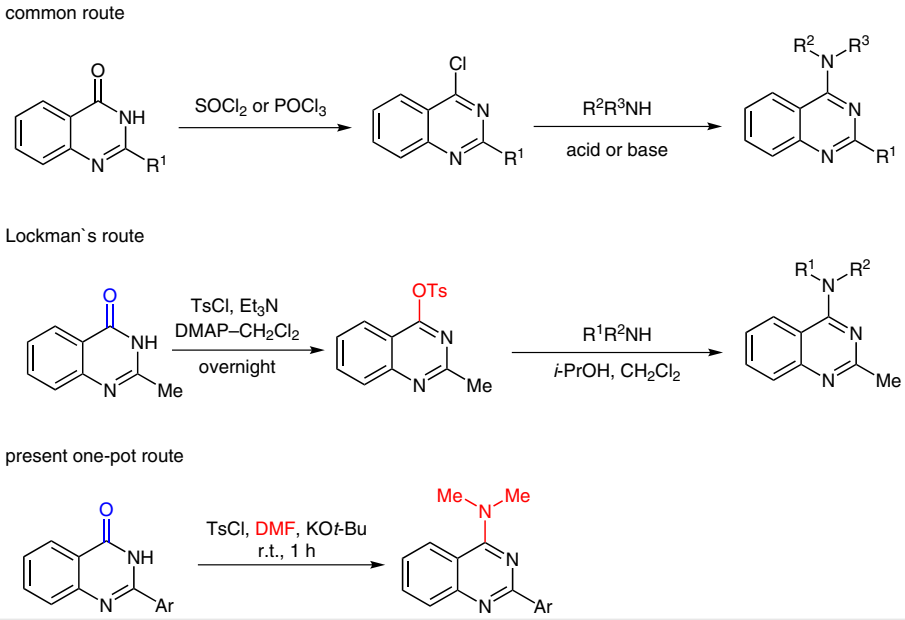
Figure 1 The structure of gefitinib (Iressa)

Quinazoline heterocycles are important scaffolds in medicinal chemistry. They are recognized as exhibiting a broad range of biological activity, such as anti-inflammatory, anticonvulsant, vasodilator, antihypertensive, antibiosis, and fibrinogen receptor antagonistic activity.[1] In particular, 4-aminoquinazolines have attracted widespread attention in recent years because of their potential pharmacological activity.[2] For example, gefitinib (Iressa), developed from 4-aminoquinazoline, is approved and marketed for non-small cell lung cancer treatment (Figure 1).[3] The most common route for the preparation of 4-aminoquinazolines is through acid- or base-mediated S_NAr substitution of 4-chloroquinazolines with amines.[4] However, the common method for the preparation of 4-chloroquinazolines is the chlorination of quinazolin-4(3*H*)-ones, which often requires acidic and harsh conditions using thionyl chloride or phosphoryl chloride as the chlorination reagent (Scheme 1).

Recently, a particular emphasis has been placed on cross-coupling reactions via C–OH bond activation of tautomerizable heterocycles, where phosphonium salts or 4-toluenesulfonyl chloride are recognized as efficient activation reagents.[5] Lockman et al. isolated 2-methyl-4-(tosyloxy)quinazoline from 2-methylquinazolin-4(3*H*)-one and then reacted it with primary and secondary amines to provide 4-aminoquinazolines in good yields (Scheme 1).[6] However, the reaction required two discrete steps to complete the reaction.

We have developed direct sulfanylations of 4-hydroxycoumarins[7] and quinazolin-4(3*H*)-ones[8] via C–OH bond activation. Prompted by our continued interest in 4-toluenesulfonyl chloride mediated C–OH bond activation, we envisioned that a small library of 4-aminoquinazolines could be constructed starting from quinazolin-4(3*H*)-ones.

In parallel, chemists have achieved important developments in the field of organic synthesis by employing *N*,*N*-dimethylformamide as a reaction precursor. Because of its specific structure, *N*,*N*-dimethylformamide can participate in many reactions by serving as a multipurpose building block for various units, such as CO, NMe_2, $CONMe_2$, Me, CHO, etc.[9] Substitution reactions of benzyl and (hetero)aryl halides leading to amines at high temperatures have been carried out using *N*,*N*-dimethylformamide as the solvent and reactant.[10] Shao and Chen also disclosed that amides could be used as the nitrogen source in palladium-catalyzed reactions with aryl chlorides.[11] In this paper, as part of our ongoing study on novel and green coupling processes,[7,12] we report the one-pot direct amination of



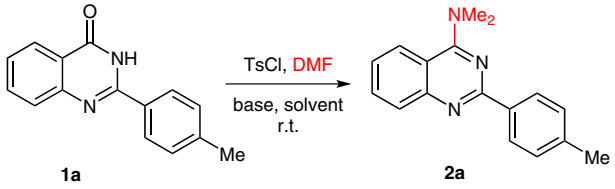
Scheme 1 Routes for the preparation of 4-aminoquinazolines

quinazolin-4(3*H*)-ones using *N*,*N*-dimethylformamide as the nitrogen source via a 4-toluenesulfonyl chloride mediated C–OH bond activated procedure (Scheme 1).

At the outset, 2-*p*-tolylquinazolin-4(3*H*)-one (**1a**) and *N*,*N*-dimethylformamide were selected as the model substrates to optimize the reaction conditions. We reasoned that the presence of 4-toluenesulfonyl chloride would enable in situ activation of 2-*p*-tolylquinazolin-4(3*H*)-one (**1a**). Based on these considerations, different bases and solvents were screened, and the results are given in Table 1.

In initial experiments, the reaction was performed in *N*,*N*-dimethylformamide with triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (3.0 equiv) as the base at ambient temperature, but no product was detected (Table 1, entries 1 and 2). Gratifyingly, the desired product 4-(dimethylamino)-2-*p*-tolylquinazoline (**2a**) was isolated in 60% yield using an inorganic base, sodium carbonate (entry 3). Slightly higher yields were obtained when potassium carbonate, potassium hydroxide, or sodium *tert*-butoxide were employed as the base (entries 4–6). Further evaluation showed that potassium *tert*-butoxide was the best base for this transformation because it afforded the desired product **2a** in 85% yield (entry 7). Other solvents (DMSO, DCE, THF, 1,4-dioxane, toluene, and cyclohexane) were subsequently screened, and *N*,*N*-dimethylformamide proved to be the most efficient solvent (entries 8–13). A control experiment showed that no reaction occurred without the addition of 4-toluenesulfonyl chloride (entry 14).

Table 1 Influence of the Reaction Conditions on the Direct Amination of Quinazolinone **1a** Using *N*,*N*-Dimethylformamide[a]



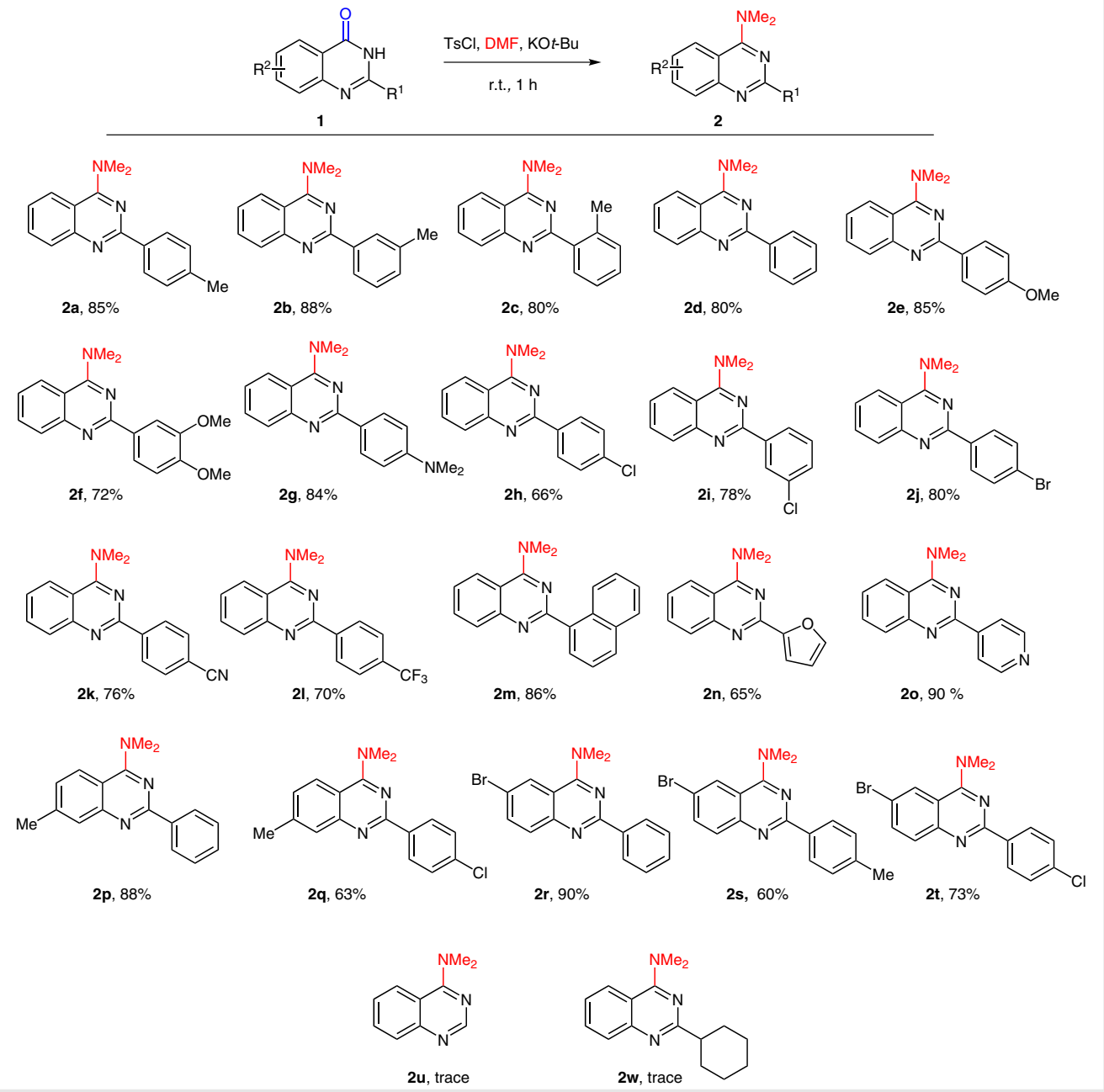
1a **2a**

Entry	Base	Solvent	Yield[b] (%)
1	Et_3N	DMF	–
2	DBU	DMF	–
3	Na_2CO_3	DMF	60
4	K_2CO_3	DMF	67
5	KOH	DMF	72
6	NaO*t*-Bu	DMF	75
7	**KO*t*-Bu**	**DMF**	**85**
8	KO*t*-Bu	DMSO	63
9	KO*t*-Bu	DCE	73
10	KO*t*-Bu	THF	78
11	KO*t*-Bu	1,4-dioxane	75
12	KO*t*-Bu	toluene	75
13	KO*t*-Bu	cyclohexane	70
14[c]	KO*t*-Bu	DMF	–

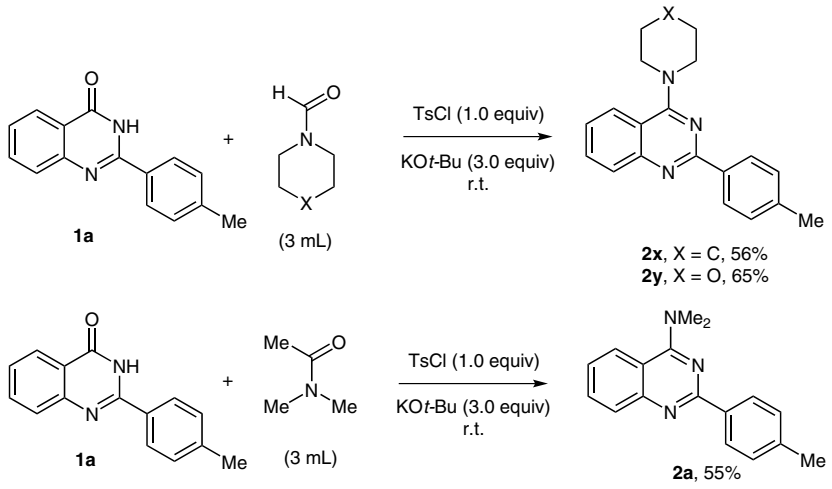
[a] Reaction conditions: **1a** (0.5 mmol), DMF (2.5 mmol), TsCl (0.5 mmol), base (3.0 equiv), solvent (3 mL), r.t., 1–12 h, air.
[b] Isolated yield.
[c] Without the addition of TsCl.

The generality and scope of this reaction were then investigated under the optimized conditions [TsCl (1.0 equiv), KO*t*-Bu (3.0 equiv), DMF (3 mL), r.t.]; the results are summarized in Scheme 2.

In most cases the corresponding products were obtained in good to excellent yields when 2-arylquinazolin-4(3*H*)-ones were used as substrates. 2-Arylquinazolin-4(3*H*)-one with electron-donating groups or electron-withdrawing groups on the aryl group were all good partners under the optimum conditions, which afforded the desired product **2a**–**l** in excellent yields. For example, 2-*m*-tolylquinazolin-4(3*H*)-one reacted with *N*,*N*-dimethylformamide to provide **2b** in 88% yield. A slightly lower yield (70%) was obtained for 4-aminoquinazoline **2l**. Additionally, other quinazolinones **1** incorporated methyl and bromo on the quinazolinone ring were examined in the reactions, which provided the expected products **2p**–**t** in good yields. 2-(1-Naphthyl)- and 2-heteroarylquinazolin-4(3*H*)-ones



Scheme 2 Direct amination of quinazolin-4(3*H*)-ones with *N*,*N*-dimethylformamide. *Reagents and conditions*: **1** (0.5 mmol), TsCl (1.0 equiv), KO*t*-Bu (3.0 equiv), DMF (3 mL), r.t., 1 h.



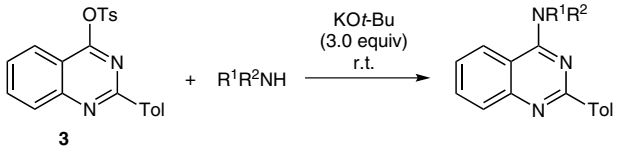
Scheme 3 Direct amination of 4-quinazolinone **1a** with piperidine-1-carbaldehyde, morpholine-4-carbaldehyde, and *N*,*N*-dimethylacetamide

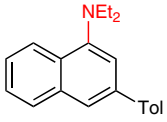
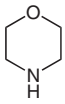
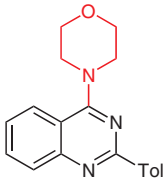
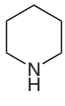
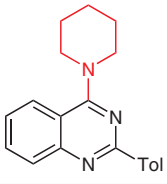
also afforded **2m**–**o** in moderate to high yields. However, similar to our previous reports[8] the reaction was unsuccessful with 2-unsubstituted quinazolin-4(3*H*)-one and 2-cyclohexylquinazolin-4(3*H*)-one even with a prolonged reaction time.

As *N*,*N*-dimethylformamide is a readily available source of dimethylamine in amination reactions, we also explored whether this reaction could be extended to other amides. When piperidine-1-carbaldehyde and morpholine-4-carbaldehyde were employed in the direct amination of 2-*p*-tolylquinazolin-4(3*H*)-one (**1a**), the expected products **2x** and **2y** were obtained in 56% and 65% yields, respectively (Scheme 3). Interestingly, *N*,*N*-dimethylacetamide also works well in the amination with **1a** to produce **2a** in 55% yield (Scheme 3).

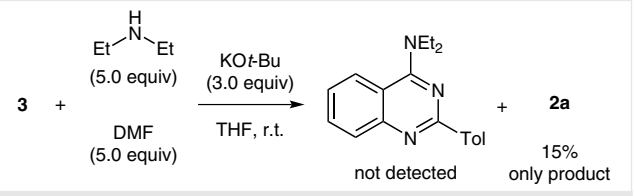
To explore the mechanism of this direct amination reaction, several control experiments were performed (Table 2). First, the key intermediate, tosylate 2-*p*-tolyl-4-(tosyloxy)quinazoline (**3**) was isolated, and it was treated with *N*,*N*-dimethylformamide under the reaction conditions to provide **2a** in 90% yield (entry 1). The reaction of **3** and dimethylamine (5.0 equiv in water) gave **2a** in 60% yield (entry 2). However when the reactions proceed under the conditions of Lockman et al., the corresponding products were obtained in 12% and 28% yields (entries 3 and 4). In the case of cyclic secondary amines, like morpholine and piperidine, the corresponding products were obtained in 58% and 37% yields (entries 5 and 6). Stirring **3** and diethylamine (5.0 equiv), *N*,*N*-dimethylformamide (5.0 equiv), and potassium *tert*-butoxide (3.0 equiv) in tetrahydrofuran (3.0 mL) at room temperature did not give the S_NAr substitution product of diethylamine and only **2a** (15%) was obtained (Scheme 4). These results indicated that in this catalytic system, formamide had higher reactivity compared to the corresponding simple aliphatic amine.

Table 2 Using 2-*p*-Tolyl-4-(tosyloxy)quinazoline (**3**) with Varying Amine Sources



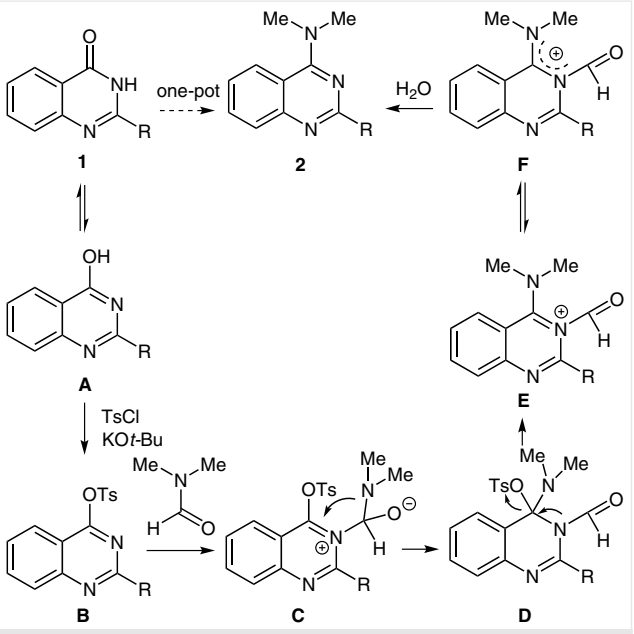
Entry	Amine	Product	Yield[a,b] (%)
1	DMF	**2a**	90
2	aq Me_2NH	**2a**	60
3	Me_2NH·HCl	**2a**	12
4	Et_2NH·HCl		28
5			58
6			37

[a] Reaction conditions: **3** (0.5 mmol), amine (5.0 mmol), base (3.0 equiv), THF (3 mL), r.t., 1–12 h, air.
[b] Isolated yield.



Scheme 4

Based on these experiments and other work,[10,13] a possible mechanism is proposed in Scheme 5. Quinazolinone **1** could isomerize to quinazolin-4-ol **A**. Treatment of quinazolinone with 4-toluenesulfonyl chloride in the presence of base (KO*t*-Bu) leads to the formation of tosylate **B**, which attacks *N*,*N*-dimethylformamide to form successive intermediates **C**, **D**, **E**, and **F**; hydrolysis of **F** gives the final product **2**. When R is H or alkyl group, only traces of expected products were obtained probably because the intermediates **C** or **D** are difficult to form without the delocalization effect of the 2-aryl group.



Scheme 5 Proposed mechanism

Finally, in order to compare the results of Lockman et al., a serial of control experiments were performed. The reactions of 4-(tosyloxy)quinazolines (intermediates) **B** with several amines were studied under the conditions of Lockman et al.; the results revealed that when the substituent at the 2-position of the quinazoline is methyl or hydrogen the reactions gave good yields but when it is aryl the yields were poor (see the Supporting Information). These results showed that the procedure of Lockman et al. can only be applied to the synthesis of 4-aminated 2-unsubstituted or 2-alkylquinazolines. While our method is efficient for the preparation of 4-aminated 2-arylquinazolines. Hence, these two reaction systems complement each other.

In conclusion, we have described a facile and efficient route for the synthesis of 2-aryl-4-(dimethylamino)quinazoline via direct amination of 2-arylquinazolin-4(3*H*)ones with *N*,*N*-dimethylformamide under mild conditions. Notably, by using the inexpensive and easy to handle 4-toluenesulfonyl chloride as the C–OH bond activation reagent, this cost-effective methodology will be attractive for further library construction.

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63 μm, standard grade). Analytical TLC was performed using glass plates precoated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~27 mbar at 25–35 °C. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. HRMS were obtained on a micrOTOF II Instrument.

4-(Dimethylamino)quinazolines 2; General Procedure

Quinazolinone (0.5 mmol) and KO*t*-Bu (1.5 mmol) in DMF (3.0 mL) were added to a round-bottom flask. The mixture was stirred for 2 min, TsCl (0.5 mmol) was added, and the mixture was stirred at r.t. for 1 h. When the reaction was complete (TLC), the mixture was quenched with sat. NaCl solution and extracted with EtOAc, and the combined extracts were dried (Na_2SO_4). The crude product was purified by chromatography (silica gel, PE–EtOAc, 15:1–10:1) to provide the corresponding product **2**.

4-(Dimethylamino)-2-*p*-tolylquinazoline (2a)[14]

White solid; yield: 112.2 mg (85%); mp 153.5–154.5 °C.

IR (KBr): 2923, 1609, 1334, 765, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.41 (s, 6 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.67 (t, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 8.45 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 41.8, 114.9, 123.9, 125.5, 128.4, 128.6, 129.0, 132.0, 136.2, 140.1, 153.0, 159.4, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3$: 264.1501; found: 264.1497.

4-(Dimethylamino)-2-*m*-tolylquinazoline (2b)[14]

Milky solid; yield: 116.2 mg (88%); mp 77.2–78.8 °C.

IR (KBr): 2916, 1608, 1283, 769, 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 3.40 (s, 6 H), 7.26 (d, *J* = 7.6 Hz, 1 H), 7.31–7.39 (m, 2 H), 7.66 (t, *J* = 8.4 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 8.36 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 41.8, 115.0, 124.0, 125.5, 125.6, 128.2, 128.7, 128.9, 130.8, 137.8, 137.9, 153.0, 159.5, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3$: 264.1501; found: 264.1500.

4-(Dimethylamino)-2-*o*-tolylquinazoline (2c)[14]

Brown oil; yield: 105.6 mg (80%).

IR (KBr): 2924, 1610, 1348, 767, 734 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.61 (s, 3 H), 3.38 (s, 6 H), 7.25–7.32 (m, 3 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.69 (t, *J* = 8.4 Hz, 1 H), 7.89–7.94 (m, 2 H), 8.03 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 41.9, 114.4, 124.2, 125.4, 125.7, 128.6, 130.4, 131.0, 131.9, 137.2, 139.6, 152.7, 162.5, 163.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3$: 264.1501; found: 264.1494.

4-(Dimethylamino)-2-phenylquinazoline (2d)[14]

Flavescent solid; yield: 100.0 mg (80%); mp 60.2–61.5 °C.

IR (KBr): 2922, 1613, 1349, 760, 741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.40 (s, 6 H), 7.34 (t, *J* = 8.2 Hz, 1 H), 7.36–7.50 (m, 3 H), 7.67 (t, *J* = 8.2 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 8.56 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8, 115.0, 124.0, 125.5, 128.2, 128.4, 128.7, 130.0, 132.0, 139.0, 153.0, 159.3, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3$: 250.1334; found: 250.1338.

4-(Dimethylamino)-2-(4-methoxyphenyl)quinazoline (2e)

White solid; yield: 119.0 mg (85%); mp 109.5–111.3 °C.

IR (KBr): 2932, 1606, 1351, 841.2, 765, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.38 (s, 6 H), 3.86 (s, 3 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 7.2 Hz, 1 H), 7.89 (d, *J* = 8.4 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 8.52 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8, 55.3, 113.6, 114.8, 123.7, 125.5, 128.5, 130.0, 131.6, 131.9, 153.1, 159.1, 161.4, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3O_2$: 280.1450; found: 280.1442.

2-(3,4-Dimethoxyphenyl)-4-(dimethylamino)quinazoline (2f)

Flavescent solid; yield: 111.6 mg (72%); mp 89.7–90.3 °C.

IR (KBr): 2933, 1601, 1344, 1262, 1089, 766 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.43 (s, 6 H), 3.95 (s, 3 H), 4.04 (s, 3 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.68 (t, *J* = 7.8 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 8.00 (d, *J* = 8.4 Hz, 1 H), 8.17–8.20 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.7, 56.0, 110.8, 111.6, 114.8, 121.7, 123.7, 125.5, 128.5, 131.9, 148.9, 151.1, 153.0, 159.0, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_3O_2$: 310.1556; found: 310.1546.

4-(Dimethylamino)-2-[4-(dimethylamino)phenyl]quinazoline (2g)[14]

Yellow solid; yield: 123.1 mg (84%); mp 138.6–141.5 °C.

IR (KBr): 2919, 1604, 1335, 1270, 766 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.94 (s, 6 H), 3.30 (s, 6 H), 6.71 (d, *J* = 9.2 Hz, 2 H), 7.19 (t, *J* = 8.0 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 1 H), 8.38 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.3, 41.7, 111.7, 114.7, 123.1, 125.5, 126.9, 128.3, 129.7, 131.7, 152.0, 153.2, 159.7, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}N_4$: 293.1766; found: 293.1750.

2-(4-Chlorophenyl)-4-(dimethylamino)quinazoline (2h)[14]

Yellow solid; yield: 93.7 mg (66%); mp 124.3–126.6 °C.

IR (KBr): 2923, 1640, 1579, 1331, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.43 (s, 6 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 8.8 Hz, 2 H), 7.69 (t, *J* = 7.8 Hz, 1 H), 7.91 (d, *J* = 8.4 Hz, 1 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 8.51 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8, 114.9, 124.3, 125.5, 128.4, 128.6, 129.8, 130.9, 132.2, 137.3, 152.7, 158.2, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}ClN_3$: 284.0954; found: 284.0949.

2-(3-Chlorophenyl)-4-(dimethylamino)quinazoline (2i)

Milky solid; yield: 110.8 mg (78%); mp 69.3–70.2 °C.

IR (KBr): 2924, 1611, 1325, 801, 729, 672 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.45 (s, 6 H), 7.33–7.41 (m, 2 H), 7.57 (d, *J* = 6.8 Hz, 1 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 8.03 (d, *J* = 7.6 Hz, 1 H), 8.51 (d, *J* = 8.0 Hz, 1 H), 8.70 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8, 115.0, 122.5, 124.4, 125.5, 127.0, 128.7, 129.7, 131.4, 132.2, 132.9, 141.0, 152.7, 157.7, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}ClN_3$: 284.0954; found: 284.0940.

2-(4-Bromophenyl)-4-(dimethylamino)quinazoline (2j)

Yellow solid; yield: 131.2 mg (80%); mp 108.2–110.6 °C.

IR (KBr): 2925, 1635, 1568, 1330, 578 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.40 (s, 6 H), 7.35 (t, *J* = 8.2 Hz, 1 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 7.67 (t, *J* = 7.2 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 8.43 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8, 115.0, 124.2, 124.5, 125.5, 128.7, 130.0, 131.3, 132.0, 138.0, 152.9, 158.3, 163.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}BrN_3$: 328.0449; found: 328.0440.

4-(Dimethylamino)-2-[4-(trifluoromethyl)phenyl]quinazoline (2l)

Milky solid; yield: 120.8 mg (76%); mp 83.6–85.1 °C.

IR (KBr): 2929, 1621, 1354, 1316, 856, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.40 (s, 6 H), 7.36 (t, *J* = 7.2 Hz, 1 H), 7.66–7.72 (m, 3 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 8.65 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.7, 115.1, 124.4, 125.1, 125.5, 128.7, 131.3 (J_{C-F} = 32 Hz), 131.6, 132.1, 142.4, 152.8, 157.8, 163.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}F_3N_3$: 318.1218; found: 318.1223.

4-*N*,*N*-Dimethylamino-2-(4-cyanophenyl)quinazoline (2k)

Colorless flakes; yield: 96.3 mg (70%); mp 184.5–185.2 °C.

IR (KBr): 2923, 2231, 1618, 1316, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.44 (s, 6 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.70–7.75 (m, 3 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 8.65 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8, 113.1, 115.1, 119.1, 124.8, 125.5, 128.8, 132.0, 132.3, 143.2, 152.8, 157.3, 163.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}N_4$: 275.1297; found: 275.1310.

4-(Dimethylamino)-2-(naphthalen-1-yl)quinazoline (2m)

Flavescent solid; yield: 129.0 mg (86%); mp 106.5–108.2 °C.

IR (KBr): 2955, 1613, 1344, 857, 769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.38 (s, 6 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 7.67–7.49 (m, 2 H), 7.67 (t, *J* = 7.8 Hz, 1 H), 7.84–7.87 (m, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.95–8.02 (m, 3 H), 8.69 (d, *J* = 8.4 Hz, 1 H), 9.07 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8, 115.0, 124.1, 125.6, 125.8, 125.9, 126.6, 127.7, 127.8, 128.4, 128.7, 129.2, 132.1, 133.4, 134.5, 136.4, 153.1, 159.2, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}N_3$: 300.1501; found: 300.1502.

4-(Dimethylamino)-2-(furan-2-yl)quinazoline (2n)

Tan oil; yield: 78.0 mg (65%).

IR (KBr): 2927, 1612, 1331, 766, 684 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.38 (s, 6 H), 6.54 (dd, *J* = 1.6, 3.2 Hz 1 H), 7.31–7.36 (m, 2 H), 7.62 (s, 1 H), 7.67 (t, *J* = 7.2 Hz, 1 H), 7.97 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.7, 111.7, 112.7, 115.0, 124.1, 125.4, 128.6, 132.1, 144.4, 152.5, 152.7, 153.3, 163.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_3O$: 240.1137; found: 240.1114.

4-(Dimethylamino)-2-(pyridin-4-yl)quinazoline (2o)[14]

Yellow solid; yield: 113.0 mg (90%); mp 111.3–113.5 °C.

IR (KBr): 2923, 1608, 1330, 772, 681 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.40 (s, 6 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.69 (t, *J* = 7.8 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 8.36 (d, *J* = 4.8 Hz, 2 H), 8.73 (d, *J* = 4.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.7, 115.3, 122.3, 124.9, 125.5, 128.9, 132.2, 144.4, 150.0, 152.7, 157.1, 163.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_4$: 251.1297; found: 251.1281.

4-(Dimethylamino)-7-methyl-2-phenylquinazoline (2p)

Milky solid; yield: 116.2 mg (88%); mp 102.6–104.8 °C.

IR (KBr): 2923, 1623, 1344, 775, 705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 3.40 (s, 6 H), 7.18 (d, *J* = 7.2 Hz, 1 H), 7.43–7.49 (m, 3 H), 7.73 (s, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 8.55 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 41.7, 112.9, 125.3, 126.0, 128.0, 128.2, 128.3, 129.9, 139.1, 142.5, 153.3, 159.4, 163.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3$: 264.1501; found: 264.1485.

2-(4-Chlorophenyl)-4-(dimethylamino)-7-methylquinazoline (2q)

Flavescent solid; yield: 93.9 mg (63%); mp 132.1–134.0 °C.

IR (KBr): 2922, 1599, 1354, 1316, 856, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 3.40 (s, 6 H), 7.18 (d, *J* = 8.4 Hz, 1 H), 7.42 (d, *J* = 8.8 Hz, 2 H), 7.70 (s, 1 H) 7.89 (d, *J* = 8.8 Hz, 1 H), 8.49 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 41.8, 112.8, 125.3, 126.2, 127.9, 128.4, 129.7, 135.9, 137.5, 142.7, 153.1, 158.3 163.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_3$: 298.1111; found: 298.1110.

6-Bromo-4-(dimethylamino)-2-phenylquinazoline (2r)

Flavescent solid; yield: 147.6 mg (90%); mp 75.2–77.0 °C.

IR (KBr): 2922, 1619, 1344, 828, 707, 539 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.36 (s, 6 H), 7.45–7.47 (m, 3 H), 7.70 (dd, *J* = 2.0, 8.8 Hz, 1 H), 7.76 (d, *J* = 8.8 Hz, 1 H), 8.09 (s, 1 H), 8.52 (dd, *J* = 1.6, 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8, 116.1, 116.8, 127.9, 128.3, 128.4, 130.2, 130.5, 135.2, 138.6, 151.8, 159.5, 162.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}BrN_3$: 328.0449; found: 328.0476.

6-Bromo-4-(dimethylamino)-2-*p*-tolylquinazoline (2s)

Brown solid; yield: 102.6 mg (60%); mp 105.6–108.8 °C.

IR (KBr): 2923, 1599, 1340, 832, 739, 540 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.42 (s, 6 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.74–7.78 (m 2 H), 8.14 (d, *J* = 2.0 Hz, 1 H), 8.42 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 41.8, 116.0, 116.6, 127.9, 128.4, 129.1, 130.4, 135.2, 135.8, 140.4, 151.8, 159.7, 162.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}BrN_3$: 342.0606; found: 342.0624.

6-Bromo-2-(4-chlorophenyl)-4-(dimethylamino)quinazoline (2t)

Yellow solid; yield: 132.1 mg (73%); mp 162.2–163.5 °C.

IR (KBr): 2924, 1622, 1319, 786, 649, 573 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.40 (s, 6 H), 7.42 (d, *J* = 8.8 Hz, 2 H), 7.72–7.77 (m, 2 H), 8.12 (d, *J* = 1.2 Hz, 1 H), 8.46 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8, 116.0, 117.0, 127.9, 128.5, 129.7, 130.4, 135.4, 136.4, 137.0, 151.6, 158.5, 162.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}BrClN_3$: 362.0060; found: 362.0089.

4-Piperidino-2-*p*-tolylquinazoline (2x)

Yellow solid; yield: 85.0 mg (56%); mp 112.3–114.6 °C.

IR (KBr): 2929, 1606, 1566, 1350, 792 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.79–1.83 (m, 6 H), 2.42 (s, 3 H), 3.79 (s, 4 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.69 (dd, *J* = 7.2, 8.4 Hz, 1 H), 7.87 (d, *J* = 8.4 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 8.45 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 24.9, 26.1, 51.0, 115.4, 124.4, 125.1, 128.4, 128.5, 129.1, 132.2, 135.8, 140.3, 152.5, 159.5, 165.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}N_3$: 304.1814; found: 304.1798.

4-Morpholino-2-*p*-tolylquinazoline (2y)

Yellow solid; yield: 99.4 mg (65%); mp 142.8–144.5 °C.

IR (KBr): 3030, 2917, 1606, 1563, 1350, 1125, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.84 (d, *J* = 4.4 Hz, 4 H), 4.93 (t, *J* = 4.2 Hz, 4 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 8.44 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 50.4, 66.8, 115.3, 124.6, 124.9, 128.4, 129.0, 129.1, 132.5, 136.8, 140.4, 152.8, 159.6, 164.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}N_3O$: 306.1606; found: 306.1605.

Acknowledgment

We are grateful to the National Natural Science Foundation of China (grant nos. 21162012 and 21362014), Jiangxi Provincial Department of Science and Technology (for Jiangxi's Key Laboratory of Green Chemistry, and no. 20122BAB203007), the Science Foundation of Education Department of Jiangxi province (grant no. GJJ10386) and the open project program of National Research Center for Carbohydrate Synthesis (grant no. GJDTZX-KF-2014XX) for their financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380550.

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